

Human Health & Disease

Mondays, Tuesdays, Thursdays and Fridays 9:00 - 11:50 AM

Lectures: Room M-112, Labs: Fleischmann

INDE 221
Spring 2010

Syllabus
Part 2



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Last Year's (2010) Syllabus

Human Health & Disease

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Inde 221 Spring 2010 Syllabus Schedule

Weekday	Date	Time	Room	Topic	Instructor
Tues	4/27	9 - 9:50	M112	Cardiac Muscle and FHC	R. Tsien
		10 - 10:50	M112	Excitation-Contraction Coupling	R. Tsien
		11 - 11:50	M112	Nernst Potential & Osmosis	D. Madison
Thurs	4/29	9 - 9:50	M112	Excitability & Conduction	R. Tsien
		10 - 11:50	FLRC	Circulatory Vessel Histology Lab	A. Connolly
Fri	4/30	9 - 9:50	M112	Cardiac Action Potential	R. Tsien
		10 - 10:50	M112	Control of Heart Rhythm	R. Tsien
Wk 5 ends		11 - 11:50	M112	Autonomic Pharmacology Overview 1	J. Whitlock
Mon	5/3	9 - 9:50	M112	ECG	R. Tsien
		10 - 10:50	M112	Lesions of Blood Vessels	A. Connolly
		11 - 11:50	M112	Thromboembolic Disease	A. Connolly
Tues	5/4	9 - 10:50	M112	Cardiac Reflexes	B. Kobilka
		11 - 11:50	M112	Autonomic Pharmacology Overview 2	J. Whitlock
Thurs	5/6	9 - 10:50	FLRC	ECG Small Groups	Faculty
		11 - 11:50	M112	Autonomic Drugs (Cholinergics)	J. Whitlock
Fri	5/7	9 - 10:50	M112	Muscle Mechanics	R. Turcott
Wk 6 ends		11 - 11:50	M112	Autonomic Drugs (Anticholinergics)	J. Whitlock
Mon	5/10	9 - 10:50	M112	Arrhythmias	P. Wang
		11 - 11:50	M112	Autonomic Drugs (Sympathomimetics 1)	J. Whitlock
Tues	5/11	9 - 10:50	M112	Ventricular Physiology	R. Turcott
		11 - 11:50	M112	Autonomic Drugs (Sympathomimetics 2)	J. Whitlock
Thurs	5/13	9 - 9:50	M112	Starling Curve and Venous Return	J. Wong
		10 - 10:50	M112	Cardiac Output and Catheterization	R. Dash
Fri	5/14	11 - 11:50	M112	Autonomic Drugs (Adrenoceptor Blockers)	J. Whitlock
		9 - 10:50	M112	Physics of Circulation	M. McConnell
Wk 7 ends		11 - 11:50	M112	Case Discussions (Autonomic Drugs)	J. Whitlock
Sat	5/15	9 - 11:00	H2152	Saturday Treadmill Session #1 (Last Name A-K) – OPTIONAL	



Last Year's (2010) Syllabus

Mon	5/17	9am-12pm	FLRC	EXAM DAY (Basic CV / Autonomics)	
Tues	5/18	9 – 9:50	M112	Smooth Muscle	R. Tsien
		10 – 10:50	M112	Ischemic Heart Disease	A. Connolly
		11 – 11:50	M112	Valvular Heart Disease	A. Connolly
Thurs	5/20	9 – 9:50	M112	Renal Circulation	S. Rockson
		10 – 10:50	M112	Hypertension	S. Rockson
		11 - 11:50	M112	Cardiomyopathy, Myocarditis and Atrial Myxoma	G. Berry
Fri	5/21	9 – 9:50	M112	Endothelium & Coronary Circulation	J. Topper
		10-10:50	M112	Angina Pectoris	J. Topper
		11-11:50	M112	Drugs Used in Hypertension	J. Whitlock
Sat	5/22	9 – 11:00	H2152	Saturday Treadmill Session #2 (Last Name L-Z) – OPTIONAL	
Mon	5/24	9 – 9:50	M112	Shock	M. Rosenthal
		10 – 11:50	FLRC	Adult Cardiac Lab	Faculty
		9 – 9:50	M112	Cardiac Anesthesia & Bypass	M. Kanevsky
Tues	5/25	10 – 10:50	M112	Exercise Physiology	R. Fishman
		11 - 11:50	M112	Ischemic Heart Disease	J. Whitlock
		9 – 10:50	M112	Congestive Heart Failure	A. Patterson
Thurs	5/27	11 - 11:50	M112	Drugs Used in Angina Pectoris	J. Whitlock
		9 - 9:50	M112	Intro to Cardiac & Tomographic Anatomy of the Heart	N. Silverman
		10 – 10:50	M112	Positive Inotropic Agents	J. Whitlock
Wk 9 Ends	5/28	11 – 11:50	M112	Congestive Heart Failure Pharmacology	J. Whitlock
		9 – 9:50	FLRC	Holiday	
		10 – 11:50	FLRC		
Tues	6/1	9 – 9:50	M112	Fetal Circulation & Congenital Heart Disease	D. Bernstein
		10 – 10:50	M112	Congenital Malformations of the Heart	G. Berry
		11 – 11:50	M112	Antiarrhythmic Drugs	J. Whitlock
Thurs	6/3	9 – 9:50	M112	Cardiovascular Pharm Case Discussions	J. Whitlock
		10 – 11:50	FLRC	Pediatric Cardiac Lab	Faculty
		9am-12pm	FLRC	EXAM DAY (End-CV)	
Mon - Tues		6/7 - 6/8	STUDY TIME		
Wed	6/9	9am-12pm	FLRC	INTEGRATED FINAL EXAM DAY	



Last Year's (2010) Syllabus

Human Health & Disease

Inde 221 Spring 2010 Syllabus Preface (CV)

The following information has been provided to communicate any important updates in the course that have been made since the previous syllabus (Inde 221 2010 Part 1, Pulmonary and Neoplasia).

TEXTBOOKS

The following book is recommended for the CV Physiology sessions:

Cardiovascular Physiology, by Berne and Levy, 8th edition (2000, paperback).

Please note: the B&L book is available for purchase at the Stanford University Bookstore. The HHD course will not be providing copies of this book.

SATURDAY TREADMILL SESSIONS

There will be two Saturday treadmill sessions that you are strongly encouraged to attend.

The session dates are Saturday, May 15 and Saturday, May 22.

Students whose last name begins with the letter A to K are scheduled to attend the treadmill session on May 15. Students whose last name begins with the letter L to Z are scheduled to attend the treadmill session on May 22. If you are unable to attend your scheduled session, please find someone in the other session to switch places with you.

Both sessions begin at 9:00am and last approximately two hours. Please meet in the CV Clinic, room H-2152, which is located next to the ECG Lab of the hospital (North ICU).

The objective of the treadmill session is to demonstrate practical applications of ECG and Echocardiography, and show you how a treadmill diagnostic is performed.



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HUMAN HEALTH & DISEASE

Spring 2010

CV Block Syllabus

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CARDIAC MUSCLE AND FAMILIAL HYPERTROPHIC CARDIOMYOPATHY

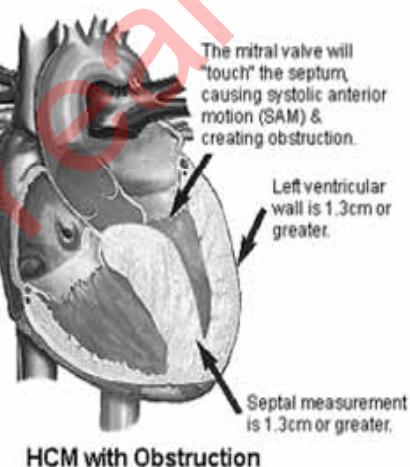
REQUIRED READING: B&L pp. 55-61

OBJECTIVES:

1. To review the important contractile proteins for the cardiac contraction
2. To appreciate the plasticity of the heart arising from the regulation of contractile protein genes
3. To appreciate the significance of those genes in the pathophysiology of hypertrophy of the heart due to either familial hypertrophic cardiomyopathy or hypertension.

I. A CLINICAL CASE: FAMILIAL HYPERTROPHIC CARDIOMYOPATHY (FHC)

- A. FHC is both a sporadic and an autosomal dominant disorder characterized by unexplained myocardial hypertrophy, a wide spectrum of clinical symptoms including arrhythmias, and early death. Sudden death can occur in both symptomatic and asymptomatic individuals. Pathological change in the heart consists of focally increased cardiac mass (regional hypertrophy) and myofibrillar disarray within varied anatomic regions of the heart. The figure illustrates septal hypertrophy. In the extreme case, the mitral valve will touch the septum, causing systolic anterior motion and creating an obstruction.



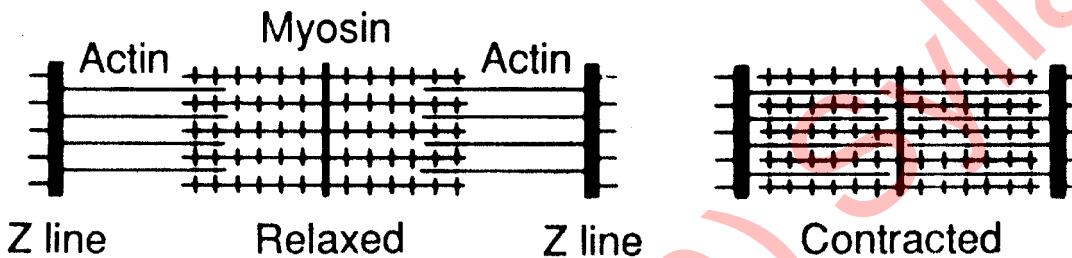
It turns out that FHC can arise from defects in any one of a number of heart cell contractile proteins. It is really a disease of the sarcomere.

Current hypotheses suggest that FHC, while a relatively uncommon disorder, may offer clues to the basis of heart failure, a very common disease that may affect half a million people a year in the U.S. alone. We will return to this theme at the end of the lecture.

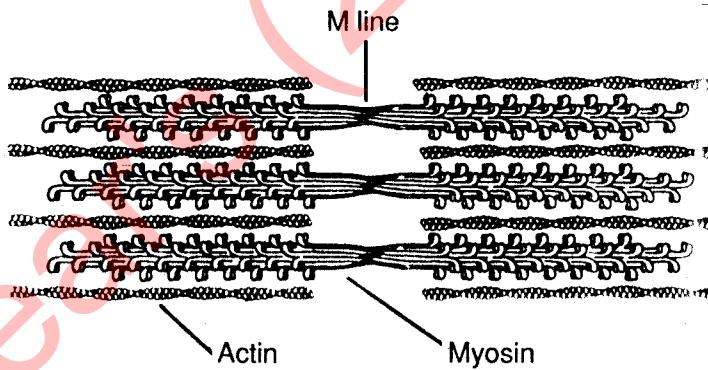


II. THE SARCOMERE AND CONTRACTILE PROTEINS

- A. Here we briefly review the structure of the striated muscle cells in cardiac and skeletal muscle. Most of you will have had ample exposure to this material in earlier courses.
- B. The sarcomere is the basic contractile unit. The z-line marks the edges of the sarcomere. The thin filaments are attached to the z-line and these filaments contain the actin. In the center of the sarcomere is the A-band which is formed by the thick filaments containing myosin that extend to either side of the M-line.



- C. The contraction of the muscle is produced by the movement of the myosin along the actin filaments. This draws the thin filaments in towards the center of the sarcomere and thereby shortens the distance from Z-line to Z-line. The overlap of actin and myosin filaments will be a short stretch at rest but in a contracted muscle, the Z-line may be pulled in almost to the edge of the thick filaments.

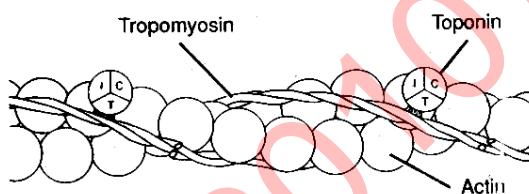


- D. The diagram shows a more detailed view of the contractile proteins that compose the sarcomere. The force generated and the velocity of contraction are dependent upon the number as well as the isoform of the contractile proteins. Each of the contractile proteins that compose a sarcomere is a member of a family of isoforms of that protein. Important differences in isoforms produce significantly different contractile properties for skeletal muscle vs. cardiac muscle in various regulatory states. Smooth muscle exhibits even greater differences in organization and physiological properties, to be discussed in a later lecture.



E. Thin filament proteins:

1. In skeletal and cardiac muscle, the thin filament proteins are actin, tropomyosin, and troponin (troponin T,C, or I). Each thin filament is attached to the Z-line material (α actinin) of the sarcomere. The heart of the thin filament is two strands of filamentous actin that coil about one another. Each filament is itself a string of actin monomers. The troponin-tropomyosin complex is associated with the thin filament and makes the sarcomere a calcium sensitive contractile structure. This complex regulates the interaction between the heads of the myosin molecule of the thick filament and the adjacent thin filament. The tropomyosin is envisaged as lying along the actin filament, blocking the myosin binding sites. Ca^{2+} binding to troponin C causes a conformational change in the rest of the troponin complex (I, C and T) and this in turn moves the tropomyosin aside and thereby activates the thin filament for contraction.



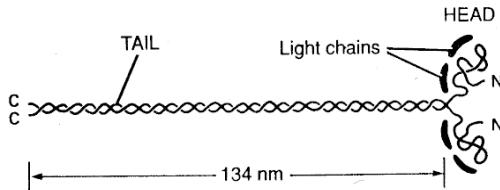
2. There are some significant distinctions between thin-filament based regulation of Ca^{2+} sensitivity in cardiac and skeletal muscle. Cardiac TnC has one less functional Ca^{2+} binding site than skeletal TnC, making the Ca^{2+} regulation more graded. In the case of cardiac muscle, the input output relation of $\log [\text{free } \text{Ca}^{2+}]$ vs tension rises steeply above 0.3 μM . The Ca^{2+} sensitivity in heart can be regulated by TnI phosphorylation, which decreases the affinity of TnC for Ca^{2+} , thereby increasing the rate of cardiac muscle relaxation.

F. Thick filament proteins:

1. Several proteins are in the thick filament but myosin is the major one, comprising the essential ATPase and major structural element. The myosin complex is two-headed and consists of two myosin heavy chains and four associated light chains (MLC). Thus, each MHC head is associated with two myosin light chains.
2. Each MHC molecule contains two functional domains, a head region and a tail or rod region. The head region is responsible for force generation and contains the ATPase site, the actin binding site, and the MHC light chain binding sites. The dimeric heavy chain molecules assemble in an



anti-parallel fashion from the center of the filament with the heads located at 14.3 Angstrom intervals along the thick filament. The anti-parallel arrangement from the center of the filament produces a bare zone, lacking in MHC heads.



3. The myosin light chains associated with each myosin complex modulate the ATPase activity of the heads. In cardiac and skeletal muscle, the ATPase activity of the myosin is always ready to go, but as we will discuss later in the course, in smooth muscle the activity is dependent on the Ca²⁺-dependent phosphorylation of one of the myosin light chains.

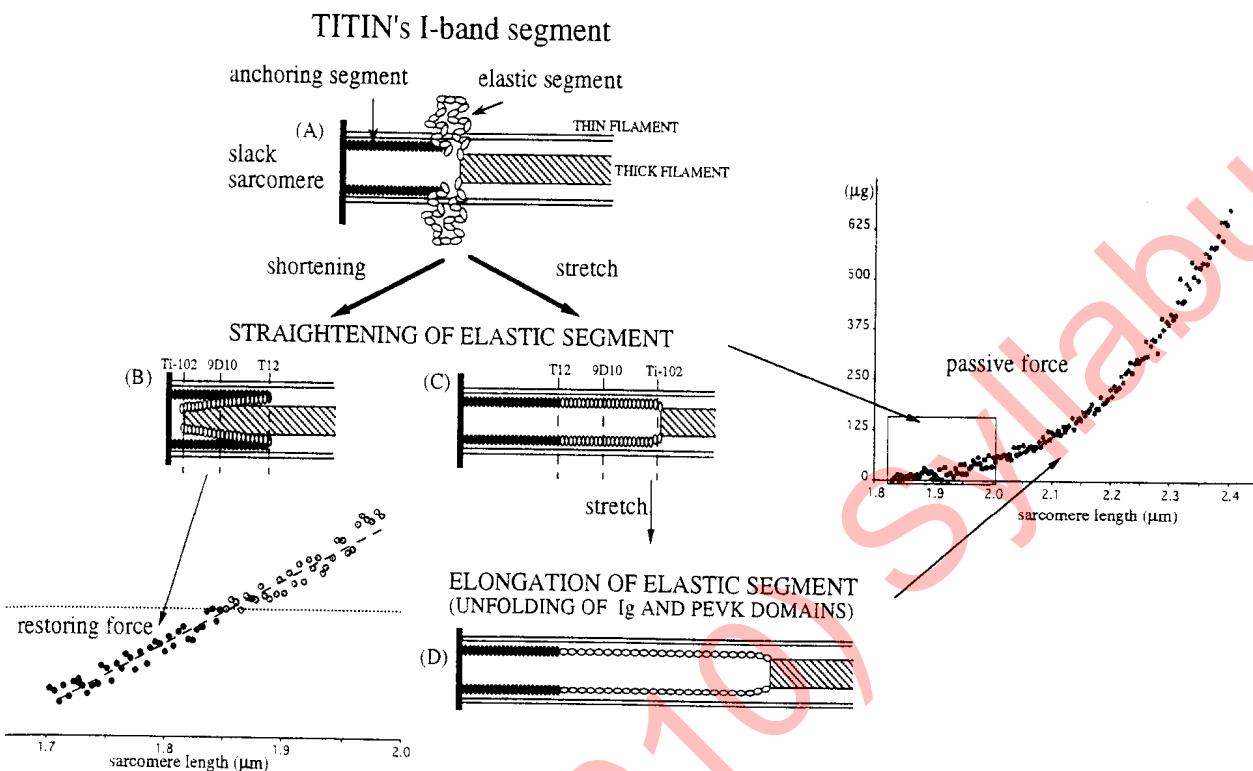
G. Other sarcomeric proteins

1. α actinin (Z-line), C-protein (thick filament) and nebulin (thin filament) respectively are present in lower amounts in the sarcomere

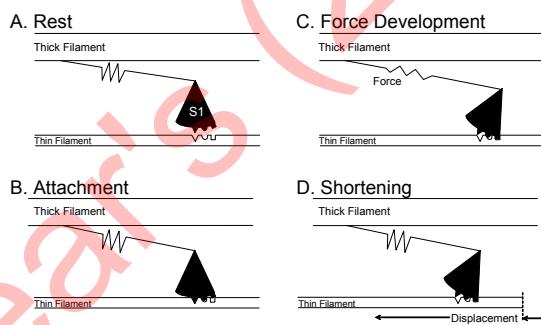
H. Titin

1. This relative newcomer to the field is proving interesting as a likely contributor to the elasticity of the muscle. The importance of elasticity will become clearer later in the course, when we discuss the mechanical properties of muscle. Titin is an enormous (3 mega-daltons), filamentous protein that spans half the length of the sarcomere and interacts with both the actin thin filament and myosin thick filament. Titin is now thought to be a major contributor to the elastance of muscle. It is thought to uncoil when the muscle is stretched, eventually acting to resist over-stretching of the sarcomere, keeping the muscle in its useful working range. On the other hand, when sarcomere length becomes very short, titin may help resist over compression and provide an elastic restoring force to quickly restore the sarcomere to resting length. This may aid efficient diastolic filling.





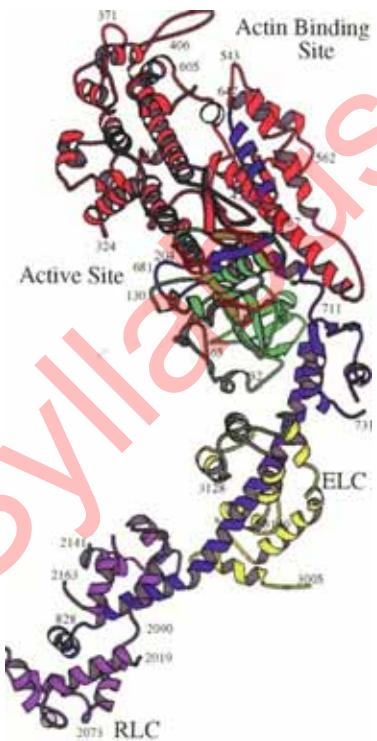
III. FORCE GENERATION BY CONTRACTILE PROTEINS



A. Huxley & Simmons 1971 model was very influential in thinking about the nature of the conformational change in myosin. It was a specific proposal for coupling chemical energy to molecular motion, involving a local conformational change, amplified by a lever arm, whereby metabolic reactions drove energy storage in the form of an extension of some kind of molecular spring (series elasticity).



- B. There is now evidence for bending within HMM itself [J.A. Spudich, Biochemistry Course], different in detail from the pivoting on the actin thin filament proposed by Huxley & Simmons, but following the same general principles: The general idea is that (1) mechanical motion is somehow linked to ATP hydrolysis, (2) the faster the biochemical cycling, the greater the Vmax, but also the greater the ATP consumption. In light of the linkage between biochemistry and mechanics, the speed of the actin-activated ATPase is critical rate-limiting process. The existence of two myosin heads is thought to confer a 2-fold increase in Vmax for actin motion in motility assays. The regulatory light chains bind to light chain binding domain of MHC, somehow assisting the lever arm action of that domain in amplifying conformational changes in head itself. It is known that light chain phosphorylation occurs in a frequency-dependent manner, which might increase Ca²⁺ sensitivity.



IV. LENGTH-TENSION RELATIONSHIP

- A. This is the rising and falling ability to support tension as muscle length progressively increases. The L-T relationship is a property of all striated muscle, and the key to the Frank-Starling Law of the Heart, as you will learn in Dr. Mark Perlroth's lectures. In skeletal muscle, where it has been best studied, the various phases of the L-T relationship have been traced to variations in the ability of the crossbridges to exert productive force.

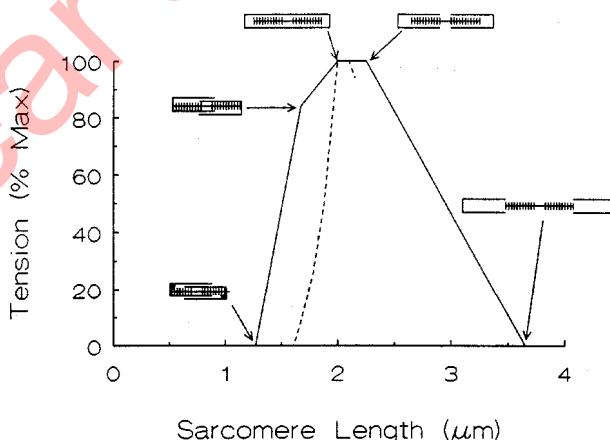


Figure 15. The length-tension relationship in frog skeletal muscle as described by Gordon *et al.* (1966) is indicated by the solid line and the inset diagrams. The length-tension relationship for cat cardiac muscle (described by Allen *et al.*, 1974) is also illustrated (broken curve).



- B. However, there are some major differences between skeletal and cardiac muscle in the position of the rising phase of the L-T curve, the important phase for the Frank-Starling Law. The cardiac L-T curve is steeper, and operates over a very narrow range of lengths (dashed curve in diagram). This phase is supported by cardiac TnC but not skeletal TnC and has been found to depend in large part on changes in Ca²⁺ sensitivity of Ca²⁺ binding to cTnC

V. CHANGES IN CONTRACTILE PROPERTIES OF THE HEART THROUGH REGULATION OF GENE EXPRESSION

The heart is capable of changing its patterns of gene expression both rapidly and dramatically in response to a variety of pathological and physiological stimuli. Such alterations are important in tuning the heart's performance in response to changing contractile demands. They are seen during the cardiac response to hormones, with pressure-induced cardiac hypertrophy, and as a physiological basis for genetic diseases such as FHM. Much of the work in this area has focused on myosin. As already discussed, the myosin heavy chain is both an enzyme (ATPase) and a structural protein (key element of thick filament). In heart, myosin heavy chain (MHC) is abundant, functionally important, and a good exemplar of the ability of the myocardium to alter itself. As you will see, these changes are highly relevant to clinical situations, including hypertension-induced heart failure and hypertrophic cardiomyopathy.

VI. THE MYOSIN HEAVY CHAIN GENE FAMILY IN HEART: α AND β CARDIAC MYOSIN

- A. The human heart contains two myosin heavy chain isoforms, called α and β , both cloned and sequenced. α MHC can be viewed as a "fast" isoform and β MHC as a "slow" isoform. That is, α MHC has high calcium and actin activated ATPase activity, and supports a high shortening velocity of ventricular fibers, while β MHC has low calcium and actin activated ATPase activity and slower shortening velocity of ventricular fibers. These isoforms illustrate the general correlation between the actin-activated ATPase activity of the myosin (biochemistry) and the unloaded maximal rate of shortening of the muscle fiber that contains it (mechanics). As already mentioned, the faster the fiber, or the higher the ATPase of its MHCs, the higher the energy cost to produce the same amount of work. The α and β isoforms differ widely with regard to ATPase activity: α is >3 times faster in Vmax, but is much less efficient energetically. It will come as no surprise, then, that in your soleus muscle, an example of a "slow" muscle used for maintained forces, the MHC is of the β type. Because the heart expends a lot of energy maintaining force against a load (you'll hear this referred to



later in the course as “tension-time work”), greater efficiency makes sense in some ways, just as for slow skeletal muscle. Clearly, the myosin heavy chain composition of a muscle fiber is important for its physiological performance.

- B. Because myosin molecules are dimers of MHC's, the dimers can exist in three forms in the human ventricle: two α 's, two β 's, or an α and a β isoform. These three myosin types can be distinguished on electrophoresis of human ventricular myosins and are often designated as V1 (α/α homodimer), V2 (α/β heterodimer), and V3 (β/β homodimer). The β isoform tends to be functionally dominant in heterodimers.
- C. The genes for the α and β MHC isoforms are located in tandem on the long arm of chromosome 14 within 4.5 kb of each other at q11-13 -- presumably, a perfect example of gene duplication. The α MHC gene lies 3' to the β MHC gene. Both cardiac genes are composed of 40 exons, 38 of which are coding, each distributed over about 30 kb of DNA, and each encoding a 223 kd polypeptide, the MHC. There is a direct correlation between the levels of α and β mRNAs, their rate of transcription and the abundance of the corresponding MHC proteins in a cardiocyte.
- D. To summarize: the members of the MHC family differ in their ATPase activity; regulation of expression of myosin genes, and in turn, the enzymatic activity of myosin determines the physiology of muscle fibers.

VII. MHC ISOFORM SWITCHING IN PHYSIOLOGICAL AND PATHOLOGICAL STATES

- A. Myosin heavy chain expression is developmentally regulated in the heart:
 1. β myosin heavy chain is the most abundant isoform in the ventricle and atria until late in fetal life. α myosin heavy chain increases transiently at birth, but β myosin heavy chain becomes the most abundant isoform in the adult ventricle, while α myosin heavy chain becomes the predominant isoform in atria throughout human life. However, both the atria and ventricle do have a minor expression of β MHC and α MHC respectively. Cardiac isoform expression can be altered by work overload, diabetes, removal of the gonads, and thyroid hormone levels.
- B. Thyroid hormone modifies the expression of the myosin heavy chain family:
 1. All members of the MHC family are responsive to thyroid hormone (T3, triiodothyronine).



2. Thyroid hormone induces transcription of some myosin heavy chain genes and represses other MHC genes.
3. α -myosin heavy chain expression in the ventricle is dependent upon thyroid hormone. (In the absence of thyroid hormone, α MHC is not expressed in the ventricle, but it is in the atrium). β MHC expression is repressed by thyroid hormone and is induced by the absence of thyroid hormone.
4. Thus, extreme changes in cardiac myosin expression are seen in diseases of the thyroid. Hyperthyroidism leads to nearly exclusive expression of α MHC in the ventricle, while hypothyroidism leads to nearly exclusive β MHC expression in the ventricle. Replacement or correction of T3 levels restores the normal amounts of these two isoforms within the ventricle.
- C. Cardiac Hypertrophy from Work Overload produces quantitative and qualitative changes.
1. There are two components to cardiac hypertrophy, a quantitative increase in cardiac mass (increase in muscle protein, fiber diameter and number of sarcomeres) and a qualitative change in the proteins expressed. Those proteins expressed mimic those expressed in fetal development. Basically, hypertrophy results in the induction of β MHC and the repression of α MHC genes in the ventricle. The amount of α MHC in most fibers decreases and more fibers appear to contain only β MHC. The rat heart is illuminating with regard to cardiac hypertrophy. α MHC predominates in the adult rat ventricle. With work overload there is a rapid induction of β MHC mRNA and the expression of β MHC in the adult rat. In human atria, where α MHC is the predominant isoform, there is also increased expression of β myosin heavy chain when work overload produces a rise in atrial pressure. Therefore, cardiac hypertrophy appears to mimic the fetal and the hypothyroid state.
2. The response to work overload is not confined to MHCs. It includes the induction of skeletal α actin, myosin light chain 1, β tropomyosin, the sodium pump, and atrial natriuretic factor (ANF). ANF expression in the adult is confined to atrial cardiocytes, but in cardiac hypertrophy, ANF reappears in ventricular cardiocytes also. Secretion of this peptide alters solute and fluid balance in the body in response to intravascular volume.

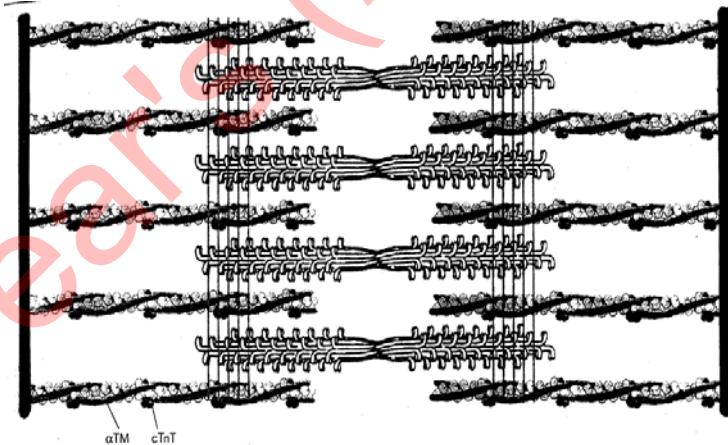


D. Heart Failure

1. The composition of human heart myosin also changes drastically in heart failure, as examined by comparison of donor and recipient hearts in cardiac transplantation procedures. A recent study showed convincing evidence of a virtual disappearance of mRNA for α MHC with cardiac failure (33% in controls, 2% in failing hearts). Striking changes were also reported in levels of MHC proteins (α isoform 7% in controls, undetectable in failing hearts). To what extent these changes are purely adaptive and beneficial or partly maladaptive is not clear. Mechanisms for switching of MHC gene expression during work overload and cardiac hypertrophy are also not well understood. They are probably not thyroid-hormone based because these hormone levels remain unchanged in work overload states.

VIII. WHAT DO FHC (A RARE DISEASE) AND HEART FAILURE (HIGHLY PREVALENT) HAVE IN COMMON?

- A. Let us now return to familial hypertrophic cardiomyopathy. Over the last few years, molecular approaches have greatly clarified the basis of FHC: it is most certainly a disease of the sarcomere, as already mentioned. It can arise from a mutation in one of several genes encoding protein components of the sarcomere. β -MHC, troponin-T, troponin-I, α -tropomyosin, MyBP-C, vMLC-1, vMLC-2, α -actin, are examples of defective proteins.



Several contractile proteins of the sarcomere. FHC mutations have been identified in these contractile proteins, which are components of both the thin filaments (α TM, cTnT) and the thick filaments (Myh, gray multiheaded domains; MyBP-C, thin gray vertical lines). These findings have led to the hypothesis that FHC is a disease of the sarcomere [2**]. As the full genetic heterogeneity of FHC becomes known, we shall learn if the other components of the sarcomere also contribute to this 'sarcomeric' disease. Thick gray vertical lines represent Z lines.

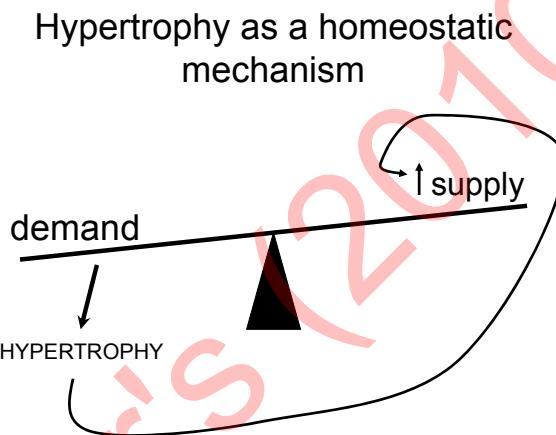


- B. One complication is that FHC is characterized by a highly variable penetrance, typically 70%. Besides genetics, additional factors of importance are environmental factors, including exercise, lifestyle. Besides heart muscle, slow skeletal muscles may also behave in a detectably abnormal manner.

IX. FAMILIAL HYPERTROPHIC CARDIOMYOPATHY VS. HEART FAILURE DUE TO PRESSURE OVERLOAD

In FHC, hypertrophy of the septum often occurs and can lead to obstruction of the ventricular outflow and other difficulties. The initiating factors are defects in one of a wide variety of sarcomeric proteins (one can think of this inadequate supply of pumping in the face of continuing demand)

In heart failure, hypertrophy of the ventricular free wall causes to a massively enlarged heart. The initiating factor is generally extrinsic, often a hemodynamic overload (one can think of this as excessive demand for mechanical output).



In both cases, it is believed that the hypertrophy and the return to the fetal pattern of sarcomeric gene expression are in an attempt at compensation, which would be fine in moderation but not in excess. Thus, hypertrophy may be a homeostatic mechanism that has simply been pushed too far.



Last Year's (2010) Syllabus

EXCITATION-CONTRACTION COUPLING

REQUIRED READING: B&L pp. 61-65

OBJECTIVES:

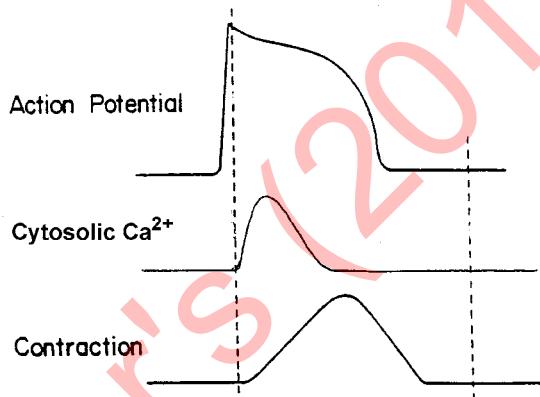
- A. Learn what E-C coupling is and how it involves cytosolic Ca²⁺
- B. Understand each element that regulates cytosolic Ca²⁺
 - 1. at the sarcolemma
 - 2. in the sarcoplasmic reticulum
- C. Understand the interplay of those elements during
 - 1. contraction
 - 2. relaxation
- D. Compare E-C coupling in cardiac and skeletal muscle
- E. Understand the regulation of cardiac contractility by digitalis.

I. WHAT IS E-C COUPLING?

- A. The heart has a limited number of mechanisms by which it can alter its force of contraction. As we discussed in the last lecture, one way is by increasing the end-diastolic length of its sarcomeres, which increases the effectiveness of the tension-developing crossbridges formed by myosin interactions with actin. This structurally based mechanism contributes to the augmentation of force during the next contraction, the classic "Frank-Starling Law of the Heart". This principle will have great importance for the overall performance of the heart as a pump, as discussed later in this course. Equally important mechanisms can produce changes in force from an unchanged diastolic sarcomere length and these usually involve alterations in the excitation-contraction (EC) coupling process.
- B. Contraction is of course a mechanical event, produced by biochemical changes in the muscle. This contraction, as you know, must be triggered by an electrical event - the cardiac action potential. The mechanism of sarcolemmal excitation will be covered in later lectures. For now, let us simply consider the fact that the electrical changes occur only at the plasmalemma: a protein deep inside of the cell cannot tell if the membrane potential is -70 mV or +20 mV. How then does the electrical signal trigger the mechanical change? The answer is, of course, through the regulation of cytoplasmic Ca²⁺ ions.



- C. Activation of contraction is due to a rise in the intracellular Ca²⁺ concentration. Normal resting Ca²⁺ is probably about 0.1 μM. Contraction is activated when intracellular Ca²⁺ rises to ~ 0.5-5.0 μM. The temporal relation between a cardiac action potential, the rise in cytoplasmic Ca²⁺, and force development is shown in Fig. 1. For reference, the duration of the action potential would be about 200-300 ms.
- D. Excitation precedes the onset of contraction by 20-25 msec. The level of membrane depolarization which must be reached for activation of the contractile process to occur (mechanical threshold) is approximately -35 to -30 mV but this is reached within a millisecond or so. The mechanical threshold potential coincides with the level at which Ca²⁺ channels begin to open. Judging by measured Ca²⁺ transients, only a few more milliseconds are required for Ca to diffuse from its entry or storage site(s), to reach threshold concentration at the troponin complex in the sarcomeres. The major portion of the latency period is attributable to the time required for crossbridges to attach, change conformation, and develop externally measurable force.



II. WHY CA²⁺ IS SUCH A UBIQUITOUS MESSENGER FOR EXCITATION-CONTRACTION COUPLING

- A. Why is it always Ca²⁺ that seems to couple electrical changes to biochemical changes? In almost every case that you might think of, Ca²⁺ is the active messenger that does the signaling: it couples the action potential to neurotransmitter release, it couples changes in electrical activity to changes in gene expression, it couples electrical activity to enzymatic changes in the cell, and of course it activates the cardiac muscle that we are now discussing.
- B. There are several reasons why Ca²⁺ emerged as the preeminent ionic messenger through the course of evolution:



1. Because it is doubly charged, a Ca²⁺ ion can engage in very strong and specific interactions with protein sites comprised of amino acids with negatively charged side chains (aspartates or glutamates). Ca²⁺ is large enough that multiple asp or glu side chains can coordinate a single ion, causing a conformational change in the parent protein. This in principle is how Ca²⁺-receptive molecules like troponin C or calmodulin work.
2. Because Ca²⁺ forms an insoluble precipitate with phosphate, one of the major internal anions derived from metabolism, cells probably evolved in such a way as to work with relatively low Ca²⁺ concentrations in their cytoplasm. Transport systems pump Ca²⁺ from the cytoplasm into the extracellular space, holding the resting Ca²⁺ level in the cytosol to approximately 0.05 μM. This is ~40,000-fold less than in the extracellular fluid. The large chemical gradient sets up a greatly favorable situation for Ca²⁺ as a signaling entity. the opening of a Ca²⁺ channel in the cell membrane, for example, allows Ca²⁺ ions to flow down that steep gradient. Because the basal Ca²⁺ concentration is so low, only a small number of ions need to flow in order to cause a large percentage change in the local internal concentration, making the signal stand out against its background. This means that there is a large dynamic range that the cell can work with.
- C. Indeed, when a voltage-gated Ca²⁺ channel opens or when Ca²⁺ is released from an intracellular pool, the movement of hundreds or thousands of Ca²⁺ ions can cause the local Ca²⁺ concentration near the mouth of the channel can soar up to 1 mM within a fraction of a millisecond. In contrast, a cell with 5 mM intracellular Na⁺ would need to flux 5 times as much Na⁺ in order to accomplish a mere doubling of the intracellular Na⁺ concentration. No wonder then that the cell has evolved so many processes that are triggered by Ca²⁺ concentration, rather than Na⁺ (or any other ion). (This does not mean that intracellular Na⁺ is not in itself important -- stay tuned and see why).
- D. Returning to excitation-contraction coupling in heart, regulation of the Ca²⁺ signal and its downstream effects is a fair amount more complicated than you may suspect. Moreover, such regulation is critical to the performance of the heart and a clear comprehension of it is key to understanding a great deal of cardiac pharmacology and pathology. The next section reviews the sources and sinks for Ca²⁺ and the proteins that regulate the movements of this ion across the sarcolemma and within the cell.



III. MYOCARDIAL ULTRASTRUCTURE AND KEY CA₂₊ TRANSPORT MECHANISMS

- A. Before proceeding to a deeper discussion of the basis of E-C coupling, it is necessary to review the fine structure of heart cells. The cells themselves are roughly cylindrical in shape, approximately 80 to μm long and 10-12 μm in diameter. Figure 1 depicts those cellular elements important in development and control of contractile function.

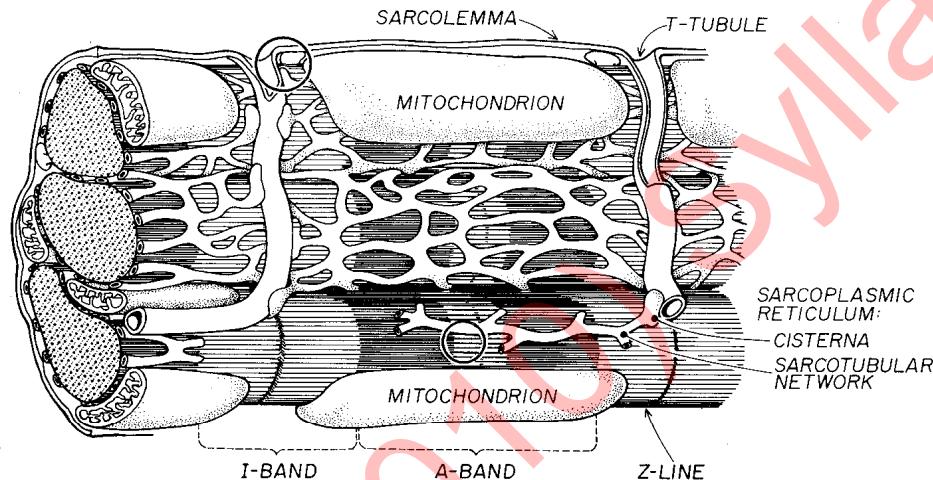


FIG. 1.9. Ultrastructure of the working myocardial cell. Contractile proteins are arranged in a regular array of thick and thin filaments (seen in cross section at the left). The A-band represents the region of the sarcomere occupied by the thick filaments into which thin filaments extend from either side. The I-band is the region of the sarcomere occupied only by thin filaments; these extend toward the center of the sarcomere from the Z-lines, which bisect each I-band. The sarcomere, the functional unit of the contractile apparatus, is the region between each pair of Z-lines; it contains two half I-bands and one A-band. The sarcoplasmic reticulum, a membrane network that surrounds the contractile proteins, consists of the sarcotubular network at the center of the sarcomere and the cisternae, which abut on the t-tubules and the sarcolemma. The transverse tubular system (t-tubule) is lined by a membrane that extends from the sarcolemma and carries the extracellular space into the myocardial cell. In contrast to the t-tubules of skeletal muscle, those of the myocardium can run in a longitudinal as well as a transverse direction. Mitochondria are shown in the central sarcomere and in cross section at the left. (From Katz. *N. Engl. J. Med.*, 293:1184, 1975.)

- B. The sarcolemma, sarcoplasmic reticulum and of course the Ca₂₊-regulated elements of the myofilaments are the essential cellular structures involved in regulating the mechanical function of the heart. The interaction of these structures controls the sequence of cardiac contraction and relaxation.

IV. SARCOLEMMA

- A. The sarcolemma is an extremely complex membrane which separates the cell interior from the extracellular milieu and controls the flux of ions into and out of the cell. These fluxes play a major role in the control of contractile force.



- B. A large increase in sarcolemmal surface area is produced by the transverse tubules ("T" tubules). These are invaginations of the sarcolemmal membrane, which occur in register with the ends of each sarcomere. They extend primarily transversely to the center of each cell. They are 100-200 nm in diameter. The "T" tubules are open to the interstitial space and therefore their lumens are, in effect, extracellular. The "T" tubular invaginations increase the cellular surface area over that of a smooth, non-invaginated cellular cylinder by almost 2.5 times. It is useful to think of the T-tubules as bringing information about the membrane potential into the center of the myocyte. If Ca^{2+} needed to diffuse from the surface into the center it would take at least 200 msec to move 6 μm . The cardiac action potential would be over and done with before the center of the fibre had a chance to hear about it. The propagation of the electrical signal along the T-tubule is, of course, much faster. T-tubules are enriched in Ca^{2+} channels so that they can accomplish the local increase in Ca^{2+} in the cell.
- C. Along with morphological entities, let's consider the important proteins and therapeutic targets that control Ca^{2+} levels in the cytosol and thereby control the activation of the sarcomere. Some of the proteins have already been briefly mentioned above, while others add a further level of control, particularly during the cardiac relaxation.
- D. Sarcolemmal Ca^{2+} flux pathways
1. Ca channels - Membrane depolarization results in activation of voltage-sensitive L-type Ca^{2+} channels and rapid Ca^{2+} influx. Because of the large inwardly directed Ca gradient, Ca^{2+} flux will always be in the inward direction. It is the L-type Ca^{2+} channel which is the target of "calcium blocker" drugs such as verapamil, diltiazem, nifedipine, etc. In the heart, as we explained above, this Ca^{2+} acts as a crucial messenger in provoking Ca^{2+} release from the major Ca^{2+} store, the SR.
 2. ATP-dependent Ca pump - A Ca, Mg-ATPase enzyme in the sarcolemma will pump Ca^{2+} out of myocardial cells using the energy stored in ATP. This pump mainly works to extrude Ca^{2+} back out of the cell during diastole. Note that the sarcolemmal Ca pump has different properties from that present in the sarcoplasmic reticulum, although both work in parallel to restore cytosolic Ca^{2+} to low basal levels.



3. Na-Ca exchange - There is a protein in the sarcolemma which catalyzes the exchange of 3 Na⁺ ions on either side of the membrane for one Ca²⁺ ion on the opposite side. The net direction of Ca transport will thus depend on the magnitude of both the Na⁺ and Ca²⁺ gradients. The contribution of the Na-Ca exchange will also be affected by the membrane potential, since the reaction involves the net movement of a charge (3 positive charges on the Na⁺ ions are exchanged for the 2 positive charges on one Ca ion). This will be very important for understanding the action of digitalis, which is discussed below.

V. SARCOPLASMIC RETICULUM (SR)

- A. This is a completely intracellular membranous system. It consists of 20-40 nm diameter closed tubules which wrap around each sarcomere. Some of these tubules terminate in flattened sacs or cisternae closely apposed to the sarcolemma at the periphery of the cell or at the "T" tubules. The function of the SR is most clearly defined in skeletal muscle where the "terminal cisternae" are the sites of release of Ca to the myofilaments for contraction and the tubules about the sarcomeres (medial or free SR) sequester the Ca during relaxation. The SR is much more sparse in heart muscle and, as we will see below, is not the only source of Ca to trigger contractions in cardiac muscle. In all muscle types, it is important to remember that this membrane system is not in direct contact with the extracellular space.
- B. Sarcoplasmic Reticulum (SR) Ca²⁺ flux pathways
 1. Ca release channels - The SR can release Ca to activate the myofibrils, via a protein called the Ryanodine Receptor. As discussed above, in the heart a very small increase in cytoplasmic Ca levels (e.g., after Ca influx through sarcolemmal Ca channels) will induce the release of large amounts of SR Ca. This is the "Ca-induced Ca release" hypothesis which is now widely accepted.
 2. ATP-dependent Ca pump - A very active Ca, Mg-ATPase can cause the sequestration of large amounts of Ca within the SR, an intracellular organelle. This pump is stimulated by phosphorylation of the SR induced by catecholamines. A regulatory subunit of the pump, called phospholamban, is phosphorylated by the cAMP-dependent protein kinase and this will cause the pump to increase its activity. This has two important consequences for the heart: 1) it will increase the rate at which cytosolic Ca²⁺ is mopped up by the SR and will therefore speed the rate of relaxation. Faster relaxation is as important as faster contraction if adrenalin is going to



make your heart beat faster. 2) It also increases the amount of Ca²⁺ in the SR because more of the Ca²⁺ goes into the SR and less goes back out across the plasma membrane. This means that there is more Ca²⁺ stored and therefore more Ca²⁺ released during the next contraction. Thus the force of contraction is increased, too. Since most of the Ca²⁺ came from the SR, naturally the SR pump must be the major mechanism for clearing Ca²⁺ from the cytosol.

VI. MITOCHONDRIA

- A. The mitochondria are much more abundant in heart muscle than in fast-twitch skeletal muscle. This is consistent with the marked dependence of the heart on aerobic metabolism. Although mitochondria possess both Ca influx and efflux mechanisms, these Ca transport pathways are relatively slow compared to those present in the sarcolemma and the SR. Thus, under normal conditions, the mitochondria have little role in fast calcium regulation, so long as they are able to supply adequate energy. In certain pathological situations (e.g., during reperfusion after an ischemic period), the mitochondria do take up large amounts of Ca.
- B. Coordination of Ca²⁺ regulatory pathways during onset of cardiac contraction.
- C. Source of coupling Ca²⁺ during excitation:
 1. The response of myocardial muscle to changes extracellular Ca is shown in the Figure below.

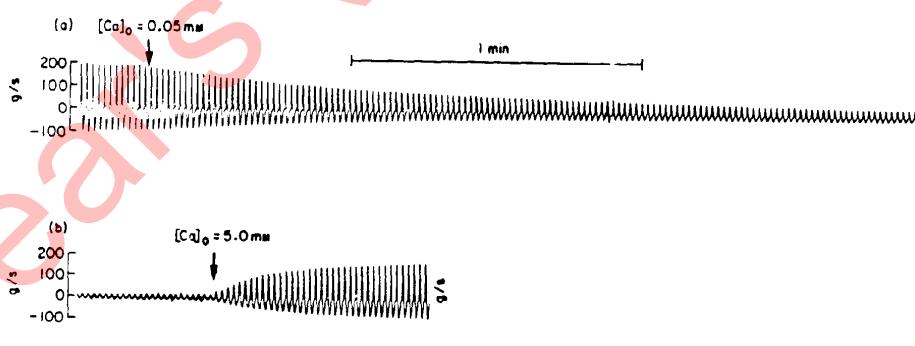


Fig. 7. This data (above) shows the prompt response of myocardium to withdrawal and addition of Ca⁺⁺ in the perfusate.

- 2. Removal of external Ca²⁺ is associated with a progressive drop in the force of contraction, spread out over tens of beats; restoration of external Ca²⁺ evokes a gradual recovery. This is in sharp contrast to skeletal muscle, where complete removal of extracellular Ca²⁺ leaves contraction undiminished over hours. Thus, the Ca²⁺ influx carried by



Ca₂₊ channels undoubtedly contributes to mechanical activation. However, as will be discussed below, the magnitude of the Ca influx is probably not sufficient to account for the force which the ventricular muscle develops. That is, more Ca₂₊ must be coming from another source during systole. This source is, of course, the SR. Understanding the difference between the activation of skeletal muscle and cardiac muscle has been accomplished only in this decade with the cloning and elucidation of the channels involved.

- a. Though the figure above illustrates the importance of extracellular Ca₂₊, it is important to realize that intracellular sources are also crucial. In skeletal muscle, intracellular sources are the only sources of consequence. In the heart, too, it is the SR and not the extracellular Ca₂₊ that is the major source of Ca₂₊ for triggering contractions.
3. For both heart and skeletal muscle, we can now rephrase the key question of EC coupling to be: How does an action potential in the cell surface and T-tubules trigger the release of Ca₂₊ from the major storage site, the sarcoplasmic reticulum (SR). The answer to this question will be quite different for skeletal muscle vs. cardiac muscle and it has only been understood in the past 10 or so years. The crucial difference is this: in skeletal muscle, extracellular Ca₂₊ is not needed at all to trigger this release from the SR. Unlike the behavior described above, skeletal muscle, when stimulated, will continue to twitch normally in the absence of extracellular Ca₂₊. In contrast, as stated above, the heart depends on the influx of extracellular Ca₂₊ to trigger the release from the SR.

VII. INITIATION OF CONTRACTION IN THE HEART

- A. In the heart cell, the following sequence of steps couples the opening of Ca₂₊ channels in the surface of the cell during the action potential plateau to the opening of Ca₂₊ channels in the SR.
 1. Cardiac action potential propagates over surface membrane and down T-tubule.
 2. Depolarization opens voltage dependent Ca₂₊ channels (cardiac L-type) that reside in T-tubule.
 3. A modest amount of Ca₂₊ enters the cell through these L-type Ca₂₊ channels.
 4. This Ca₂₊ reaches nearby portions of the SR membrane where it binds to a large, trans-membrane protein called the ryanodine receptor (RyR2).



5. The ryanodine receptor is the Ca^{2+} release channel of the SR membrane and is triggered to open by the binding of Ca^{2+} ions by its cytosolic domain.
6. Once open, the ryanodine receptor allows massive amounts of Ca^{2+} to flood out of the SR.
7. Ca^{2+} ions bind to troponin-C and trigger contraction.

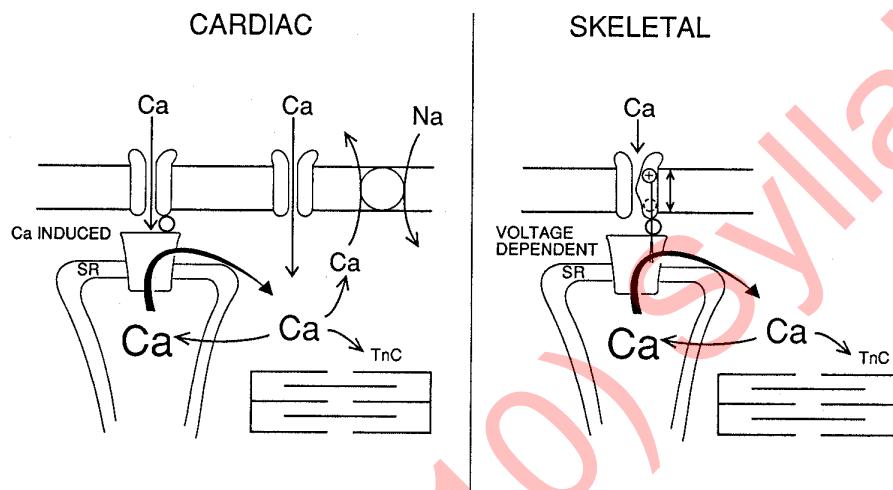


Figure 71. Mechanisms of E-C coupling in cardiac and skeletal muscle for which evidence is strongest. In cardiac muscle Ca entry via I_{Ca} can activate contraction both directly and also by inducing Ca release from the SR. The existence and importance of a physical link between the sarcolemmal and SR Ca channels in cardiac muscle is unclear. In the steady state the amount of Ca which enters the cell via I_{Ca} is probably extruded via Na/Ca exchange. In skeletal muscle the physical link between the sarcolemmal Ca channel (or dihydropyridine receptor) appears to be critical in electromechanical coupling (where sarcolemmal depolarization induces opening of the SR Ca release channel). Transsarcolemmal Ca fluxes do not appear to be important in skeletal muscle E-C coupling and Ca cycles mainly between the SR and the cytoplasm.

VIII. INITIATION OF CONTRACTION IN SKELETAL MUSCLE

- A. In skeletal muscle, the names of the players are very similar but because the two tissues express slightly different isoforms of the channels, the mechanism is significantly different.
 1. Skeletal muscle action potential propagates down T-tubule.
 2. Depolarization opens voltage dependent Ca^{2+} channels (skeletal L-type) that reside in T-tubules. The amount of Ca^{2+} that enters through these channels appears to be of no immediate significance to triggering contraction.
 3. The L-type channels, however, are in direct biochemical contact with ryanodine receptors (RyR1) in the SR membrane. To accomplish this close contact, the SR membranes and t-tubule membranes line up opposite one another in very close contact at specialized junctions called "triads". At the triad, the conformational change in the L-type Ca^{2+} channel that is produced by the voltage change is



somewhat transmitted to the ryanodine receptor via their direct contact.

4. This conformational change induces the ryanodine receptor to open.
 5. Once open, the ryanodine receptor allows massive amounts of Ca^{2+} to flood out of the SR.
 6. High cytosolic levels of Ca^{2+} bind to troponin-C and trigger contraction.
- B. To summarize: in the heart, the entry of 'seed' Ca^{2+} ions from outside is the critical signal to open the Ca-release channel in the SR; in skeletal muscle, it is the direct contact of the T-tubule channels with the SR channels that triggers the release. Surprisingly, then, the skeletal Ca^{2+} channel is essential for contraction, but because it serves as a voltage sensor, not because it is letting Ca^{2+} to flow into the cell. It turns out that these major differences in physiology were due to small differences in the isoforms of the proteins expressed. In the present case, small differences in the isoforms of L-type Ca^{2+} channels and ryanodine receptor engender very different modes of controlling Ca^{2+} release from the SR.

IX. SUMMARY OF SEQUENCE OF ACTIVATION AND RELAXATION IN HEART MUSCLE

- A. When the membrane is depolarized by the action potential, the Ca channel is activated and Ca flows into the cell. This source of Ca is essential for the activation of contraction in the heart. This Ca will "trigger" release of more Ca from the SR and, as we have stressed before, this is the largest source of Ca^{2+} . In addition, depolarization will cause Ca influx through Na-Ca exchange, but the magnitude of this Ca influx is probably small (at least under normal physiological conditions). As Ca is bound to troponin C (TNC), inhibition of actin-myosin crossbridge interaction is reduced and the force-generating bridges are formed.



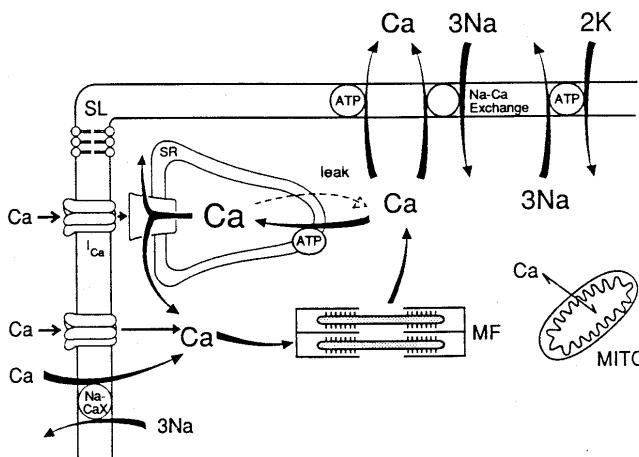


Figure 21. General scheme of Ca cycle in a cardiac myocyte. Ca can enter via I_{Ca} channels and Na/Ca exchange. Ca current may also control the SR Ca release by the SR Ca release channel/ ryanodine receptor/ foot protein. Ca is removed from the myofilaments (MF) and cytoplasm by the SR Ca-ATPase pump and the sarcolemmal Ca-ATPase pump and Na/Ca exchange.

- B. Active force development will persist until Ca concentration falls and Ca is removed from TNC. This removal occurs as membrane repolarization cuts off Ca entry to the cell and as Ca is pumped into the SR surrounding the sarcomeres. In addition, Ca may be extruded from the cell by the sarcolemmal ATP-dependent Ca pump and Na-Ca exchange. Both the sarcolemmal and sarcoplasmic reticular Ca pumping systems contribute to bring about cardiac muscle relaxation: in a steady state situation, all the Ca^{2+} that came out of the SR must go back in through the SR pump, while all that flowed in through the sarcolemma Ca^{2+} channels or Na-Ca exchange must get pumped back out by the surface pump or Na-Ca exchange. In the presence of adequate amounts of ATP, the fall in cytosolic Ca^{2+} allows crossbridges to detach and relaxation to progress. The exchanger is an important pathway for getting the Ca^{2+} back out across the membrane during diastole. During systole, the exchanger operates in the reverse direction (because it is electrogenic) and cause a small amount of additional Ca^{2+} to flow into the cell as some Na^{2+} is extruded. This dual function is schematized in the Figure.



X. SOME WAYS THAT EXCITATION-CONTRACTION (E-C) COUPLING CAN BE MODULATED

- A. Interventions which alter contractile state are those which induce changes in the rate of force development in the absence of a change in end-diastolic fiber length. They produce their effects through the EC coupling system and the Ca²⁺ ion. There are several ways in which the delivery (or removal) of Ca²⁺ to the myofibrils can be varied. Here we focus on effects secondary to changes in sodium concentration. In a later lecture, we will discuss adrenergic regulation.
1. Change of external Na or Ca. These are, of course, not normal physiological occurrences but are useful experimentally. Increased Ca outside increases contractility since more Ca will move into the cell through the Ca channel and Na-Ca exchange. Change of external Na affects Na-Ca exchange according to the equation:

$$\begin{aligned} C_{ai} &= (N_{ai})^3 e^{-EmF/RT} \\ C_{ao} &= (N_{ao})^3 \end{aligned}$$

where the subscripts i and o refer to internal and outside ion concentrations, Em is membrane potential, and F, R and T have their usual meanings (see Dan Madison's lecture on Nernst Potential). Because of the third power dependence on Na⁺ (recall that three Na⁺ move for each Ca²⁺), the ratio of internal and external Ca²⁺ concentrations will change drastically with Na⁺ concentration. For example, increases or decreases in external Na will cause decreases or increases in contractility, respectively.

2. Change in internal Na during changes in heart rate. Contractility is very sensitive to internal Na⁺. This is again due to the sensitivity of the Na-Ca exchange system to Na⁺, and indirect effects on cytosolic Ca²⁺. For example, increasing heart rate causes a small rise in intracellular Na⁺ (due to the increased frequency of opening of Na⁺ channels). This in turn contributes to increased contractility, a phenomenon long known as the "staircase effect" because the twitch amplitude undergoes dramatic changes as the frequency is stepped.
3. Change in internal Na during digitalis inotropy.

A leading example of an inotropic agent is digitalis, used for medicinal purposes for at least 200 years in the Western world and a lot longer in Asia. Digitalis is the generic name for compounds called cardiotonic steroids (for example, cardiac glycosides such as ouabain). These are administered to augment force development in the failing heart. The digitalis glycosides are capable of



increasing force development by 50-60% and can completely reestablish cardiac compensation in many instances.

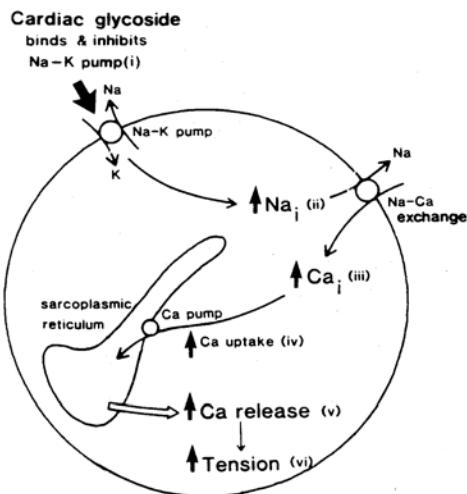


FIG. 8. Diagram of a cardiac muscle cell showing the conventional view of the mechanisms underlying the positive inotropic actions of cardiotonic steroids (the hypothesis of Na⁺-K⁺-pump inhibition and Na⁺/Ca²⁺ exchange). These drugs bind to and inhibit the Na⁺-K⁺ pump (i), thereby elevating the intracellular Na⁺ concentration (ii); this increases the cytosolic free Ca²⁺ concentration, Ca_i (iii). In turn, this leads to an increase in the Ca²⁺ content of the SR (iv), so that Ca²⁺ release from the SR (v) and tension (vi) are increased when the muscle is subsequently activated. (From ref. 3, with permission.)

NOTE: DIAGRAM FOCUSES ON INCREMENTAL EFFECT OF RAISING Nai.

- B. Though some details remain to be decided, the mechanism of action of digitalis is now generally agreed upon. Digitalis is a specific inhibitor of the Na-K pump in the sarcolemmal membrane. Such inhibition produces a small net increase in Na at the intracellular side of the membrane. This increase has the net effect of increasing cytosolic Ca²⁺ through the operation of the Na-Ca exchange system (see above). During systole, when the exchanger moves Na⁺ ions out of the cell in exchange for inward Ca²⁺ movement, the increased intracellular Na⁺ will favor greater Ca²⁺ influx. During diastole, when the exchanger helps move Ca²⁺ out of the cell, the elevated intracellular Na⁺ will hamper the Ca²⁺ efflux and allow more Ca²⁺ to be sequestered in the SR, for later release. Together, these changes in Ca²⁺ movements explain the positive inotropic action of the drug and give further support to the idea that the Na-Ca exchange system is of fundamental importance in control of ionic movements and force development of the heart.



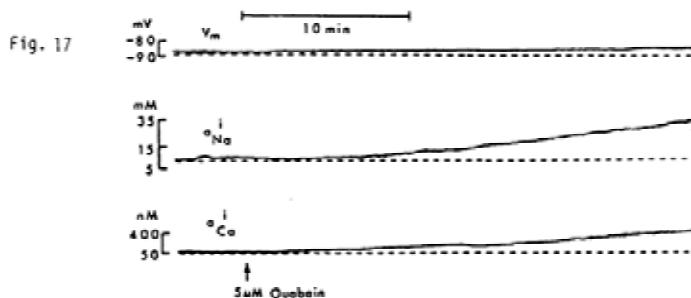
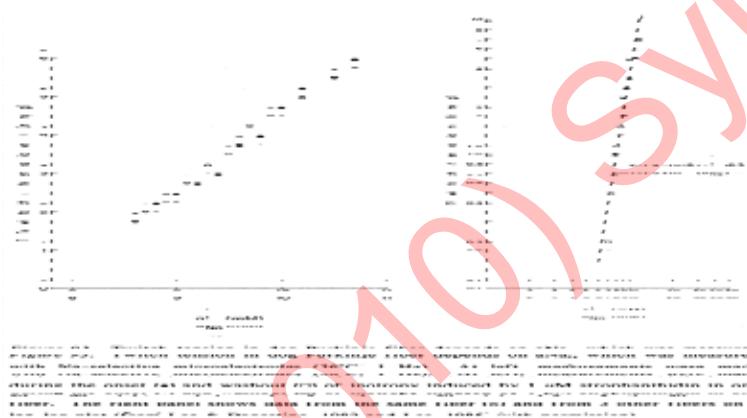


Figure. Direct measurements of intracellular Na^+ and intracellular Ca^{2+} and effect of ouabain block of the sodium pump.



This figure shows the astoundingly steep dependence of contractile force on intracellular Na^+ .

- C. Since the glycosides' effect is to inhibit the sarcolemmal Na-K pump they also induce a cellular K⁺ loss. This loss amounts to only a few millimoles at the time the peak therapeutic inotropism is attained and has nothing to do with the desired inotropic effect of the drug. If excessive glycoside is administered however, K⁺ loss increases and this loss is responsible for the appearance of toxic electrophysiological effects of the digitalis compounds.
- D. When cells exposed to digitalis progress to the toxic state, they lose substantial intracellular K⁺, which tends to accumulate in narrow extracellular spaces outside cells. This increases the $[K]_o/[K]_i$ ratio (bringing it closer to unity), and, as described by the Nernst equation, makes the resting membrane potential less negative. The maximum diastolic potential of automatic Purkinje cells is thus brought closer to threshold. In addition the pacemaker depolarization rate (phase 4) increases. Both of these increase the spontaneous firing rate of these cells. The diminished negativity of the resting membrane reduces the rate of opening of the fast Na channels so that the rate of rise of the action potential spike is decreased. Still another toxic effect is a shortening of the action potential plateau.



- E. In summary, the digitalis glycosides produce their desired inotropic effect through their ability to inhibit the cellular Na-K pump and thereby induce an increase in $[Na]_i$ that in turn, leads to stimulation of Ca^{2+} influx through a transsarcolemmal Na-Ca exchange system. The toxic effects of the drug also relate to the Na-K pump inhibition but are attributable, at least in part, to the losses of K^+ induced by the inhibition.

Last Year's (2010) Syllabus



Last Year's (2010) Syllabus

NERNST/EQUILIBRIUM POTENTIALS AND RESTING MEMBRANE POTENTIAL

REQUIRED READING: B & L, pp. 9-12:
Ionic Basis of the Resting Potential.

AT THE END OF THIS LECTURE, THE STUDENT SHOULD UNDERSTAND:

- A. When and why an ion will be in equilibrium across a cell's membrane
- B. The concept of an equilibrium potential, and how it is important for determining ion fluxes across cell membranes
- C. The basis of a cell's resting potential
- D. The relationship between an ion's equilibrium potential and conductance in determining the cell's membrane potential at any instant in time.

I. ION EQUILIBRIUM

- A. First, the messy math. It is actually not all that messy and provides a good basis for understanding ion fluxes across membranes. If you understand the following three equations, you will have a pretty good understanding of the bases for these fluxes.
 1. The Nernst equation: tells you the membrane potential at which a particular ion will be in equilibrium

$$E_{ion} = \frac{RT}{F} \ln \frac{[ion]_o}{[ion]_i}$$

E_{ion} = the equilibrium potential for an ion

R = the noble gas constant

T = the temperature in kelvin

F = Faraday's constant

$[ion]_i$ = the concentration of that ion inside the cell

$[ion]_o$ = the concentration of that ion outside the cell

2. Goldman-Hodgkin-Katz equation: Similar to the Nernst equation, tells you where the membrane potential will rest when more than one ion is involved.

$$E_m = \frac{RT}{F} \ln \left(\frac{(P_{Na^+}[Na^+]_{out}) + (P_{K^+}[K^+]_{out}) - (P_{Cl^-}[Cl^-]_{in})}{(P_{Na^+}[Na^+]_{in}) + (P_{K^+}[K^+]_{in}) + (P_{Cl^-}[Cl^-]_{out})} \right)$$

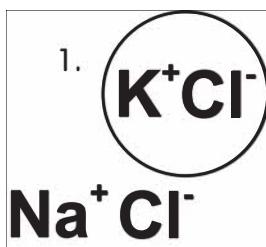
P_{ion} = the permeability of the membrane for an ion



Em=membrane potential

- B. Keep these equations in mind while considering this more intuitive approach. Consider the following artificial situations:

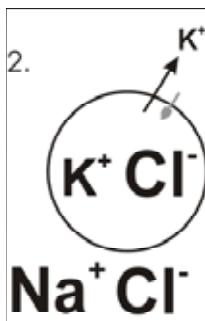
1. A round cell has equal concentrations K⁺ and Cl⁻ inside, equal concentrations of Na⁺ and Cl⁻ outside. As a starting condition, no ions are allowed to cross the cell membrane. Consider also that you are recording the electrical potential difference (voltage) between the inside and outside of the cell. In this condition, the voltage across the membrane will be zero, because all charges in this system are fully compensated (i.e. each positive charge has a partnered negative charge on the same side of the membrane) (Figure 1)



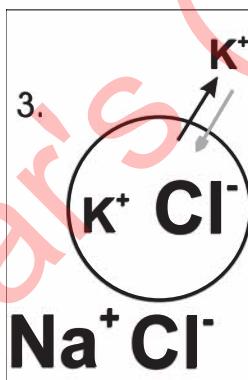
2. Now, make the membrane permeable to only K⁺ ions, but not Na⁺ or Cl⁻. What happens? When given the opportunity, K⁺ will flow down its concentration gradient from the inside to the outside of the cell. For an uncharged species, this flow would continue until the concentration gradient is fully dissipated. However, since K⁺ is charged, its movement will result in the separation of + and – charges across the membrane, since the Cl⁻ ions are not free to follow K⁺ out of the cell. This will produce a voltage across the cell membrane. As more K⁺ flows out, this voltage will grow larger. This voltage, also known as the membrane potential, will resist the further net flow of K⁺ out of the cell (the uncompensated negative charges will slow the efflux of K⁺ charges out of the cell). Thus, there are now two forces acting on the K⁺ ion; a) the concentration gradient pulling K out, and b) the membrane potential resisting its outward flow. This will slow the net flow of K⁺ out of the cell. (Figure 2)



Black arrow = concentration force; Gray= voltage force



3. Eventually, as K⁺ flows out, the inward force of this voltage will grow to exactly compensate the outward concentration force. At this point, the system will be in equilibrium, with outward and inward rates of K⁺ flow being equal.(Figure 3) The value of the membrane potential where this equilibrium for potassium ions is reached is called "The Equilibrium Potential for potassium" or E_K. The value of the equilibrium potential depends on the size of the concentration gradient. If you increase KCl concentration inside the cell, you increase force-pushing K⁺ out of the cell, and thus, also the size of the voltage needed to make the net flow stop. What the NERNST EQUATION does is to allow you to calculate the value of the equilibrium potential for an ion, if you know the concentrations of the ion inside and outside the cell. In a heart cell, E_K is equal to about -90 mV.



II. EQUILIBRIUM POTENTIAL, NERNST POTENTIAL AND REVERSAL POTENTIAL

- A. What is the difference between these three terms? Well....they are spelled differently. Seriously, they are all names for the same thing – the value of the membrane potential where an ion is in equilibrium. Equilibrium potential, because its value tells you where the ion is in equilibrium. Nernst potential, because you can calculate it with the Nernst equation. Reversal potential, because knowing this value lets you predict which direction ions will flow across the membrane.



B. Understanding reversal potential:

1. The concept of a reversal potential is one of the most important parts of understanding the electrical behavior of cells such as heart cells. Consider again, our round cell in equilibrium (Fig 3). In equilibrium there is no net K⁺ current across the cell membrane. But if you perturb that equilibrium by injecting charges into the cell (never mind how, for now), you will change the voltage across the membrane. Injection of positive charges will dissipate the membrane potential (or depolarize it). This will decrease the inward voltage force, putting it at a disadvantage relative to the outward concentration force, and the net flow of K will be out of the cell. On the other hand, if you instead inject negative charges, this will increase the membrane voltage (hyperpolarize), and put the voltage at the advantage, driving K⁺ into the cell. Thus, depending on which way you perturb the membrane potential from its equilibrium value, K ions will flow in the opposite direction across the membrane. Hence the term “reversal potential”.

III. HOW FAST WILL K⁺ FLOW ACROSS THE MEMBRANE?

A. In other words, how large is the potassium current?

The net size of an ion current is determined by two factors: 1) The conductance of the membrane for that ion, and 2) The driving force for that ion. Conductance is the reciprocal of resistance. When a cell is at the reversal potential, there will be no net flux of that ion. If the membrane potential of the cell is moved away from the reversal potential, then there will be an unbalanced force driving ions across the membrane. The net size of that force will be determined by how far from the reversal potential the membrane potential is moved. In other words, the difference between the membrane potential and the reversal potential will be the *driving force* on that ion ($E_m - E_{ion}$). But even a large driving force won't push ions across a membrane if the membrane is impermeable to that ion. Thus, the amount of current that flow across the membrane is given by:

$$I_{\text{ion}} = g_{\text{ion}}(E_m - E_{\text{ion}}) \quad (\text{the current equals the conductance times the driving force}).$$

Where:

I_{ion} = the current carried by an ion across the membrane

g_{ion} = the membrane conductance for that ion (proportional to the number of ion channels for that ion that are open)

E_m = the membrane potential

E_{ion} = the reversal potential for that ion

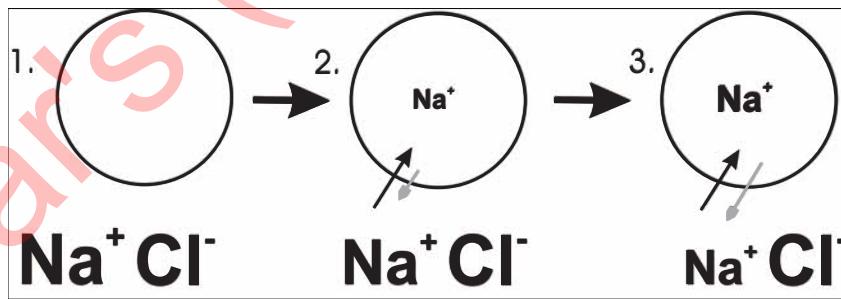


$(E_m - E_{ion})$ = the driving force for that ion

IV. WHAT ABOUT CASES WHERE MORE THAN ONE ION CAN FLOW ACROSS THE MEMBRANE?

A. The basis for understanding a cell's membrane potential at any instant in time, including at rest.

1. In our original example, even though there was a large concentration gradient for sodium ions, we set the conditions such that the membrane was impermeant to sodium. An important point to understand is that regardless of any concentration gradient, if there is no permeability for an ion, that ion will not contribute to the cell's membrane potential. Think of it this way: Even though there is sodium outside but not inside the cell (in our artificial example), all the charges on that sodium are compensated by the paired chloride ions, so no voltage is generated by sodium, let alone a cross membrane voltage. But what if sodium were permeant?
2. Consider the reverse of our earlier artificial example: a cell that is impermeable to potassium but permeable to sodium. For sodium ions, the concentration gradient is directed toward the inside of the cell, so as sodium flows down its concentration gradient, the opposing voltage that develops will be in the opposite direction as it was for potassium (i.e. this voltage will be slowing inward Na^+ current). Thus, the equilibrium potential for sodium (E_{Na}) will have a positive value. In heart cells, the value of E_{Na} is about +70 mV.



- B. If a cell is permeable to only one ion, then its membrane potential will be equal to the equilibrium potential for that ion.

1. But what about a case where a cell is permeable to both K^+ and Na^+ ? If both ions are permeant, then both will make a contribution to the membrane potential of the cell. How much of a contribution each makes, depends on the equilibrium potential for each ion, on the membrane conductance for each ion, and on the driving force exerted on each ion. Consider a case where we set the conductance for K^+ and Na^+ at equal non-zero values. If g_{Na^+} and g_{K^+} are equal, then the membrane potential will



- rest half way between EK and ENa; each will make an equal contribution to the membrane potential. If EK > ENa then the membrane potential will rest closer to EK than ENa.
2. Conversely, if EK < ENa then the membrane potential will be found closer to ENa.
 3. Most cells rest at a potential slightly positive of EK. This is because a cells resting permeability to potassium is much higher than its permeability to sodium. However, during the early phase of a cardiac cell's action potential, the sodium permeability of the cell's membrane is higher than its K permeability. This is why the peak of the cardiac action potential is positive, because the cell is tending toward ENa.
 4. Of course, real cells have membrane conductance to several ions, not just K⁺ and Na⁺. Every ion that is permeant will contribute something to the resting potential, in proportion to its equilibrium potential and membrane permeance. The Goldman-Hodgkin-Katz (GHK) equation contains terms for each permeant ion's concentration gradient and permeability, and lets you calculate the membrane potential in a multi ion system. The GHK equation can be used to calculate a cell's resting potential, the location of the peak of the action potential, or the membrane potential at any instance in time, as long as the values for concentration gradient and membrane permeance for each ion are known.
 5. One common misconception is that the concentration gradient and the membrane voltage will depend on each other in a circular fashion. For example, that the initial movement of K⁺ out of the cell will dissipate the concentration gradient, which will in turn, change the equilibrium potential. Except in a few special cases, this does not generally happen. Because the charges are separated across only the very small thickness of the membrane, only a few thousand charges need move before the system reaches equilibrium. Because a cell has trillions of K⁺ ions inside, the concentration changes negligibly. However, if a cell is held in a non-equilibrium condition for a long period of time, the concentration gradients can eventually be dissipated. An important point, particularly with regard to resting membrane potentials in a multi-ion system, is that the resting potential, while stable, does not represent a true equilibrium condition. Consider a two -ion system, K⁺ and Na⁺, where EK = 10(ENa). In this case, a cell would rest ~ 1/10 of the distance from EK to ENa. But in this case, the cell is at the equilibrium potential for neither ion, so neither ion is in equilibrium. In other words, at rest, there will be a steady flow of K out of the cell and a steady



flow of Na into the cell. Thus, in order to maintain their ion concentration gradients over the long term, cells must employ active transport to move ions back into or out of the cell against their concentration gradients.

- C. Here are some real concentration numbers for a cell (in mM):

Inside	Outside
An- 131.5	An- 0
Na+ 9.0	Na+ 141
K+ 136	K+ 4.0
Ca++ 0.0001	Ca++ 2
Cl- 3.5	Cl- 119.0
HCO ₃ - 10.0	HCO ₃ - 26.0

(An- = large impermeant anions, usually those charges contributed by proteins in the cell)

V. QUESTIONS:

1. Based on these numbers, what are the equilibrium potentials for Na, K and Ca? For purposes of this calculation, you can use the simplified version of the Nernst equation:

$$E_{ion} = -61.5 \log \frac{[ion]_i}{[ion]_o}$$

2. Assuming a cell with permeabilities for Na of 2, K of 20 (assume all other ions to be impermeant), and the concentrations listed above, where what would the resting potential of this cell be?



Last Year's (2010) Syllabus

EXCITABILITY AND CONDUCTION IN THE HEART

OBJECTIVES:

- A. Understand the structural basis of intercellular communication in heart
- B. Clarify the functional implications of current flow from one heart cell to the next
- C. Become acquainted with the normal pathway for impulse spread through the heart

Cardiac action potentials serve many purposes. They form the cellular basis for pacemaker activity, impulse spread and control of cardiac contraction. Despite this variety of functions, there are ample reasons for believing that impulses in cardiac cells follow the same principles as in other excitable tissues. Thus, your knowledge of neuronal excitability from the Neurobiology Course will provide a useful foundation for understanding action potentials in heart. We shall draw upon such similarities while focusing on unique aspects of cardiac activity.

One characteristic of nerves is that a single axon in a whole nerve may be stimulated intracellularly and there will be no excitation in any of the other nerve fibers. An impulse in one cell does not generally spread to another cell. The same is true of skeletal muscle. The muscle fibers are not electrically coupled, and this arrangement permits considerable flexibility in allowing the central nervous system to specify the strength or temporal pattern of the whole muscle action.

In heart or smooth muscle the situation is quite different. If a strip of quiescent heart muscle is dissected and stimulated locally, the entire piece of tissue will actively contract. The all-or-nothing law applies in that there is either a full contraction or none at all. This behavior once led to the notion that heart muscle was syncytial, i.e., that the cytoplasm was continuous throughout the tissue. But in the early 50's electron microscope studies showed that heart cells are distinct; that each cell is completely bounded by plasma membrane. Despite its multi-cellular structure, we still speak of heart muscle as a functional syncytium since an action potential spreads electrically to all of the individual cells in the tissue.



I. STRUCTURAL BASIS OF CURRENT FLOW BETWEEN HEART CELLS

- A. Electron-microscope studies have provided a likely candidate for the low resistance pathway between cardiac cells: a region where the membranes of two adjacent cells are in very close opposition (see figure). This morphological specialization has the appearance of a spot weld, and has been termed the gap junction. (Terms such as nexus, and close junction have also been used.)

The gap junction usually occurs near, but is distinct from, mechanical connections between adjacent cells: the fasciae adherentes and the macula adherentes (desmosomes). The actin (thin) filaments insert into the fasciae adherentes at the end of the cell.

There is good circumstantial evidence that the gap junction is the pathway for intercellular current flow. Thus, conduction may be reversibly blocked by increasing the tonicity of the external solution, and this effect occurs in parallel with a separation of the cells at the gap junction.

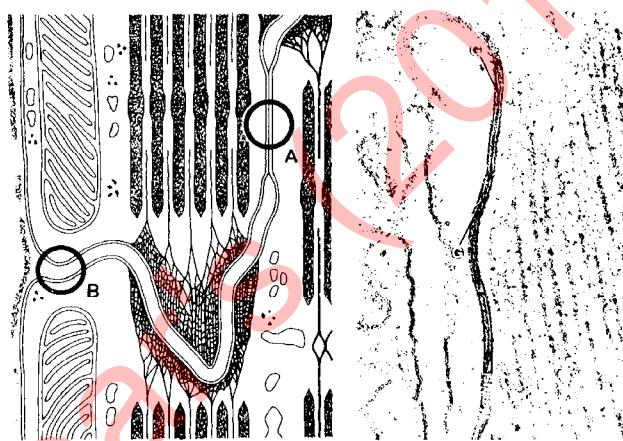
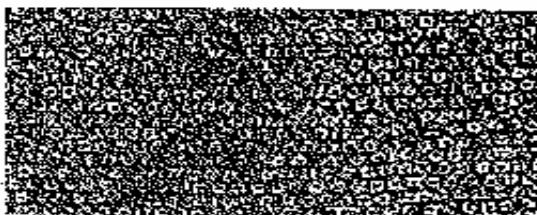


Fig. 1. Left, a region of close contact between two heart cells, including ordinary extracellular space (B) and a specialized narrowing where membranes appear to fuse, a gap junction (A). Right, an EM of a gap junction (labelled "G").

The ultrastructure of the gap junction has been studied in lanthanum-stained or freeze fracture preparations. These morphological studies have shown that gap junctions are composed of a regular arrangement of subunits.





Electron micrograph of isolated gap junction from rat liver. The preparation has been stained to show the connexons, which are organized in a hexagonal lattice. The densely stained central hole in each connexon has a diameter of about 2 μ m.

When viewed en face the subunits appear to be packed in a hexagonal array with a 9-10 nm center-to-center spacing.

Each subunit has a central zone, probably an aqueous channel, with a diameter on the order of 1-2 nm. The "channel" is believed to provide the pathway for intercellular current flow.

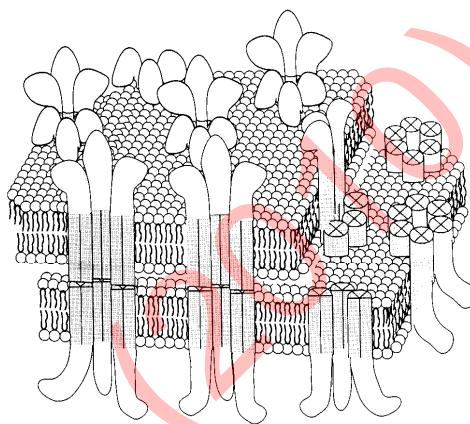


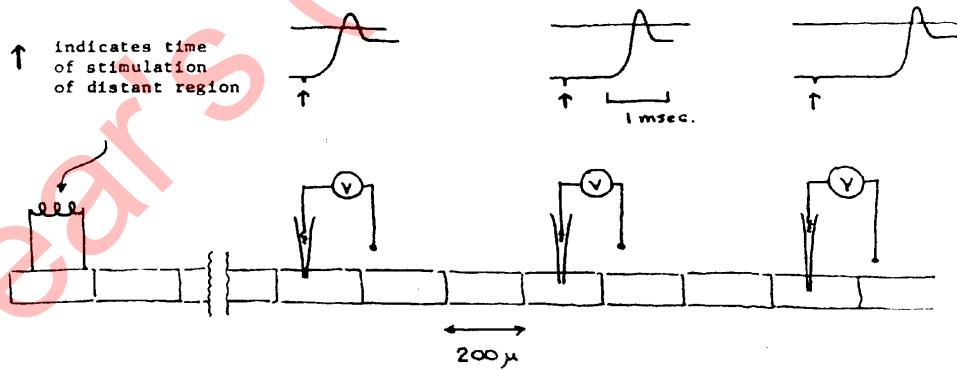
FIGURE 5 Structural model of a gap junction based on electron micrographic and X-ray diffraction studies of isolated liver and heart gap junctions.

The structural evidence is complemented by experiments studying cell-to-cell movements of various tracer substances. These began with measurements of 42K movements within ventricular muscle bundles. Tracer potassium redistributed longitudinally over many cell lengths, with an effective diffusivity that supports the idea that K⁺ ions would be the major carrier of intracellular current. Additional studies have characterized the diffusivity of larger particles, including tetraethylammonium, procion yellow and fluorescein. So far the results show a simple inverse relationship between diffusivity and molecular weight. Procion yellow is the largest molecule studied so far, and has dimensions of 0.5 nm x 1 nm x 2.7 nm. This establishes 1 nm as a plausible lower limit on the diameter of a hypothetical gap junction channel, in fairly good agreement with estimates from structural data.



II. WHAT CONSEQUENCES ARISE FROM GAP JUNCTION COUPLING BETWEEN HEART CELLS?

- A. Action potential propagation in heart relies on the same kind of local circulating current mechanisms that work in axonal conduction.
1. Since an action potential occurs in each cell, it is natural to ask whether excitation spreads electrically, as in nerve. Do electrical currents flow between the distinct cells, and if so, how? If current did flow between adjacent cells, one would expect, on structural grounds alone, that the pattern of current flow in the whole heart would be spatially complex. For now, it will be simpler to consider the spread of excitation in a strictly one-dimensional structure. A number of fiber-like preparations have been used for the study of the spread of excitation in heart: trabeculae from mammalian ventricles or the atrium of the frog, or mammalian Purkinje fibers. The Purkinje fiber is a specialized muscle tissue which mediates the spread of the excitation signal from the A-V node to the working ventricular muscle. (Later we will discuss its role in conduction defects). This is a useful electrophysiological preparation because the cells are quite large and because the contractions are weak enough to allow stable microelectrode recording.
 2. Imagine recording from a Purkinje fiber in which the cells are arranged in a single column:



3. The initial rising phase of the spike resembles an action potential in squid giant axon. The spike appears with increasing delay as the recording microelectrode is moved further from the stimulated region. Estimating the speed of propagation, we find a value of about 3 meters/sec in Purkinje fiber, which is comparable to the conduction velocity in a frog skeletal muscle fiber at room temperature. This is much slower than the speed of conduction in myelinated nerve, but it is more than adequate to provide a near-synchronous excitation of the ventricle.



- B. Extracellular current paths are important for the completion of a local circulating current.
1. Extracellular recording methods are made possible by the fact that current flows in complete loops. Current flowing along the axis of the Purkinje fiber or muscle bundle must return via the extracellular space. The extracellular current flow must cause at least small voltage drops in that space that can be used in clinical recordings.

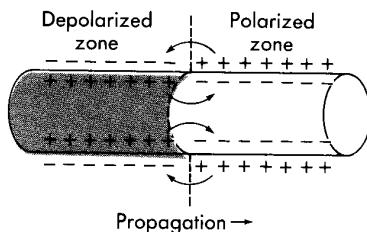
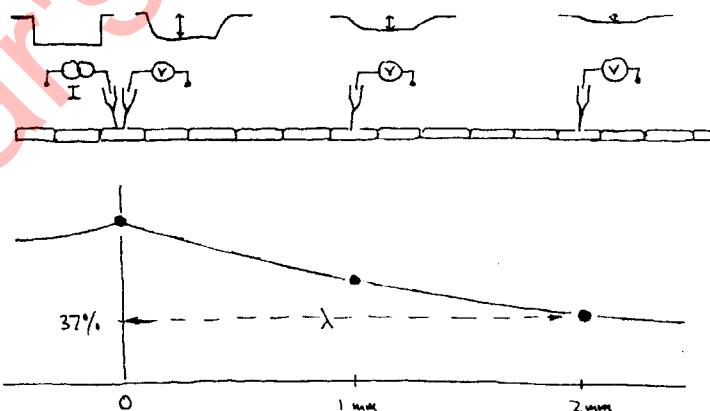


Fig. 2-15 ■ The role of local currents in the propagation of a wave of excitation down a cardiac fiber.

- C. Spread of depolarization can take place even without action potentials since there is no threshold for intercellular communication.
1. To show that current readily flows from cell to cell, we can inject current through one microelectrode and look for a voltage response in another cell nearby. To emphasize that no spikes are necessary, one can even inject hyperpolarizing currents.



2. The voltage deflections (negative in this example) fall off in amplitude only gradually, decrementing to $1/e$ ($=37\%$) of maximum at a point about 2 mm away from the site of current injection -- approximately 10 cell lengths away! Clearly, currents can spread over several cell lengths, even in the absence of spikes. This is an indication of the good job



performance of gap junctions and the intracellular ion carrying species (mainly K⁺). Spread of depolarization without spikes can allow impulses to propagate for considerable distances through regions where the impulse generating mechanism is disabled.

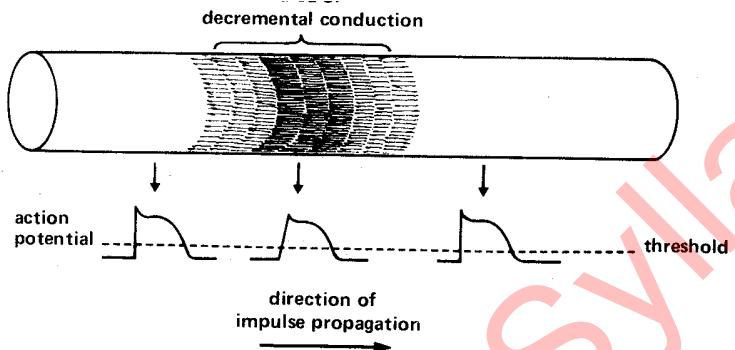


FIG. 21.4. Effects of decremental conduction on the amplitude and rate of rise of the action potential. When an impulse transmitted from left to right in a strand of cardiac muscle (top) encounters a region of decremental conduction (shaded), the action potential (bottom) becomes smaller and more slowly rising. If the impulse is transmitted through the region of decremental conduction into normal tissue (right), a normal action potential is once again generated, although its arrival is delayed.

- D. Transitions in action potential configuration are gradual (e.g. in pacemaker regions).
 - 1. Current flow between adjacent cells tends to counteract the possibility of abrupt disparities in intracellular potential and therefore appreciable asynchrony. It is difficult, then, to speak of a single pacemaker cell; rather, there is an area of tissue with indistinct boundaries which imposes its own electrical timing on surrounding regions. In normal heart, the sinoatrial node is the source of the dominant rhythm.



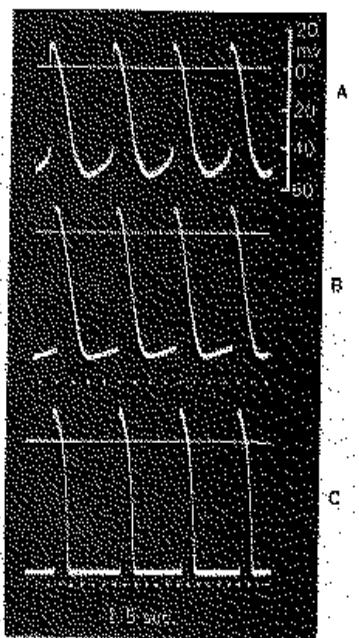


Fig. 4-5. Transmembrane action potentials from various regions of frog heart. A and B, Records from different fibers in sinus venosus. C, Record from atrial muscle fiber. In A note rapid depolarization of membrane during diastole (pacemaker potential), leading to generation of action potential, low "resting" potential, small overshoot, and long duration of action potential, all of which indicate that this fiber is initiating cardiac impulse. Record in B is from reserve pacemaker located elsewhere in sinus venosus. Pacemaker potential here is flatter and onset of action potential abrupt. Such a reserve pacemaker could become active if activity of true pacemaker is suppressed. Record in C, from atrial muscle fiber, shows typical conducted potential. Level of membrane potential in this fiber is considerably higher than that shown in A and B, and during diastole it remains at a constant level. (From Hutter and Trautwein.⁴³)

2. The pacemaker area is, by definition, the first to fire in each heart beat. It is identified by recording a characteristically smooth approach to the action potential upstroke, often called a pacemaker potential. Neighboring cells may also undergo slow pacemaker depolarization, but this is a rapid upstroke, generated by propagation of excitation from the dominant pacemaker region. Under certain conditions (localized suppression of the usual pacemaker by intense vagal activity) such latent pacemakers can assume control. Some types of arrhythmia are thought to spread from ectopic foci (maverick pacemakers) outside the normal sinoatrial area.
- E. Unlike synapses with chemical transmitters, electrical junctions cannot in themselves provide significant time delay in the spread of an impulse.
 1. For some time it was believed that the conduction delay in the A-V node was attributable to the slow action of a chemical transmitter. The correct explanation comes from microelectrode studies which show that the conduction velocity in the A-V node is just exceedingly slow (as low as 0.05 m/sec, 60-fold slower than that of a healthy Purkinje fiber). One undesirable consequence of the sluggish conduction is the poor "margin of safety" of impulse spread through this region. Not surprisingly, A-V block is a commonly occurring conduction defect.



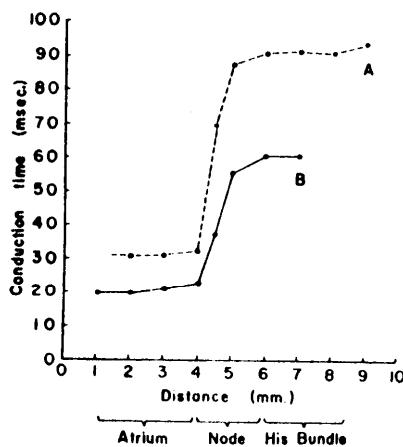
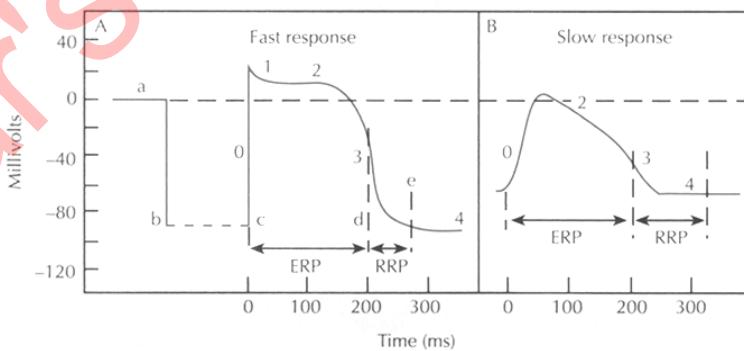


FIG. 5. Graphs of "conduction" time across A-V node from 2 different experiments. Zero time represents time of application of driving stimulus to atrium. Conduction time is employed because velocity requires knowledge of fiber length rather than inter-electrode distance.

- F. The electrical properties of the gap junctions are inherently compatible with either fast or slow conduction.
- As we shall discuss later, the conduction speed depends largely on the size of the inward current and the speed with which the inward current turns on. There are two different kinds of conduction in the heart with different prevalence in different regions. The large fast currents carried by Na^+ support rapid conduction ("fast response"), the smaller, more slowly rising currents through Ca^{2+} channels support slow conduction ("slow response").



- G. Gap junctions can support biochemical communication between cells
- Electrical coupling is the most obvious role of gap junctions in heart, but it may not be the only function. Since gap junction channels are large enough to allow passage of small molecules such as amino acids or nucleotides, it seems reasonable to ask if biochemical communication also takes place. One might imagine, for example, that cell-to-

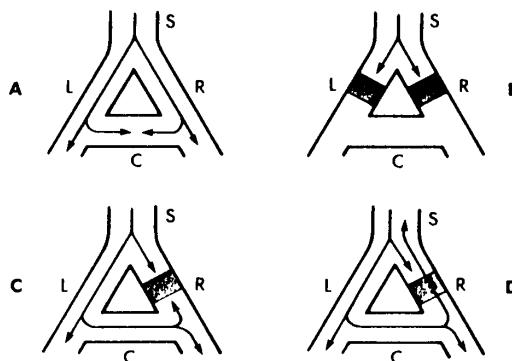


cell movements of ATP or other high energy phosphates might help equalize the metabolic state of cardiac cells. Such "metabolic cooperation" might be particularly important in cases of localized ischemia. There is evidence that cyclic AMP can diffuse from one cell to the next , possibly promoting the even distribution of messages from sympathetic inputs.

III. PATHOPHYSIOLOGICAL CONSEQUENCES OF CURRENT FLOW BETWEEN CELLS

- A. The ease of current flow between cells is detrimental when an area of tissue is injured; however, the permeability of gap junctions is regulated.
 - 1. Damage to a localized region (as in a myocardial infarction) causes electrical spread of depolarization to surrounding areas. Fortunately, heart muscle (unlike skeletal muscle or nerve) can use its ability to regulate gap junctions in order to heal over within a minute or two after injury. Cardiac gap junctions can reversibly decrease their permeability when there are significant and sustained rises in Ca^{2+} or H^+ concentrations or both. These regulatory mechanisms provide the cell with a way of controlling the intercellular communication, and possibly conduction velocity and transfer of second messengers. A rise in intracellular Ca^{2+} can be triggered by cellular injury, a drop in intracellular pH accompanies ischemia. Thus, the damaged or necrotic cells can gallantly uncouple themselves from their healthy neighbors.
- B. Electrical communication in heart muscle can be a two-way street.
 - 1. This is in contrast to certain electrical junctions between nerve cells, where a marked bias is shown in favor of one direction of current flow. Electrical coupling in heart or smooth muscle is even more unlike chemical communication, which is often distinguished experimentally by its completely unidirectional nature. In a chemical synapse, transmitter is released by one cell (pre-synaptic) and acts specifically on another (postsynaptic) cell; the chemical machinery for release or response is usually restricted to only the pre-or postsynaptic cell respectively; thus, transmission must be one-way.
 - 2. The possibility of bi-directional spread of excitation is important clinically, since some types of cardiac arrhythmia are thought to arise from retrograde (wrong-way) conduction.





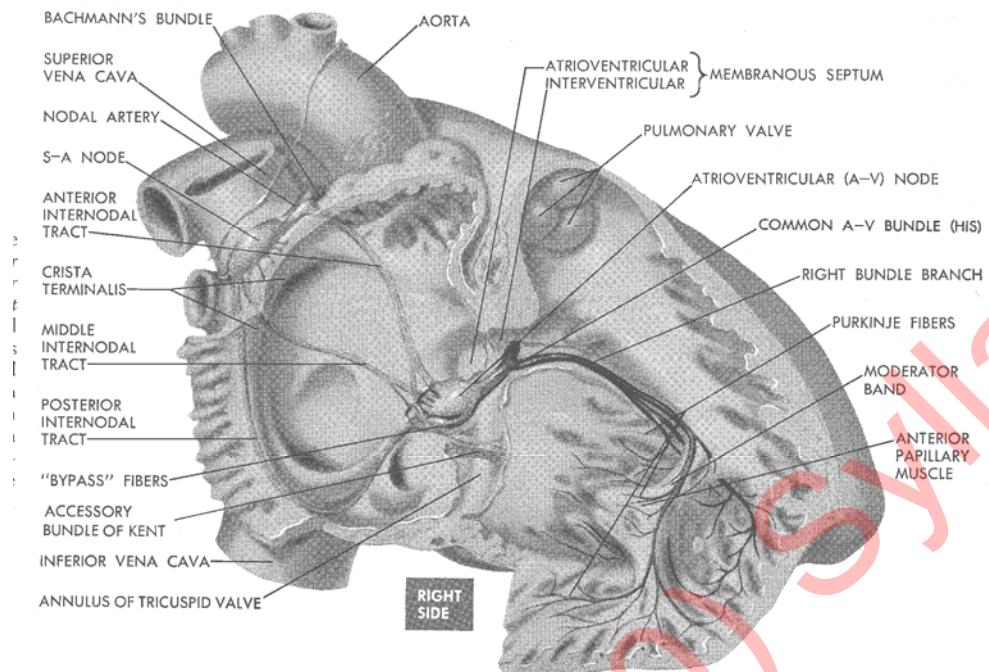
- a. The Figure describes the role of unidirectional block in the phenomenon called reentry. In panel A, an excitation wave traveling down a single bundle of fibers (S) continues down both left (L) and right (R) branches. The depolarization wave enters the connecting branch (C) from both ends and is extinguished when the opposing impulses collide. In panel B, the wave is blocked in both L and R branches. The impulse does not penetrate, but no harm is done. In panel C, bidirectional block exists in branch R. In panel D, unidirectional block exists in branch R. The antegrade (forward heading) impulse is blocked, but the retrograde impulse is conducted through. This could happen if the electrical mass of C was much greater than that of S (easier for log to ignite twig than twig to ignite log). If the retrograde impulse propagates slowly enough, it will arrive after bundle S has recovered its responsiveness. This retrograde impulse "reenters" S and can cause repetitive and possibly arrhythmogenic firing. More about reentry and how it can be pharmacologically ablated in the next lecture.

IV. NORMAL PATTERN OF CARDIAC IMPULSE SPREAD

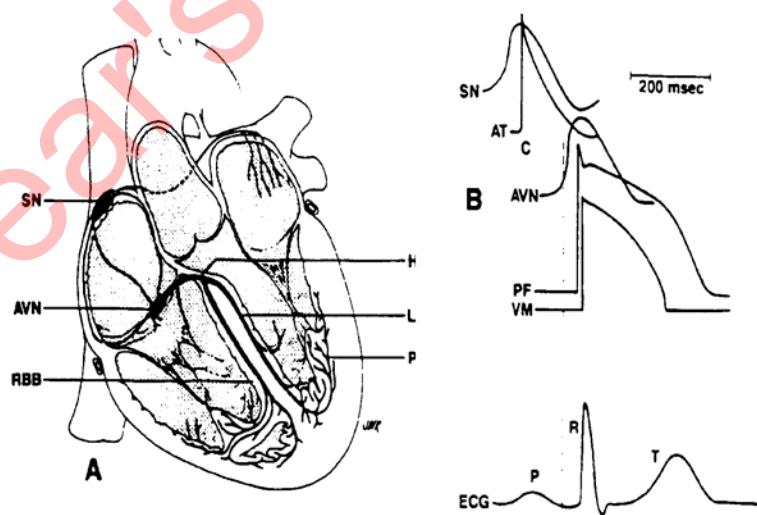
Let us now consider the sequence of events in the spread of excitation in the normal human heart.

- Firing of sinoatrial node (normal pacemaker).
- Conduction of impulse by atrial wall, and more rapid conduction by specialized tracts (anterior, middle, and posterior internodal pathways) conveying excitation to A-V nodes (see figure below).





- C. Common bundle of His carries excitation along septum to:
- D. Right and left bundle branches. There are two branches on the left side (anterior and posterior). The branches are composed of Purkinje tissue with relatively fast conduction velocity (2-4 m/sec.). The branches ramify extensively, and the conducting tissue undergoes a gradual morphological transition into working myocardium. The Purkinje "tree" excites the ventricles more or less.



Last Year's (2010) Syllabus

Circulatory Vessel Histology

Circulatory Vessels

Cardiovascular

- Transport oxygen and other nutrients to tissues
- Carry metabolic waste products away from tissue
- Regulate body temperature
- Transport cells of immune system, hormones, proteins

Lymphatic

- Drain extravascular fluid from tissue
- Return lymph fluid to cardiovascular tissue

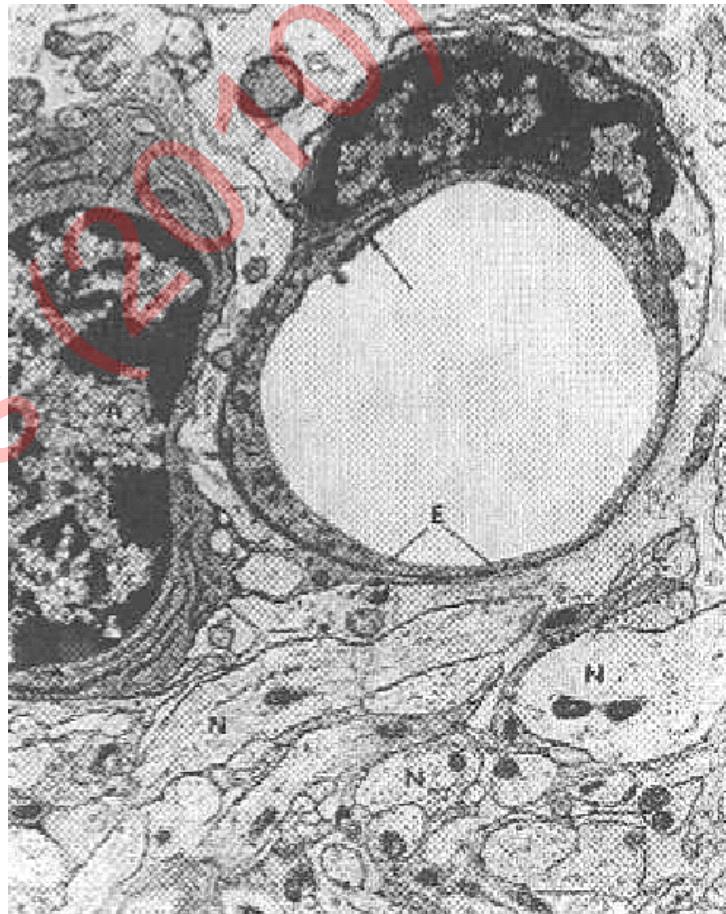
Goals: to identify the vessel types and know their function as it relates to both light and electron microscope structure.

Recommended:

Reading:

- (1) Wheater: chapter 8 or Junueira and Carnerio: chapter 11
- (2) Cross and Mercer: chapter 6, in particular, pgs 148, 150, 152, 154 and 160

Interactive slides on CWP



Vessel Type	Where	Internal Elastic Lamina	Characteristics	Valves	Vasa Vasorum	Function
Elastic Artery >1 cm	Aorta, common carotid, subclavian	Yes	Thick media with both muscle and 50-60 elastic lamella	No	Sometimes	<u>Conduction</u> ; maintain blood pressure under high pumping load
Muscular Artery 2-10 mm	Iliacs, vertebrals, coronaries, cerebral Art.	Yes	Thick media; more muscle than elastic fibers	No	No	Distribution to organs; change vessel diameter with smooth muscle according to sympathetic control
Small Artery Arteriole 10-100 μm	Ubiquitous	Yes, but thin	1-6 muscle layers in media	No	No	Distribution to tissues; control resistance with sm. muscle tone; maintain peripheral blood pressure
Capillary 4-10 μm	Ubiquitous	No	No media or adventitia; occasional pericyte	No	No	Exchange of fluid and gas with tissues
Venules 10-50 μm	Ubiquitous	No	No media or adventitia; pericytes	No	No	Migration site of WBC into tissues via diapedesis; histamine acts here
Medium Veins 1-10 mm	Ubiquitous	No	Thin wall; adventitia more abundant than media	Yes (>2mm)	No	Capacitance - low pressure high volume
Large Veins > 1 cm	Interior vena cava, portal vein	Usually no	Adventitia dominant with longitudinal muscle	Yes	Yes	Transport blood back to heart



GENERAL CHARACTERISTICS

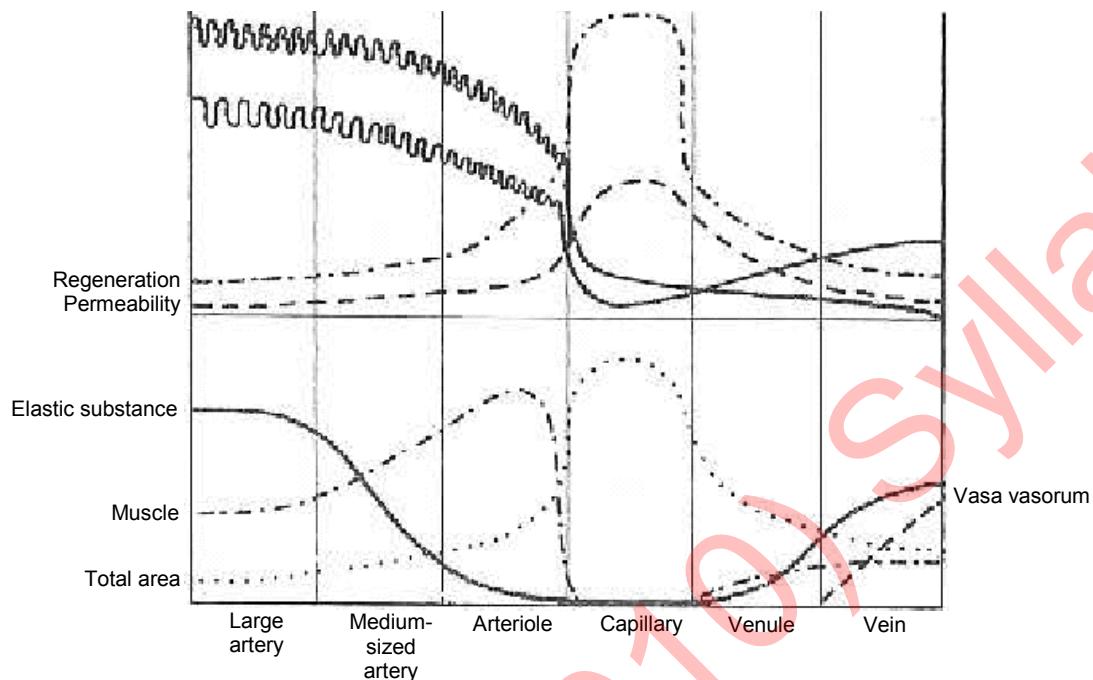
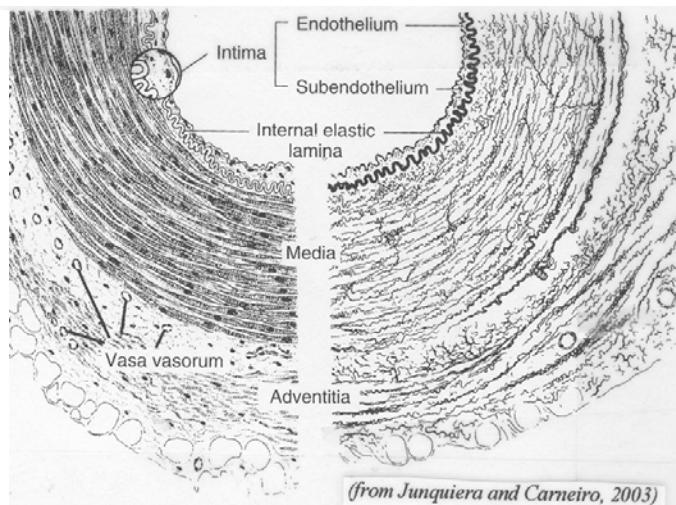


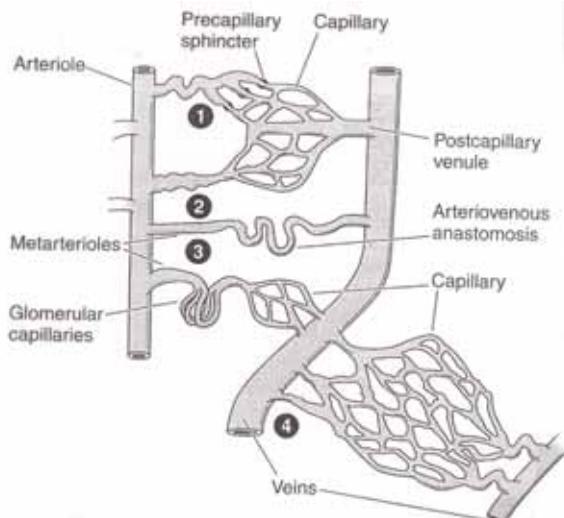
Chart relates the general characteristics of blood circulation (top) and the structure of blood vessels (bottom.) The arterial blood pressure and rapidity of flow decrease and become more constant as distance from the heart increases. This decrease coincides with a reduction in elastic substance and an increase in smooth muscle in the arteries. Regeneration and permeability are highly developed in the capillaries. (from Junquiera and Carneiro, 2003)

BLOOD VESSEL WALL ORGANIZATION

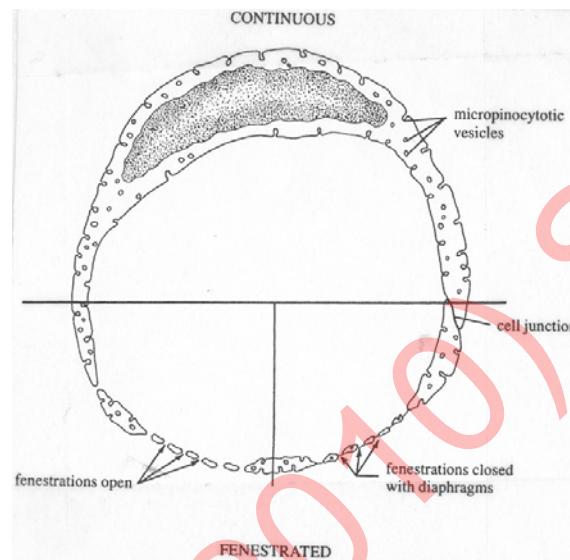
LAYERS:

- Tunica Intima (longitudinal)
 - Endothelium
 - Basal lamina
 - Subendothelial CT
 - Internal elastic lamina (arteries)
- Tunica Media (circular)
 - CT and smooth mm
 - Elastic lamina (in elastic arteries)
- Tunica Adventia (longitudinal)
 - Mainly CT
 - Vasa vasorum
 - Smooth mm (in large veins)





(from Junquiera and Carneiro, 2003)



MICROCIRCULATION

1. Typical sequence of arteriole, capillary, venule, vein
2. Arteriovenous anastomosis
3. Arterial portal system (e.g. kidney)
4. Venous portal system (e.g. liver)

Types of Capillaries

Type	Structure	Permeability
Continuous	endothelium is not interrupted; most common type; tight junctions well-developed	varies from highly impermeable (brain) to increasing permeability with vesicular transport (muscle)
Fenestrated	endothelial cytoplasm interrupted by fenestrae (60-90nm) either covered by a thin diaphragm (endocrine glands) or open (kidney)	varies with the openness of the fenestrations; found in areas where rapid transport between vessel and tissue required
Sinusoids	specialized capillaries with wide lumens and associated macrophages; frequently fenestrated with discontinuous basal lamina (liver)	extensive exchange and monitoring of traffic between vessel lumen and surrounding tissue; exchange can include cells (spleen)



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HEART AND VESSELS – SLIDES

I. HEART

Slide 7 Ventricle (H&E)

Review the characteristics of the myocardium of cardiac muscle that makes up most of the tissue. In particular note branching fibers, central nuclei and intercalated discs.

Find the surface of the section lined by a simple squamous epithelium. This is the endothelial lining of the heart ventricle. This endothelium is continuous with the endothelial lining of the aorta. Connective tissue under the endothelium contains bands of collagen and fibroblasts. The endothelium and underlying connective tissue make up the endocardium.

Between the endocardium and myocardium you will notice groups of Purkinje fibers. These large specialized cardiac muscle cells contain very few myofibrils and function as part of a specialized conduction system that coordinates the contraction of the heart.

The outer covering of the heart, the epicardium is not observable on this slide.

II. ARTERIES

A. Slide 24 Aorta (MAz) (C&M 160 for ultrastructure)

The aorta is a large elastic artery characterized by the presence of 50–60 elastic laminae in its media. Much of the thickness of the wall of this vessel is made up by the media. With high magnification note the relative proportion of blue stained collagen, pink smooth muscle, and unstained elastic tissue. (The blue stained collagen is Type I. Type III is also present but requires special staining). The internal elastic lamina can be seen immediately beneath the endothelium. Most slides show also an adjacent muscular artery.

B. Slide 56 External ear (Elastic stain)

Look in the loose connective tissue near the elastic cartilage in this section and you will see a muscular artery and its companion vein. (Not present in all slides; you may have to share with a neighbor). The internal elastic lamina of this small artery is very prominent because of the elastic fiber stain; in some places the external elastic lamina may be seen. Note the differences in orientation of elastic fibers in intima and media. The intima of the artery is atypically thick. Note too the difference in wall thickness between the artery and vein.



C. Slide 51 Monkey lip (MAz)

In about the middle of this section you will see a medium sized muscular artery cut in cross section. Note the striking refractile internal elastic lamina and the pink staining smooth muscle (25–40 layers) of the tunica media (note that the smooth muscle nuclei are twisted into a corkscrew characteristics of contraction). The external elastic lamina (between the media and adventitia) is less pronounced. The connective tissue comprising the adventitia is oriented mostly longitudinally and most of the collagen bundles here (stained blue) are thus cut in cross section. Remember that in blood vessels the components of the adventitia are arranged longitudinally, those of the media are circular, and those of the intima are longitudinal.

III. MICROCIRCULATION

A. Slide 51 Monkey lip (MAz)

For a good view of capillaries as they appear in random section, look in the connective tissue just beneath the stratified squamous non-keratinized epithelium lining the inside of the lip (this epithelium is thicker than that lining the outside of the lip). The lumen of the capillaries will be very small. Venules, with an equally thin wall but a wider diameter, are found in the same area. Also attempt to find an arteriole. These will be a bit lower in the dermis (the connective tissue immediately under the epithelium). What other tissues can you identify on this slide?

B. Slide 23 Mesentery spread (flat mount, H and E) (C&M 150-156 for ultrastructure)

This is not a section, but a piece of mesentery mounted under a coverslip. Study it first under low power. Observe the large, lymph vessel and smaller blood vessels running alongside it and extending into other parts of the mesentery. The lymph vessel contains valves that consist of a pair of pockets arranged on opposite walls. The pockets open downstream ensuring unidirectional flow.

Vessels in the arterial and venous line run together in pairs. Find an arteriole and its companion venule. Arterioles have a smaller lumen, endothelium and a smooth muscle media; venules have a wider lumen and a thin endothelial lining. By adjusting the fine focus of your microscope, you can follow the smooth muscle nuclei as they encircle the arteriole. Trace small branches from the arteriole to see them become capillaries, and, if possible, follow them back to a venule. Capillaries are distinguished by a lumen size as small as a single red blood cell.



IV. VEINS

A. Slide 92 Kidney (MAz)

Study the large vessels in the hilar (indented) region of the kidney. There are sections through several large muscular arteries. In addition observe several medium-sized thin-walled veins, which are collapsed and hence have an irregular lumen. Note the paucity of smooth muscle in the walls of these veins.

B. Slide 25 Portal vein (MAz)

You may not have this slide; please use your neighbor's. This is a cross section of a large vein which has been opened up and laid flat before sectioning. The luminal side contains coagulated blood. Observe the bundles of smooth muscle cells (red) and collagen (blue), which make up the thick adventitia. Smooth muscle cells can also be seen in the media. Large veins are the only vessels with smooth muscle in the adventitia.

CARDIOVASCULAR WORD LIST

adventitia
arteriole
arteriovenous shunts
blood brain barrier
continuous capillary
diapedesis
elastic arteries
elastic lamina
elastic recoil
endothelium
fenestrated capillary
intima
lymphatic

media
medial myocyte
metarteriole
muscular arteries
pericyte
pinocytotic vesicles
portal systems
sinusoid
subendothelial connective tissue
thoracic duct
valve
vasa vasorum
venule



Last Year's (2010) Syllabus

CARDIAC ACTION POTENTIAL

OBJECTIVES:

- A. Sodium channels support rapid propagation
- B. Refractory period controlled by sodium channel inactivation
- C. Sodium channels as targets of antiarrhythmic agents
- D. Calcium channels support slow propagation and help control action potential duration
- E. Calcium channel inactivation helps trigger repolarization
- F. Calcium channels as targets of “calcium blockers” and sympathetic neurotransmitter

In the last lecture we saw that the action potentials in different regions of the heart show considerable diversity. This is not too surprising in view of the variety of roles that electrical activity must play:

conduction ranging from

rapid (in the His-Purkinje system) to

slow (within the AV node)

rhythmicity natural pacemaking in the sinoatrial node,
latent pacemaking in the atrioventricular node and Purkinje tissue
non-spontaneous activity in atrial and ventricular myocardium
(but these tissues may be capable of repetitive activity in certain types of arrhythmia)

initiating and modifying contraction in the atria and ventricles. Unlike spikes in skeletal muscle, cardiac action potentials not only trigger contractions but also have considerable influence on contractility

In this lecture, we will deal with the ionic basis for cardiac action potentials. Not surprisingly in view of these different functions, the underlying ionic mechanisms in various parts of the heart are somewhat different. However, the general principles are very much the same.



I. SODIUM CURRENT AND EXCITABILITY

- A. Let us deal with the most familiar part of the action potential first. The upstroke of the cardiac action potential closely resembles the spike in other excitable tissues. In ventricular and atrial muscle and in Purkinje fibers (where rapid conduction is critical) the ionic basis is quite similar to nerve. The rapidly rising phase is generated by an increase in Na conductance (g_{Na}) as in the squid giant axon. If most of the external Na ions are replaced by choline (or NaCl replaced by dextrose) the following changes are observed:

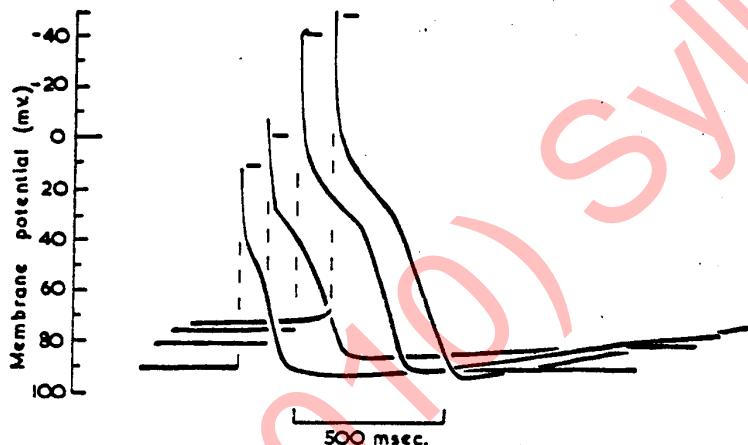


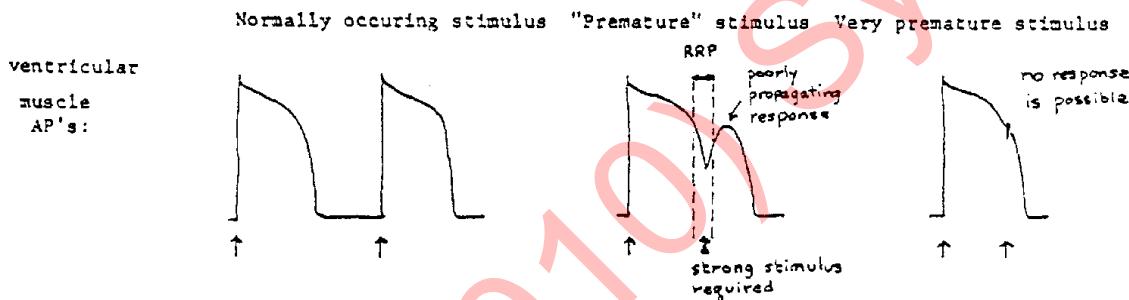
FIGURE 6. Effect of sodium concentration on the size and shape of action potential. Kid Purkinje fiber. The extracellular sodium content was (from left to right) 13, 22, 100, and 150 per cent of the normal. The horizontal lines indicate expected changes in the height of action potentials if membrane is assumed to be exclusively permeable to sodium ions.

1. The rate of rise of the upstroke decreases. Conduction velocity also is reduced.
 2. The action potential crests at a less positive potential.
 3. The action potential is briefer (the plateau configuration is much less pronounced). This suggests that some Na current may also contribute to maintaining the plateau.
- B. Similar changes take place when Purkinje fibers or working heart muscle are treated with tetrodotoxin, a specific sodium channel blocker. The effects of TTX and sodium removal indicate that cardiac membranes have sodium channels which are similar to those in other excitable tissues. (Later molecular cloning showed that they are not identical) Large changes in extracellular sodium concentration must be imposed to seriously reduce the conduction velocity. Although such changes do not occur within the clinical range of plasma sodium concentrations, changes in other ion concentrations (K^+ , Ca^{2+}) have indirect effects on the impulse generating mechanism which prove to be very important.



II. THE REFRACTORY PERIOD IN CARDIAC MUSCLE

- A. We have suggested that the Na channel mechanism in heart is similar to that in nerve or skeletal muscle. But heart differs from other excitable cells in one important sense: it has a much longer refractory period, lasting tenths of a second rather than a few milliseconds. During the refractory period the muscle is completely unresponsive to electrical stimuli. This behavior was noted as long ago as 1876 by the French physiologist Marey, who observed that stimuli falling within the early part of mechanical systole were unsuccessful in eliciting any additional contraction. More recently, electrical recording has shown that the refractoriness is associated with the absence of a propagated action potential.



- B. There is an intermediate situation between full refractoriness and no refractoriness. In the partial or relative refractory period (RRP, see below) the propagated response is a rather watered-down version of the full-blown action potential. A stronger-than-usual stimulus is needed to produce this response, and once it is generated, it propagates very slowly. Such poorly-propagated responses arise in cases of defects in heart rhythm (arrhythmias). An erratic pacemaker, or the existence of more than one pacemaker can give rise to premature "stimuli". The poorly-propagating response will cause excitation of some regions, but not of others; these regions will therefore show varying excitability for the next pacemaker signal, and eventually, complete asynchrony may result.

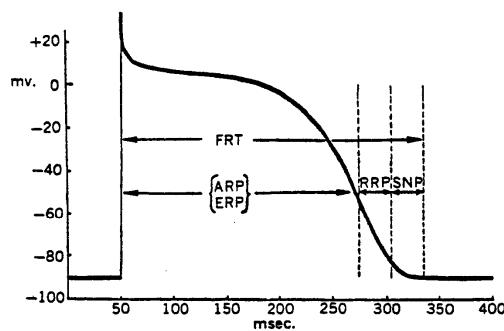
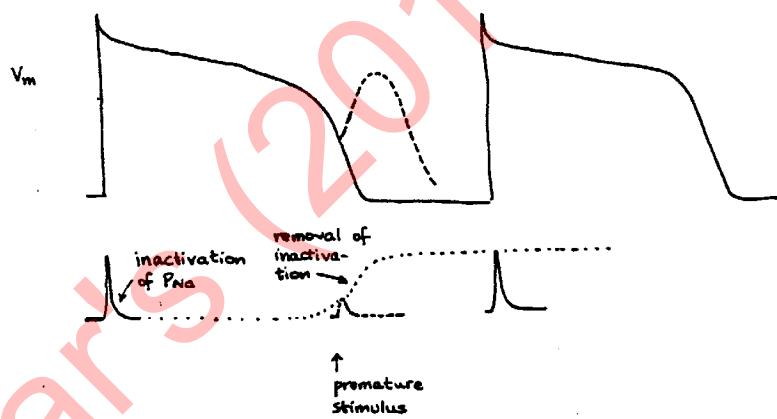


Fig. 4-10. Relationship between transmembrane action potential from single ventricular muscle fiber and excitability of fiber to cathodal stimulation. FRT, Full recovery time; ARP-ERP, effective refractory period; RRP, relative refractory period; SNP, supernormal period. (From Hoffman and Cranefield.)

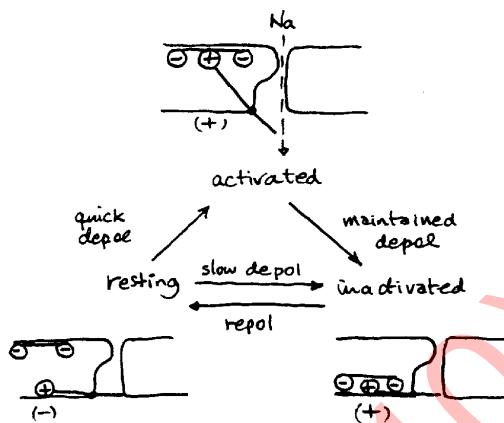
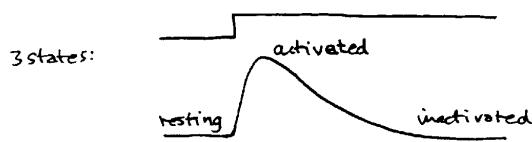


- C. What is the explanation for the long-lasting refractory period in cardiac muscle? The answer lies in the relatively prolonged plateau. The above figure shows that the ability to propagate a second action potential is restored rapidly once repolarization has proceeded to a sufficiently negative level (about 10-20 mV positive to the usual resting potential). In fact, agents which shorten or prolong the action potential also produce similar changes in the duration of refractoriness.
- D. Why is repolarization required for the recovery of excitability? This point may be puzzling, since the plateau potential exceeds (is positive to) the threshold for eliciting an action potential in the first place. If anything, one might expect the membrane to be more excitable. Yet this clearly is not the case.
- E. The answer lies in the behavior of the sodium channels (g_{Na}). In heart, as in nerve, g_{Na} is switched on by a sudden depolarization from the resting potential. g_{Na} does not remain elevated, but declines within a few milliseconds to a very small value. The decline in the face of continued depolarization is called "inactivation".



- F. The membrane potential must be returned to a level near the resting potential in order to reverse the inactivation process. As the inactivation is removed, the sodium channels become available once again for rapid opening in response to a depolarization beyond threshold, as shown in the figure on the following page.





- G. Weidmann was the first to show how membrane potential influenced the availability of sodium channels in heart. He used the rate-of-rise of action potentials as a means of measuring sodium current, and studied the effect of changes in the steady potential preceding sudden stimuli:

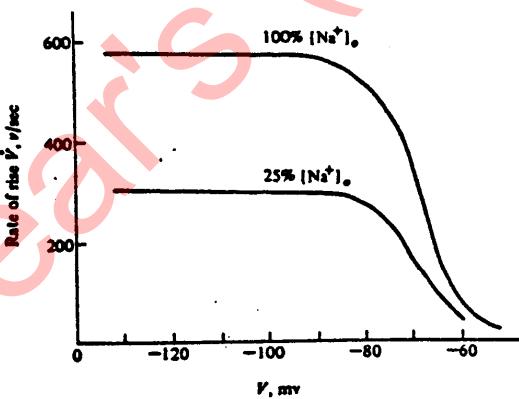


Fig. 6.7 Relationship between clamp potential V and maximum rate of rise of action potential. The membrane is held at V for 50 msec, following which an action potential is elicited. Reducing $[\text{Na}^+]_o$ to 25 percent of full strength reduces the magnitude but not the shape of the curve. (After S. Weidmann, *J. Physiol.*, 127:213 (1955).)

- H. The availability of sodium channels is strongly dependent on membrane potential over the range between -90 mV and -60 mV. This explains the gradual recovery of excitability during the final repolarization phase of the action potential. In a diagrammatic way,



{ Removal of Na channel inactivation}



plateau mechanisms → repolarization → recovery of excitability

(slow) (rapid)

- I. One function of the plateau, then, is to postpone the recovery of excitability, thereby preventing premature excitation (why would re-excitation during systole be detrimental?) In this light, it is worth noting that Purkinje fibers in experimental animals repolarize some 50-100 msec later than the ventricular muscle further downstream. The delayed repolarization in conducting system may serve to protect the ventricular muscle from the possibility of premature excitation during the so-called "vulnerable period" when the myocardium is partially refractory. During this period the ventricles are particularly susceptible to the initiation of arrhythmias by a single premature excitation. The longer Purkinje fiber plateau may ensure that impulses cannot reach the ventricles until they have fully repolarized. The relationship between membrane potential and sodium channel availability also explains a phenomenon called accommodation, where slow, subthreshold depolarizations decrease the conduction velocity and rate-of-rise of a subsequent stimulated action potential. This process occurs in axons and sensory receptors as well as heart muscle, and it is caused by inactivation of sodium channels. It is an important phenomenon in Purkinje fibers because drugs such as epinephrine or digitalis can cause accommodation by promoting slow diastolic depolarization.

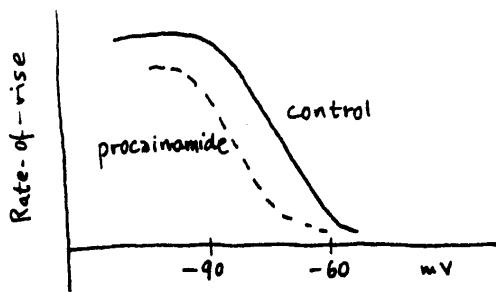
III. AGENTS WHICH AFFECT IMPULSE CONDUCTION

Agents can alter the availability of the sodium channels, and the conduction of the impulse, in different ways.

1. They can influence the membrane potential before the arrival of the impulse, or
2. They can shift the channel availability curve along the voltage axis.
- A. Potassium ions act in the first way: The inactivation curve is unchanged, but membrane potential is altered. Clinically observed variations in plasma K concentration produced changes in membrane potential in the critical range between -90 mV and -60 mV (remember Nernst potential lecture).



- B. Quinidine, procainamide, lidocaine and certain other anti-arrhythmic drugs influence conduction by the second mechanism, by altering the relationship between membrane potential and inactivation. With these drugs present, a greater degree of repolarization must occur before the membrane recovers responsiveness. The refractory period is therefore prolonged.



- C. At the normal resting potential, the drug reduces the membrane responsiveness (and concomitantly decreases excitability and conduction velocity). This takes place because lidocaine and other agents in its class bind preferentially to inactivated channels. By mass action, this drags channels away from the resting state. The reduction can be counteracted by hyperpolarizing the membrane, thereby pulling channels back into the resting state. If the membrane potential is made negative enough, the ability of inactivated channels to bind the drug will eventually be overcome. In this sense, the drug action is fundamentally different than the effect of reducing $(Na)_o$, which works across the board regardless of membrane potential.
- D. Molecular analysis shows that lidocaine and related drugs binds directly to cytoplasmic mouth of the sodium channel pore, interacting with residues in domain IVS6, which also have a strong role in interaction.

IV. CALCIUM CURRENTS AND SLOW RESPONSES

- A. Many studies have shown that sodium channels are not absolutely necessary for conduction of the cardiac impulse. Calcium channels can also underlie propagated activity when the normal sodium channels are blocked or inactivated. This calcium current (sometimes called "slow inward current") is relatively small compared to the fast sodium current. It underlies slowly-rising, sluggishly propagating impulses called slow responses when the fast sodium current is not effective. These were briefly mentioned in the Excitability and Conduction lecture.

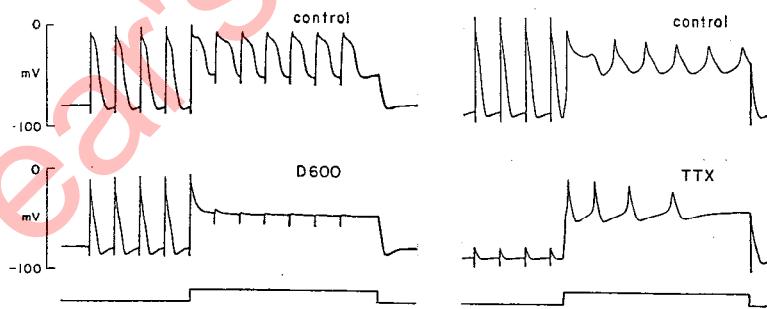


- B. The Na^+ channels and Ca^{2+} channels have been distinguished by voltage clamp experiments. At a more descriptive level, fast (Na channel) responses and slow (Ca channel) responses can also be distinguished in several ways (Table 1):

Table 1

	<u>rapid response</u>	<u>slow response</u>
conduction velocity (Purkinje fibers)	2-3 m/s	0.1 m/s
safety factor (ability of impulse to surmount short regions of block)	high safety factor (robust conduction)	low safety factor (fragile conduction)
ionic basis	mainly Na^+ channels	mainly Ca^{2+} channels
pharmacological blockers	tetrodotoxin, local anesthetics	verapamil, D600, nifedipine, divalent ions like Mn or Cd
sensitive to sympathetic hormone?	no (apart from changes) in membrane potential	strong enhancement
inactivated by mild depolarization?	yes, completely inactivated at -55 mV	no, inactivation requires strong depolarization
sensitive to elevated serum $[K]_o$?	yes, blocked	not blocked even at 16 mM $[K]_o$

- C. The table indicates that the fast and slow responses differ in their ionic basis and their response to membrane potential. They also show contrasting sensitivity to pharmacological agents. Verapamil (an antiarrhythmic agent) and its derivative, D600, can block slow responses without seriously affecting the normal fast responses while the opposite is true for tetrodotoxin and lidocaine.



- D. Effects of a verapamil derivative (D600) and tetrodotoxin on two types of electrical activity in Purkinje fibers. Each panel shows responses to external stimuli, initiated from the normal diastolic levels (near -80 mV) or from a partially depolarized voltage (near -50 mV), achieved by application of a rectangular current pulse.



- E. The mechanism of action of ca antagonists is very similar to that of lidocaine and other local anesthetics na channels. The drugs preferentially interact with the inactivated state of the channel. Hence, their potency of binding is greatly increased when tonic membrane depolarization causes the channel to inactivate. The key amino acids are also in the cytoplasmic pore region, at a location involved in inactivation.

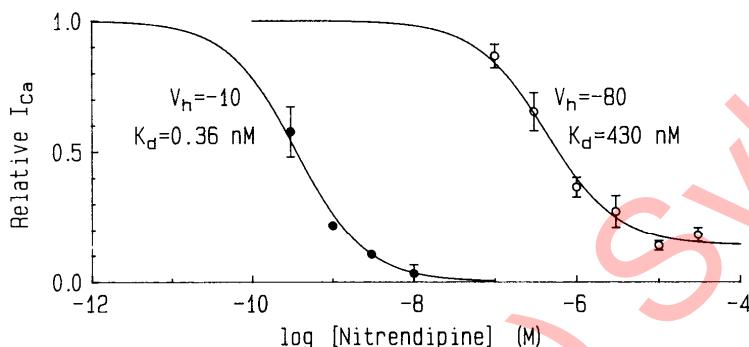


Figure 31. Different I_{Ca} blocking effectiveness of nifedipine in canine cardiac myocytes depends on holding potential (V_h). The apparent K_d for I_{Ca} block decreased by 1200-fold when V_h was depolarized from -80 to -10 mV (curves are fit to original data taken from Bean, 1984). Incomplete block when $V_h = -80$ might be due to a fraction of I_{Ca} which is not through L-type Ca channels.

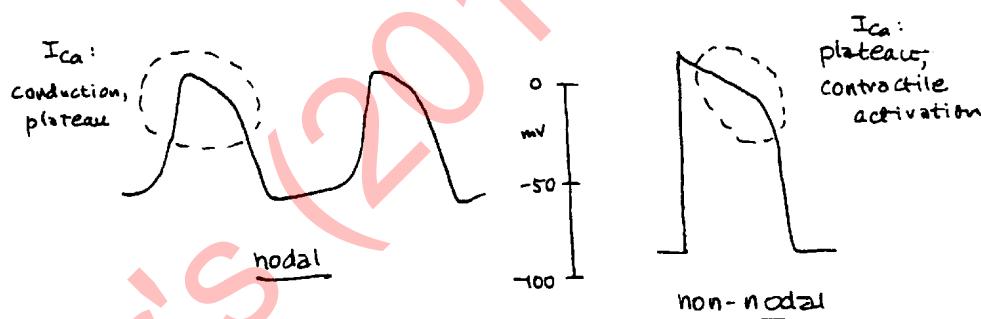
V. SLOW RESPONSES IN NODAL TISSUE

- A. Action potentials in the sinoatrial or atrioventricular nodes have many earmarks of slow response activity. In the nodal cells the membrane potential normally remains positive to -65 or -70 mV. Conduction velocity is slow -- on the order of 0.05 m/sec over a limited region of the A-V node. Such slow conduction contributes to the lag between atrial and ventricular excitation and allows proper ventricular filling. Nodal action potentials are relatively insensitive to elevated potassium concentration ($[K]_o$ ranging up to 10 mM or more) and are not blocked by tetrodotoxin. On the other hand Ca antagonists such as Mn²⁺, La³⁺, nifedipine or verapamil markedly inhibit the ability of nodal cells to generate or conduct impulses.
- B. In non-nodal regions, slow responses are produced when fast sodium channels are blocked or inactivated. This raises questions about the basis of naturally occurring slow responses in nodal cells. Recent experiments indicate that both SA and AV nodal membranes possess sodium channels, but that they are inactivated by the relatively depolarized potentials that nodal cells experience. This is due in large part to the absence of a special kind of K⁺ channel (IK1), open at negative potentials, that supports the resting potential in non-nodal tissue (see lecture on Control of Cardiac Rhythm).



VI. SLOW INWARD (Ca) CURRENT IN NON-NODAL TISSUE

- A. In normally functioning atrial muscle, ventricular muscle or Purkinje tissue, the resting potential is negative enough to largely remove sodium channel inactivation. The Ca²⁺ current is overshadowed by the much larger sodium current during the upstroke of the action potential. However, the Ca²⁺ current has other functions which are just as important:
- B. Supporting plateau. The Ca²⁺ current plays a leading part in underlying the plateau phase of the action potential. The size of the Ca²⁺ current helps determine the height and duration of the plateau and, indirectly, the refractory period. Repolarization is triggered by a combination of two processes: progressive inactivation of the Ca²⁺ current, and slow turning-on of a small potassium current. Once the balance is tipped in favor of outward K currents, the membrane potential repolarized towards E_K.
- C. Activating contraction. Ca²⁺ entry is important for excitation-contraction coupling because it gives a direct supply of activator Ca²⁺ to the contractile machinery. Additional Ca²⁺ is provided by release from intracellular stores in the sarcoplasmic reticulum.



D. ROLES OF Na⁺ AND Ca²⁺ CHANNELS IN VARIOUS HEART CELLS

Specialized Conducting Tissue

	<u>Na⁺ channels</u>	<u>Ca²⁺ channels</u>
SA node, AV node	Na current not operative (potentials are not normally negative enough to remove inactivation)	Ca current generates upstroke and allows propagation
Purkinje, His bundle	Na current supports rapid conduction	Ca current underlies plateau, and also may allow slow responses when the Na current is reduced. This may lead to: (1) ectopic impulses (2) reentry
Working Myocardium	Na current supports conduction	Ca current underlies plateau and activates contraction



- E. Action potential repolarization takes place when Ca current inactivates and K current activates. Ca channels inactivate 10-100x more slowly than sodium channels, in a manner largely dependent on cytoplasmic Ca^{2+} and calmodulin. The K channels also turn on much more slowly than their counterparts in nerve axons. As a result, these changes tip the balance in favor of outward repolarizing current and thus terminate the plateau.
- VII. SYMPATHETIC HORMONE REGULATION OF Ca^{2+} CHANNELS AND OTHER Ca^{2+} SYSTEMS**
- A. Sympathetic hormone (epinephrine) interacts mainly with β -adrenergic receptors to exert coordinated effects on mechanisms controlling electrical activity and intracellular Ca^{2+} . The power of this modulation is illustrated by electrical and mechanical recording from ventricular muscle exposed to increasing concentrations of isoproterenol (specific for β -adrenergic receptors). Note the higher (but not longer) plateau, the larger (but not more delayed) peak force, the faster relaxation. All of functional advantage for the heart in a fight or flight response!

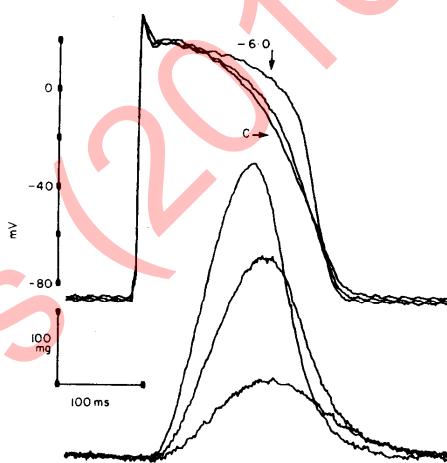


FIG. 1. Effect of isoproterenol on the action potential (above) and contraction (below) of dog papillary muscle. The progressively increasing force traces show the control contraction and the twitch in the presence of $10^{-7.7}$ and 10^{-6} M isoproterenol (steady-state effects). The corresponding transmembrane potential records show that isoproterenol elevates the plateau. Each trace was made by connecting digitalized data points with a computer. (From Nathan and Beeler, ref. 10.)

The increased Ca^{2+} influx through L-type channels is one important part of this response.



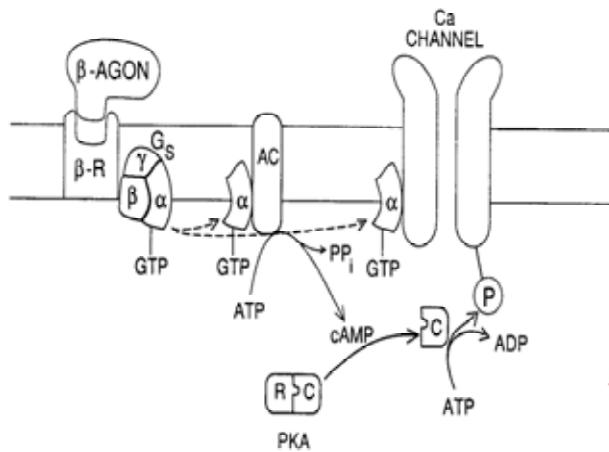
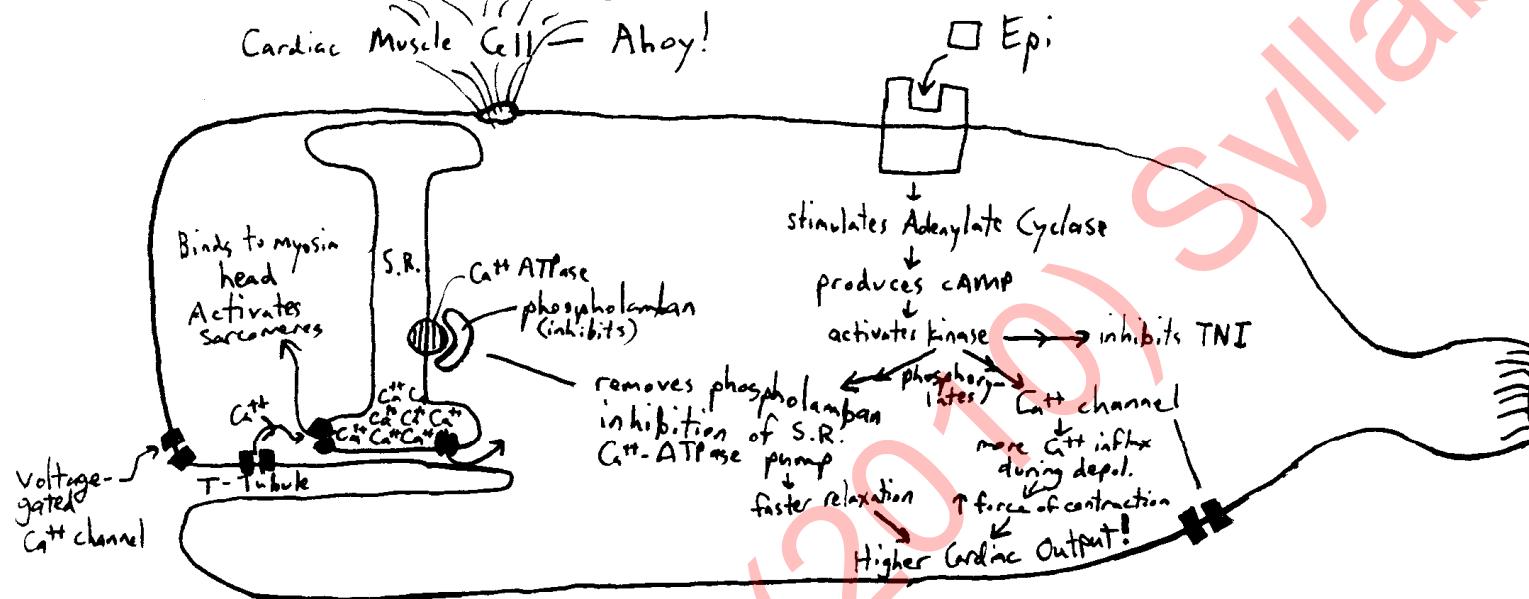


Figure 33. Dual pathways for activation of Ca channels by β -adrenergic stimulation. The "classic" pathway is via stimulation of adenylate cyclase (AC, via activation of the GTP binding protein G_s), increased [cAMP] and phosphorylation of the Ca channel by the catalytic subunit (C) of the cAMP-dependent protein kinase (PKA, where R is the regulatory subunit of PKA). A novel pathway is via a direct effect of the activated α subunit of G_s on the Ca channel (β -agon = β -agonist and β -R = β receptor, based on a

- B. The increase in Ca^{2+} channel activity is only one aspect of the multi-pronged response to adrenergic stimulation. Multiple pathways participate, mostly but not entirely via cAMP activation of PKA.
1. increased Ca^{2+} current /phosph of $\alpha 1$ subunit / stronger contraction, higher plateau
 2. increased K^{+} current /phosph of IKr channels /maintenance of action potential duration
 3. increased Ca^{2+} uptake by SR Ca^{2+} pump /phosphorylation of phospholamban, disinhibition of Ca^{2+} ATPase / faster relaxation, more completely filled store, greater Ca^{2+} release
 4. reduced Ca^{2+} sensitivity /phosphorylation of Tn-I /faster relaxation
 5. [covered in later lecture] increased I_h /direct action of cAMP, not PKA mediated /inward current turns on faster, more completely, faster pacemaker
- C. All of this is summarized by a local artist with a nautical bent:



Overview of the Ryanodine Receptor and Catecholamine Effects on Excitation:



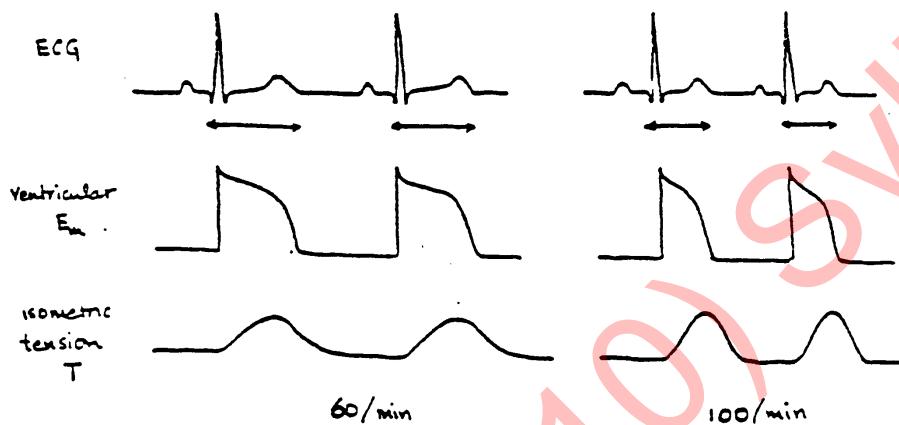
If the myocardial cells are exposed to adrenergic transmitters, the B-adrenergic receptor stimulates a cAMP pathway that activates a kinase which phosphorylates the sarcolemma calcium channel (more Ca²⁺ enters --↑ contraction), phosphorylates phospholamban (increases Ca²⁺ uptake into SR--speeds relaxation, ↑ contraction), and phosphorylates Troponin I (inhibits Ca-Troponin C binding -- speeds relaxation). Thus B-adrenergics hasten both systole AND diastole.



Last Year's (2010) Syllabus

CONTROL OF HEART RHYTHM AND LONG Q-T SYNDROME

Imagine a patient whose heart rate suddenly rises from 60/min to 100/min. If we record his/her electrocardiogram, we find an immediate shortening of the Q-T interval, corresponding to the ventricular action potential duration, in response to the rate increase.



This can also be illustrated in a table of mean Q-T intervals for different heart rates for adults and children:

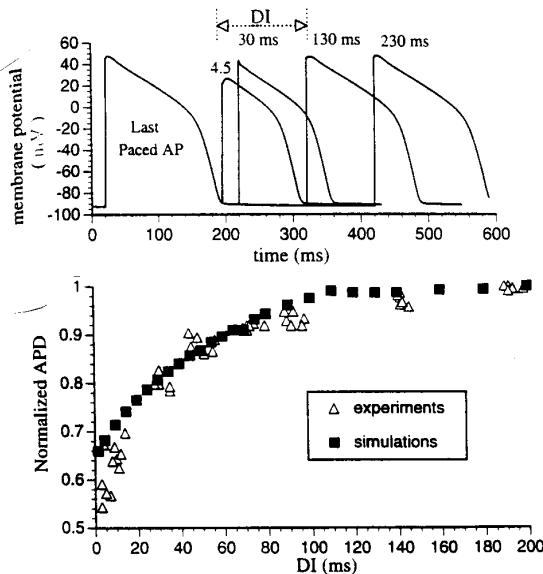
Heart rate (beats/min)	Total cardiac interval (s)	Q-T interval (s)	% electrical systole	% electrical diastole
40	1.50	0.45	30	70
60	1.00	0.39	39	61
80	0.75	0.35	45	55
100	0.60	0.31	52	48
120	0.50	0.28	56	44
150	0.40	0.25	62	38
180	0.33	0.23	70	30

Modified from Burch.

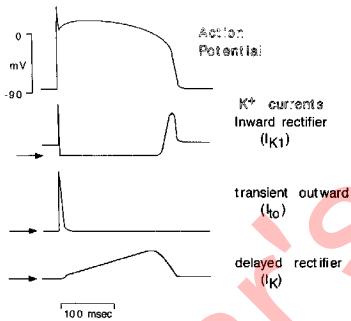
This electrical adaptation is clearly useful to the proper pumping action of the heart; unless the mechanical systole is shortened, there would be no diastolic time left for ventricular filling.

The frequency-duration relation may be observed at the level of isolated ventricular muscle cells. It is expressed as an increasingly abbreviated action potential duration (APD) the closer the action potential comes to the one preceding it (decreased diastolic interval).





Thus, the cardiac action potential is highly modifiable, to a much greater extent than the rather stereotyped spikes in most other forms of excitable tissue.



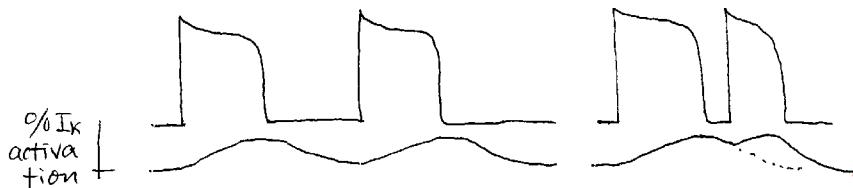
The modification of ventricular action potential duration makes sense if one recalls that the repolarization is initiated by the shutting off of inward current (Ca channel inactivation) and the turning on of outward potassium current (K channel activation).

There is a particular class of potassium channels, known as “delayed rectifier” K⁺ currents, or simply “IK”, that activate slowly during the plateau, and then deactivate (turn off) following repolarization. These work along with K⁺ channels that turn on briefly to set the initial level of the plateau (Ito) and those that control the final repolarization and resting potential in working myocardium (IK1). For now, let’s focus on IK only.

How the operation of IK explain the frequency-duration relation? Each action potential leaves behind it some residuum of the time-dependent permeability change which decays away gradually over the next 0.1-0.3 sec after the repolarization. For example, K channel activation decays and Ca channel inactivation is gradually reversed (channels become available again). If the next action potential is elicited prematurely, its plateau will be shorter because the various channels would already have a head-start toward the condition that set up the previous repolarization and



therefore need less time to reach that state. This explains why premature (extrasystolic) action potentials are abbreviated, as shown above. Their duration is not specifically related to heart rate as such, but rather the proximity of the extrasystolic stimulus to the previous repolarization. (Can you restate this in terms of the ECG and its key intervals?)



I. LONG Q-T SYNDROME

- A. Defects in cardiac action potential repolarization lead to a cluster of diseases known as the Long QT syndrome (LQTS). Long QT syndrome is an inherited disorder that causes sudden death from cardiac arrhythmias. Electrocardiograms of patients with LQTS show an abnormality in cardiac repolarization and a prolonged QT interval.

This observation led to the initial hypothesis that LQT is caused by an imbalance in cardiac autonomic innervation. Therapy for LQT was focused on the autonomic nervous system, and included maneuvers such as cervical sympathectomy and β -adrenergic receptor antagonists. Unfortunately, these treatments did not prevent arrhythmia in all patients, nor did they resolve the underlying abnormality in repolarization. In extreme cases, the action potential repolarization fails altogether, giving way to spontaneous rhythms called "early after-depolarizations" (EADs) that can propagate slowly through the ventricle and give rise to a dangerous arrhythmia known as "torsade de pointes" (twisting of points, so named because of the appearance of the ECG).

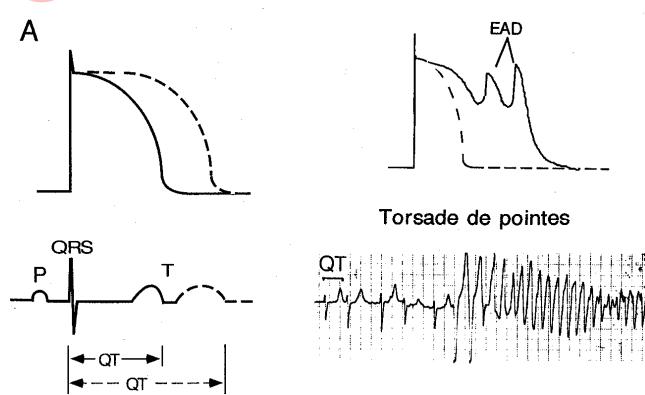


Figure 5



- B. We now know that LQTS can arise from multiple causes. Hereditary LQTS ("Genetic" in Fig. 6) arises from specific molecular defects in ion channels, some of the very channels that supply the inward and outward currents which determine how long the plateau lasts. "Drug-induced" LQT is actually a serious clinical problem, arising as a side-effect of medications, including certain antiarrhythmics, antihistamines and antibiotics.

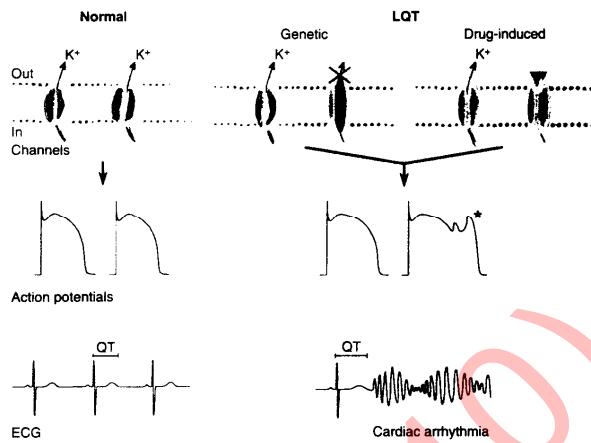


Figure 6

- C. The etiology of both kinds of LQT can be summarized very schematically as follows.

slowed K channel opening → retarded AP repolarization → delayed T-wave, long Q-T, early after depolarization
slowed Na channel inactivation

- D. To understand the various forms of LQTS, it is helpful to dig a little deeper into the nature of the channels that support the delayed rectifier potassium current. It turns out there are two types of IK, known as IKr and IKs, each with their own molecular basis and distinctive properties. IKr turns on more rapidly, but its ability to pass outward repolarizing current is strongly limited at positive potentials. IKs turns on slowly, but can pass very large outward currents. Defects in either one can cause LQTS.

- E. Genetic defects have been found in LQT patients, in the single kind of subunit making up tetramers of IKr and in either of the two kinds of subunits making up IKs. Thus, multiple types of potassium channel (and a sodium channel) can give rise to multiple forms of long Q-T syndrome.

- F. Different forms of LQT highlight multiple factors controlling repolarization:



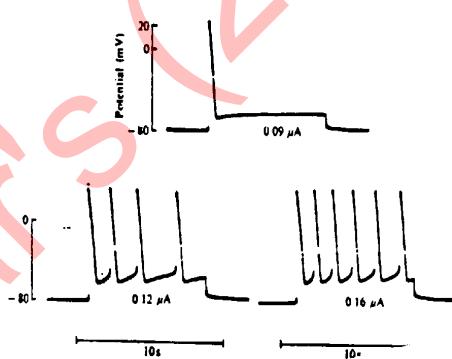
Disease Type	Chromo-some	Channel Type (nickname)	Defining Characteristic(s)	Defective Feature
LQT2	7	I_{Kr} (HERG)	fast activating, maximal at ~0 mV	fails to assemble with normal subunits or acts as dominant negative
LQT1	11p	I_{Ks} (α subunit, KVLQT1)	slowly activating current grows ever-outward at positive potentials	Defective outward current
LQT5	21	I_{Ks} (β subunit, minK)	same as above	Defective outward current
LQT3	3p	I_{Na} (SCN5A)	sodium current	deletion with intracellular loop, causing delayed or incomplete inactivation

- G. The subclassification of LQT forms is relevant to the choice of therapy.
1. In LQT2, defects in I_{Kr} (HERG) can generally be corrected by potassium supplementation. This makes sense because these potassium channels show a rapid form of inactivation that limits their contribution to outward current over the voltage range where repolarization occurs, thereby sparing ion gradients during the relatively long action potential plateau. Raising the external potassium concentration opposes the inactivation, probably because these ions bind near the outer mouth of the channel where the inactivation mechanism would otherwise pinching off the channel.
 2. In LQT3, defects in the sodium current arise because of delayed or incomplete inactivation and can be counteracted by administration of a sodium channel blocker that acts preferentially on inactivated or open Na channels. (Shades of treatment of re-entrant arrhythmias, covered in the last lecture).
 3. These forms of LQT syndrome are generally autosomal dominant. This means that an individual with a mixture of functional and dysfunctional K⁺ channel proteins will suffer from abnormal repolarization. This is due in part to the fact that mixtures of wild-type and mutant subunits behave abnormally, and because the cardiac AP relies on the full panoply of outward currents to repolarize properly.



II. IONIC BASIS OF STABLE RESTING POTENTIAL IN VENTRICLE AND ATRIUM

- A. Let us turn now to the question of what makes nodal regions spontaneously rhythmic. In working heart muscle (ventricular or atrial myocardium), there is no appreciable undershoot or diastolic depolarization, despite the fact that slow changes in K permeability occur in the wake of an action potential. The lack of pacemaker activity can be explained by the presence of another potassium channel that confers significant potassium permeability at the resting potential (I_{K1} , or "resting K channel" or "inward rectifier", not to be confused with the other I_K 's you've heard of already). I_{K1} is strong enough to hold the resting membrane potential close to E_K . Even though I_{K1} decays, there isn't enough inward current to force the membrane potential away from E_K . This explanation is supported by measurements with ion-sensitive microelectrodes, which show that the difference between the resting potential and E_K is very small in working myocardium.
1. However, pacemaker activity can be artificially induced in working myocardial tissue by weak steady depolarizing current. The current can be applied by using an external source, or by allowing local circuit current from a depolarized region. The Figure shows an example from strips of frog atrium, subjected to current pulses of increasing strength.

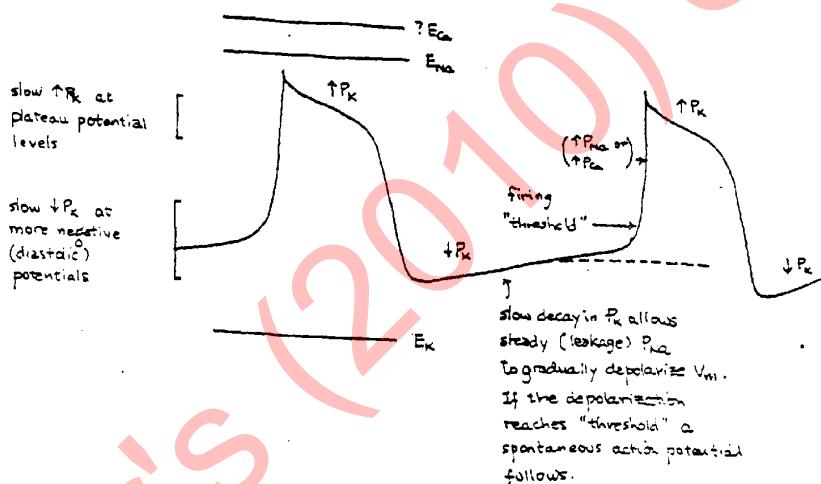


- B. The figure shows that the smallest amount of depolarizing current produces a diastolic depolarization which fails to reach threshold. (There is some analogy here to the undershoot following the action potential of the squid axon). Slightly larger amounts of current produce diastolic depolarizations that do reach threshold and produce repetitive activity. Some cardiologists have proposed that similar repetitive firing may result from the interaction of normal myocardium and tissue which is partially depolarized by ischemia. Such hypothetical "ectopic foci" could play a role in arrhythmias.



III. SIMILAR PRINCIPLES APPLY TO PACEMAKER ACTIVITY IN NODAL TISSUE

- A. Pacemaker activity in cells of the SA node (or AV node, or Purkinje fibers) takes place without application of current. The depolarizing pressure is provided by the membrane itself. One factor is a resting permeability to sodium ions (different channels than the TTX-sensitive ones). Another factor is a lack of resting K channels (IK1). The combination of background sodium permeability (P_{Na}) and no IK1 keeps the nodal membrane potential away from E_K . Because voltage-gated K⁺ channels experience significant driving force ($E_m - E_K$), their shutting-off engenders diastolic depolarization in nodal cells. When the diastolic depolarization which follows one action potential reaches threshold and triggers the next action potential, the cell acts as a pacemaker.



- B. Each cycle of membrane potential is associated with a fluctuation in PK (permeability of IK channels). Although some regenerative inward current (probably ICa) underlies the rapid depolarization, it is clear that the basic period of the oscillation must be largely dependent on the slowly occurring permeability changes: a slow increase in PK that triggers the repolarization, and a slow decay in PK that governs the slope of the pacemaker potential. Provided that the threshold for the upstroke remains unchanged, the rate of slow PK decay thereby determines the diastolic interval.
- C. Another contributing factor in nodal tissue is the turning on of an inward cation current known as I_h , whose channels are opened by hyperpolarization, not depolarization like the ion channels you've heard of thus far. The contribution of I_h to the nodal rhythm has been estimated at about 30%, based on blockade of I_h with 1-2 mM cesium ion.



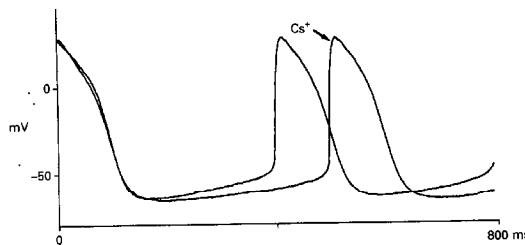
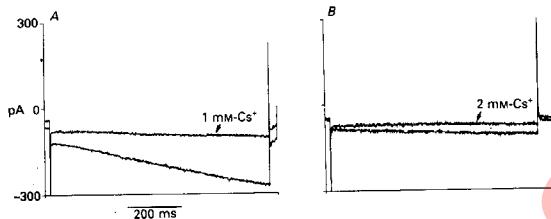


Fig. 2. Whole-cell nystatin-permeabilized patch clamp recording of spontaneous activity in an isolated SA node cell before and during superfusion with Tyrode solution containing 2 mM-CsCl.



IV. MODIFIERS OF RHYTHMIC ACTIVITY

- A. Parasympathetic influence. Stimulation of the cardiac branch of the vagus nerve decreases the rate of the heart beat. In the 1920's Loewi discovered that the vagal inhibition was mediated by a chemical substance; this was the first known chemical transmitter. "Vagusstoff", as he unswervingly named it, was later identified as acetylcholine. ACh is also the transmitter substance in the neuromuscular junction, and the preganglionic nerve endings in the autonomic ganglia.
 - 1. The action of acetylcholine in heart is best known from microelectrode recording in the sinus venosus (pacemaker area) of the frog. There, ACh increases both the efflux and influx of K; the membrane resistance also decreases. The "shunt" for potassium lies in parallel with the usual membrane ionic currents. The potassium specificity of the effect was a clear contrast with the neuromuscular junction, where ACh also generates a shunt, but one that allows movement of Na⁺ as well as K⁺ ions, thus exciting the skeletal muscle cell.



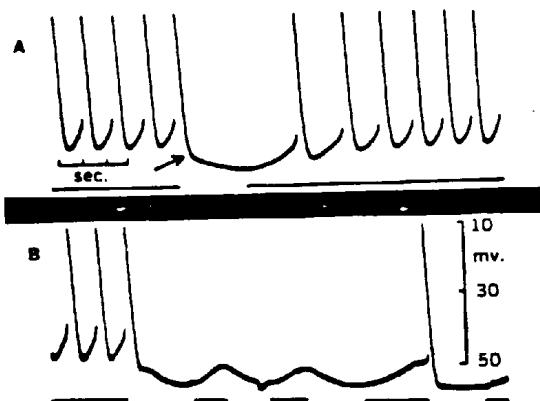
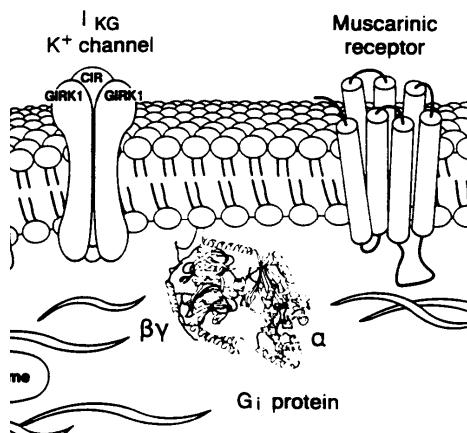


Fig. 4-11. Effects of vagal stimulation on transmembrane potential of pacemaker fiber in sinus venosus of spontaneously beating frog heart. Record in A shows vagal stimulation at rate of 20 pulses/sec., as indicated by break in solid line at bottom of tracing. At arrow, note beginning of hyperpolarization of membrane and inhibition of pacemaker action potential. Several seconds after vagal stimulation ceases, membrane slowly depolarizes to a level at which action potentials are again generated. Record in B shows effects of intermittent (20/sec.) stimulation on same fiber as shown in A. Note hyperpolarization of membrane during vagal stimulation and slow return (depolarization) toward threshold when stimulation is discontinued. Note also escaped beat at beginning of fourth stimulation period. (From Hutter and Trautwein⁴¹)

2. Small degrees of vagal stimulation inhibit the pacemaker by effectively counteracting the depolarizing influence of a steady leak to sodium ions. With more vigorous stimulation, a noticeable (10-20 mV) hyperpolarization may be recorded, as the membrane potential presumably approaches EK. (This dramatic behavior underscores the fact that the usual maximum diastolic potential of pacemaker cells is at least 10-20 mV positive to EK, due to the lack of IK1) The hyperpolarization can inhibit spontaneous activity for many seconds; the pacemaker activity resumes promptly after vagal stimulation is terminated. Sometimes the site of pacemaker activity may shift momentarily to a less severely inhibited region of the sinus, a phenomena referred to as vagal escape.
3. The properties of the channel activated by ACh in heart are now well-known. The channels are like IK1 channels, but have the special characteristic of undergoing local regulation by G proteins, hence the label IKG.
4. The onset of vagal inhibition occurs within the time of a single heartbeat. The speed of the cholinergic action is due to the local nature of the signaling system. ACh binding to muscarinic receptors activate G proteins (mostly G_i), liberating G_{βγ} subunits, that bind directly to the IKG channels, causing them to activate. The following diagram summarizes the signaling pathway for muscarinic activation of the specific potassium channels.





5. Another mechanism of cholinergic action has been revealed by voltage clamp experiments. Calcium currents are reduced by very low concentrations of ACh. This effect is the opposite of the adrenergic one, and it would decelerate pacemaker activity by promoting a longer interval between repolarization and the next upstroke.
- B. Sympathetic influences. You already know that the SA node is accelerated by the action of sympathetic hormones. Two catecholamines are involved: norepinephrine, released from fine nerve endings in the immediate vicinity of SA node (and AV node), and epinephrine, liberated by the adrenal medulla and delivered to the heart via the circulation. These two hormones have similar actions on heart rate (chronotropic effect) and contractility (inotropic effect). Both actions involve β adrenergic receptors and are antagonized by β blockers like propranolol.

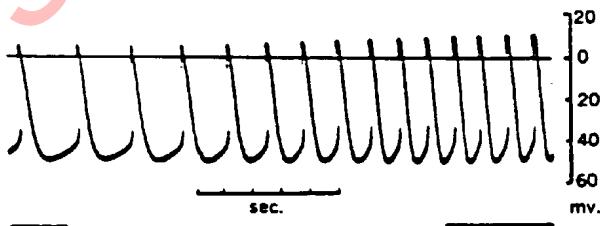


Fig. 4-12. Effect of sympathetic stimulation on pacemaker fiber in sinus venosus of frog heart. Stimulation (20/sec.) indicated by breaks in solid reference line at bottom of tracing. Note increase in slope of pacemaker potential, amplitude, and overshoot of action potential as heart rate increases. (From Hutter and Trautwein.⁴³)

1. The acceleratory effect of sympathetic amines takes the form of a steepening of the diastolic depolarization. The ionic mechanism has been worked out in Purkinje fibers and extended to nodal tissue. In both cases, the pacemaker depolarization is speeded by a selective effect in increasing the inward cation current I_h . Epinephrine increases the rate and the extent of the turning-on of the inward current, which produces a steeper pacemaker. The effect is supported by a



direct action of cAMP on the inward current channel, rather than activation of PKA. Another possible acceleratory mechanism for the nodes involves Ca channels. As already described in a previous lecture, sympathetic amines are known to increase Ca current. Increases in ICa in the SA node shift the threshold for the upstroke toward more negative potentials. This also helps decrease the interval between action potentials and thereby accelerates the overall rate.

V. SUMMARY

In summary, this lecture has presented K⁺ channels and non-selective cation channels (I_h) that fill out the set of ion channels involved in cardiac action potentials, along with the Na⁺ and Ca²⁺ channels that support excitability and fast and slow responses. The long QT syndrome can arise from genetic and iatrogenic causes and provides a clinically relevant perspective on the multiplicity of repolarizing K⁺ channels. Nodal pacemaker cells are interesting because they lack the channels that set the resting potential of working myocardium (I_{K1}) but have in compensation extra helpings of the special channel types that support the actions of sympathetic acceleration (I_h) and parasympathetic braking (I_{KG}).

- A. The following table summarizes what we've covered on ion channels and their role in cardiac activity. Transporters can generate current too, but are not included here.

<i>Channel Name</i>	<i>AP Role</i>	<i>Comment</i>
I _{Na}	sodium channel	upstroke, fast propagation, plateau lidocaine and other anti-arrhythmics stabilize inactivation
I _{Ca,L}	L-type calcium channel	plateau, slow response increased by sympathetic hormone
I _{K1}	resting K ⁺ channel (inward rectifier)	resting potential in working myocardium absent in nodal cells
I _{to}	transient outward K ⁺ channel	quick early repolarization helps govern difference between endo and epicardium
I _{Kr}	I _K channel, rapid activating (but limited)	termination of plateau affected in LQT2
I _{ks}	I _K channel, slowly activating (but large)	termination of plateau affected in LQT1 and LQT5
I _{KG}	G-protein activated K ⁺ channel	parasympathetic response directly mod'd by G β
I _h	hyperpolarization-activated cation channel	sympathetic response turn-on enhanced by cAMP

It isn't simple by any means, but keep in mind the multiple roles that cardiac action potentials play in all aspects of cardiac function!



Last Year's (2010) Syllabus

AUTONOMIC DRUGS OVERVIEW I

Reading assignment: Katzung (10th ed.), Chapter 6

LEARNING OBJECTIVES:

- A. Learn the two divisions of the ANS, the tissues innervated, and the responses of those tissues to nerve stimulation.
- B. Understand the concept of neurochemical transmission, the evidence that supports the concept, and the relevance of the concept to pharmacology.
- C. Learn the biosynthesis, storage, release, and termination of action of acetylcholine (Ach) and norepinephrine (NE). Learn how drugs inhibit these processes.
- D. Learn the receptor classes (and subclasses) that mediate responses to Ach and NE. Learn the tissue distributions and the responses that the receptors mediate.

I. TOPICS

- A. Anatomy of ANS
- B. Chemical transmission of nerve impulses
- C. Receptors for neurotransmitters
- D. Drug action at ANS synapses



Last Year's (2010) Syllabus

Electrocardiogram (ECG)

OBJECTIVES:

- A. basic elements of standard ECG
- B. relationship of extracellular potentials to extracellular current flows
- C. ECG leads as perspectives on the pathway of excitation
- D. patterns of excitation during QRS complex and other waves
- E. other recording configurations and the extra information they provide

In previous lectures electrical current flows and potential differences were shown as they occur at the plasma membrane, using intracellular (transmembrane) recordings. The concept of extracellular current flow was introduced along with the concept of the spread of electrical signals along a cylindrical structure such as a long axon or Purkinje fiber. The key principle is this: intracellular paths of current flow along the axis of such structures need to be completed by corresponding return paths of extracellular current flow. Since the extracellular current encounters some small resistance, extracellular electrodes close to the conducting structure can record small potential differences. This is the principle of all the clinical recordings that you are likely to encounter, including the electroencephalogram (EEG), electro-oculogram (EOG) and electromyogram (EMG), as well as the electrocardiogram (ECG or EKG) that we discuss here.

The electrocardiogram is an extracellular recording of small signals due to the flow of electrical current outside the heart. In this case the potential changes are not picked up in the extracellular fluid immediately surrounding the cardiac cells but at the surface of the body. Between an electrode on the right arm and the left leg, a normal recording looks as follows:



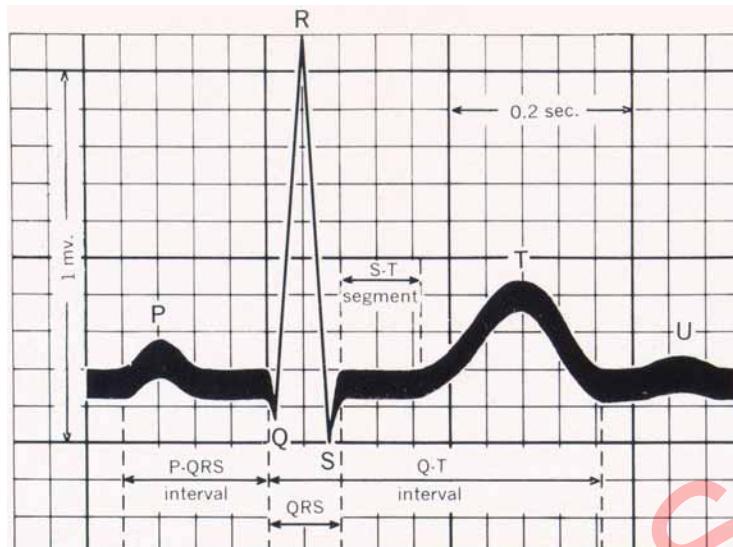


FIGURE 1

The P wave results from the depolarization of the atria. The second set of deflections, called the QRS wave, is produced by the depolarization of the ventricular cells. The final deflection, the T wave, results from ventricular repolarization.

I. PRINCIPLE OF EXTRACELLULAR RECORDING

- A. How is it possible to detect any potential differences on the surface of the body? The surface signals arise from the spread of excitation in the heart. Consider a mass of cells at some instant during the cardiac cycle where an active region exists together with an inactive region.

Figure 2.

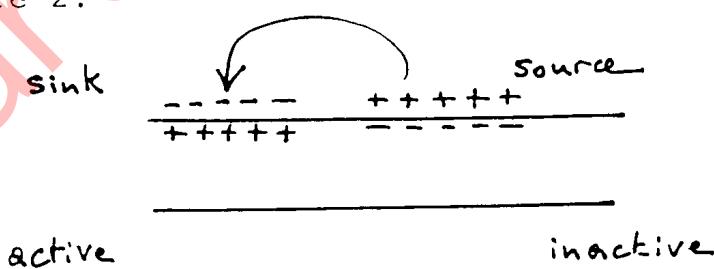


FIGURE 2

- B. The diagram shows an active depolarized region (inside positive) on the left, and a region still at rest (inside negative) on the right. As the depolarization spreads from left to right, intracellular current flow also proceeds from left to right, but the return flow of extracellular current outside the myocardial cells passes from right to left (curved arrow). Focusing on the extracellular electrical pattern in the fluid and tissue surrounding the heart (volume



conductor), it is as if current were generated by a current source (right) and a current sink (left).

- C. When the source and the sink are physically very close together, or viewed from a great distance, they can be described as a current dipole. A dipole is an equal number of positive and negative charges separated by an infinitesimally small distance. A dipole has properties of magnitude (amplitude), sign (a certain sense, positive or negative) and direction (orientation in space). These features can be conveniently represented by a vector with corresponding properties. Typically, the vector representation of the dipole is used as a shorthand representation of the electrical forces generated by the wave of excitation. The magnitude, sign and direction of the dipole are symbolized respectively by the length of the arrow, the sign of the electromotive force is indicated by the arrowhead, and the orientation is represented by the direction of the arrow. As you shall see, the orientation is a critical factor in determining how this force will be registered on the ECG. It is a question of how closely the forces generated by the dipole are aligned with the optimal orientation of a particular recording configuration, known as a "lead".

II. ELECTROCARDIOGRAPHIC LEADS

A detector such as an electrometer or ECG machine works on the same principle as a voltmeter you can buy in the hardware store. The detector measures a potential difference between two different points in the space, with one point connected to the terminal called the positive electrode (red wire) and the other point connected to the other terminal, called the negative electrode (black wire). The ECG machine responds to the magnitude and polarity of the signal. When the positive electrode sees a positive voltage relative to the other electrode, an upward (positive) deflection is registered. An ECG lead refers to a specific connection of the two terminals of ECG machine to two different points in space (in this case, on the body surface). Thus a lead has both a sign and a direction. Graphically, a lead is represented by a straight line in space between the two terminals.

III. HOW EKG LEADS GIVE INFORMATION ABOUT THE SPREAD OF EXCITATION

- A. The relative magnitude of the potential (E) recorded along a lead is given by the projection of the dipole moment (graphically represented by a vector) onto the straight line connecting the electrodes. By conventional geometry, this is proportional to the vector moment (m), and to the cosine of the angle between the vector and the line.



$$E = m \cos \alpha$$

or graphically presented in Figure 3:

$$CD = AB \cos \alpha$$

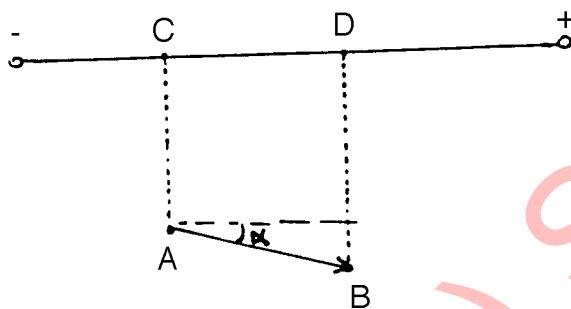


FIGURE 3

- B. Thus, when the heart vector is exactly parallel to the axis of lead, the projection is maximal. On the other hand, when the vector is perpendicular to the axis of the lead, the projection is minimal. In between orientations yield projections varying by $\cos \alpha$ which can range from 1 to 0. The projections of a vector can be considered as the "shadow" on the lead axis, with light falling in perpendicularly. The size of the shadow will depend on the angle of the vector with relation to the lead.

IV. EINTHOVEN LEADS

- A. When we attach the (+) electrode to the left arm (L) and the (-) electrode to the right arm (R), we are using one of the leads (lead I) first introduced by Wilhelm Einthoven centuries ago. His invention of the string galvanometer allowed the first high-fidelity recording of the ECG. One can think of the limb electrodes as ways of gaining access to electrical forces within the body trunk, in the case of lead I, along a vector running from right shoulder to the left shoulder.



- B. The standard bipolar limb leads in electrocardiography (Einthoven leads) are:

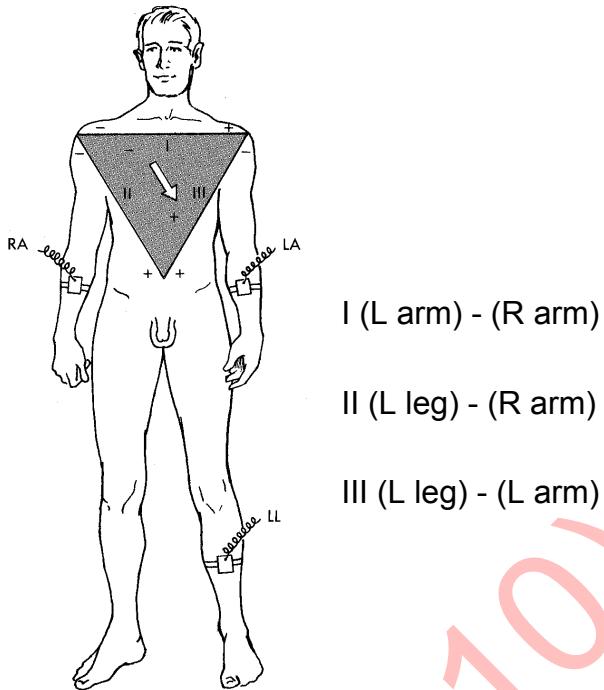


FIGURE 4

- C. In a more diagrammatic fashion, each lead can be depicted as an arrow, where the arrowhead represents the positive terminal. The three leads are often shown as lying in a single frontal plane along a more or less equilateral triangle, as illustrated in Figure 5.

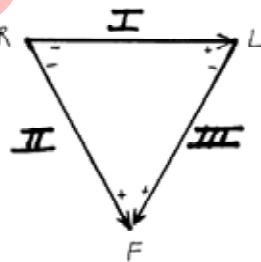


FIGURE 5

V. SPATIAL SPREAD OF VENTRICULAR DEPOLARIZATION AND GENERATION OF THE QRS COMPLEX

- A. Now we are ready to examine the correspondence between the spread of cardiac excitation and its registration on a specific EKG lead. We will take as an example the ventricular depolarization. Initially the depolarization is directed from left to right into the septum and from endocardium to epicardium. The average



position of the vector is as shown in arrow 1. Somewhat later the main spread is downwards to the apex when the entire electrical front can be represented by the direction of arrow 2. Finally depolarization reaches the last portion of the heart in a posterior and left direction vector 3 and vector 4.

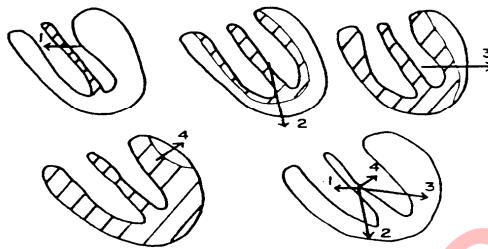


FIGURE 6

- B. Obviously, the vector evolves during the cardiac cycle in a continuous fashion with all intermediate positions before, after and between the positions 1,2,3. A continuous representation of the vector during the cardiac cycle is shown in vectocardiography as a complete loop. Figure 8 shows the relative deflections on lead II, as given by projecting the vector of excitation onto the appropriate lead line. Since the projection of vector 1 is opposite in sign to the sign convention of the lead, it is shown in the EKG as the negative Q wave. Vector 2 is of the same sign as the lead, and also larger than vector 1; it projects as a positive deflection, the positive R wave. Vector 4 is again of opposite sign and smaller and projects as the negative S wave.

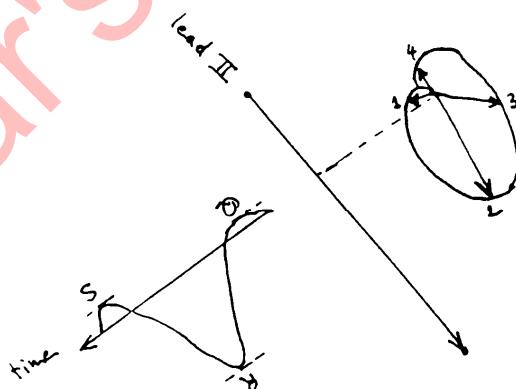


FIGURE 7

- C. Projections of the same events on other leads I and III give reconstructions of the normal EKG tracings recorded with these configurations. See Figure 8.



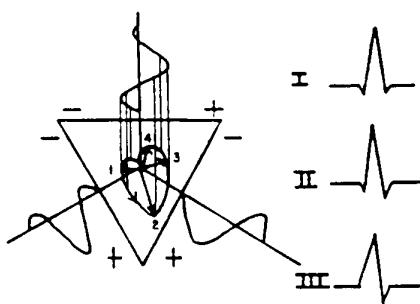


Figure 8

VI. OTHER WAVES OF THE STANDARD EKG

- A. The same analysis can be made for the atrial depolarization. The cardiac vector is essentially oriented downwards and to the left, resulting in a loop as shown in Figure 9. The resulting P wave in the standard leads is thus positive.

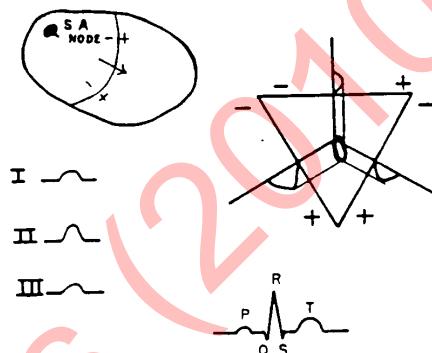


FIGURE 9

- B. During ventricular repolarization one would expect the vector to be exactly opposite to that during ventricular depolarization, i.e. a sink preceding a source instead of a source preceding a sink. However, the timing of repolarization is such that it proceeds from the outside to the inside: thus, the last part depolarized is the first to be repolarized. This restores the vector to be downward and thus in the same general direction as the R wave, i.e. positive in Einthoven leads I and II. The "normal" T vector loop is shown in Figure 10, although variations on this pattern are relatively common. Note that the repolarization of the atria gives rise to a small RT wave that is usually hidden by the QRS complex.



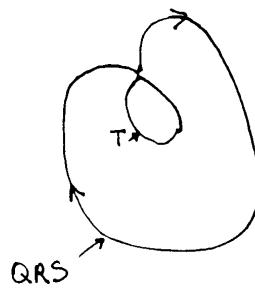


Figure 10

VII. OTHER RECORDING CONFIGURATIONS GIVE ADDITIONAL ADVANTAGES FOR QUICKLY SIZING UP ELECTRICAL FORCES

- A. The potential at each of the corners of the triangle of Einthoven (Figure 5) can also be recorded as a unipolar lead, where the potential at either RA or LA or LL is compared to a zero reference electrode. By connecting the RA, LA and LL together, Wilson provided such a reference point, the so-called Wilson central terminal. Relative to this central terminal, the exploring electrode can be positioned on any particular site of the body. These unipolar leads (V leads) give rather small signals when the potential is thus recorded on either of the three corners of the triangle and referred to the Wilson central terminal. Later, Goldberger showed that the shape of these recordings is not substantially altered by interrupting the connection between the central terminal and the site to be studied. The resulting leads augment the amplitude of the recording by 50% and are therefore called the augmented unipolar limb leads. These are designated as aVR, aVL and aVF. See Figure 11 for the arrangement of these leads and the recorded signals. For now, ignore V1-V6.

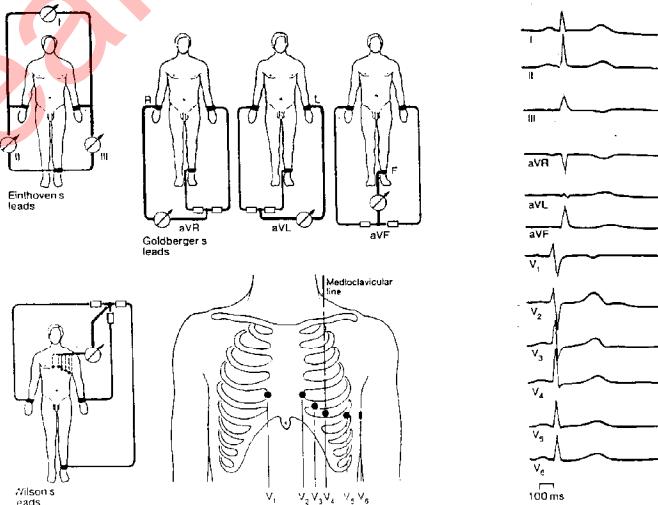


Figure 11



- B. The aVR, aVL and aVF leads are oriented on angles which exactly bisect the three corners of the Einthoven triangle as shown in Figure 12.

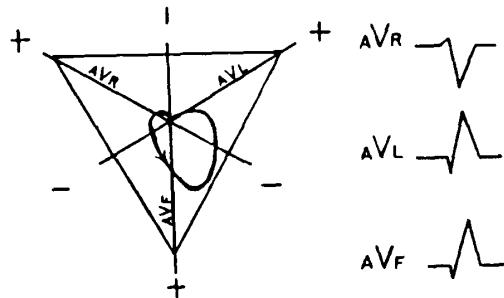


Figure 12

- C. The combination of the six standard leads in the frontal plane, i.e. I, II, III, aVR, aVL and aVF provides us with a hexaxial reference system as shown in Figure 13, which is important to determine the electrical axis of the QRS complex.

Lead	Degrees
I	0° to + 180°
aVR	+ 30° to - 150°
II	+ 60° to - 120°
aVF	+ 90° to - 90°
III	+ 120° to - 60°
aVL	+ 150° to - 30°

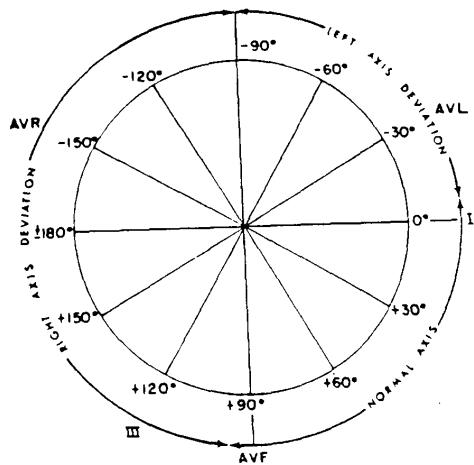


Figure 13



VIII. SIX PRECORDIAL LEADS (V1-V6) COMPLETE THE 12-LEAD ECG

- A. Thus far, all the leads discussed were in the frontal plane. Vectocardiography considers the frontal, the sagittal and the transverse plane together. Six additional unipolar electrocardiographic leads -- the precordial leads -- provide information in the transverse plane. They use as reference the central terminal of Wilson and place the exploring electrode at six sites across the precordium. These precordial leads are called V1, V2, V3, V4, V5 and V6 as shown in Figure 11. By virtue of bringing the exploring electrode much closer to the heart the typical signals recorded from V1, V2, V3, V4, V5 and V6 cannot be correctly interpreted as projections of vectors on leads which are remote as compared to the size of the dipole. On the other hand, precordial leads provide more direct information about specific sites within the ventricle.

IX. ELECTROCARDIOGRAPHY IS AN EMPIRICAL SCIENCE

- A. Finally, it is important to keep in mind that there are simplifications inherent in this explanation of the electrocardiogram and its vectorial interpretation:
1. that the electrical activity of the heart, while being the sum of many dipoles, can at any time be represented by a single dipole.
 2. that the volume conductor is an infinite one, or at least a spheric one, whereas the body has in fact a rather irregular shape.
 3. that the conductivity of the medium be homogeneous, which is definitely incorrect for the thorax.
 4. that the dipole, or the heart, be at the center of an equilateral triangle (neither is true).
 5. that the leads be at an infinite distance as compared to the size of the dipole.

The importance of the electrocardiogram ultimately rests on its diagnostic value as an empirical tool to detect alterations in cardiac rhythm, in conduction pathways, in serum electrolytes and myocardial oxygenation. This will be made clear in the ECG small group exercise.



LESIONS OF BLOOD VESSELS

Required Reading: Robbins and Cotran Pathologic Basis of Disease. 8th edition, [pp. 487-519](#).

Blood vessels can be involved by all major categories of pathology, such as Congenital, Infective, Autoimmune, Neoplastic, Traumatic, Metabolic, and Toxic mechanisms. This lecture will present only a brief introduction to the broad range of vascular diseases, with a more thorough discussion of atherosclerosis.

I. CONGENITAL VASCULAR PATHOLOGY

- A. Anomalous vasculature patterning
- B. Coarctation of aorta
- C. Hemangiomas
- D. Berry Aneurysms
- E. Arterio-venous malformations

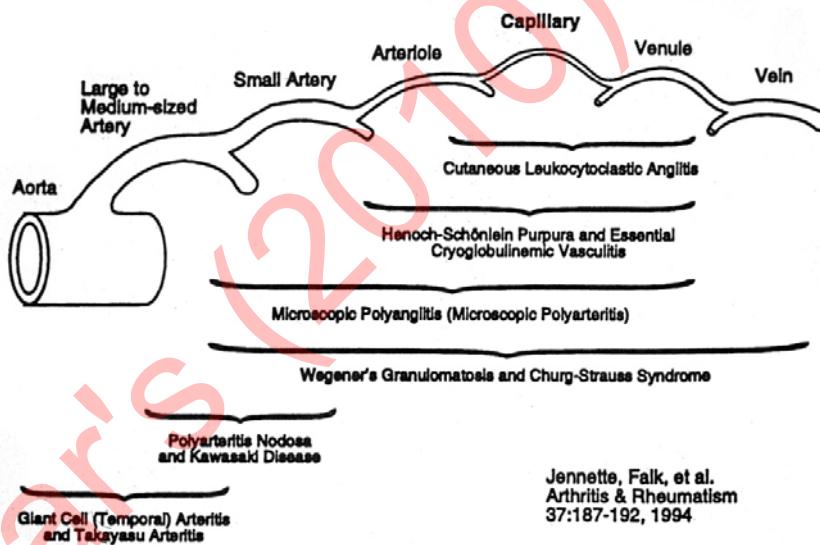
II. VASCULITIS

- A. Infective: Syphilis, TB, bacterial, fungal, rickettsial, viral.
- B. Noninfective: These are immune-mediated but they typically involve different types of patients, tissues and vessel sizes. Acute vasculitides have more necrosis, fibrin, and granulocytes. Chronic ones show lymphocytes, macrophages, plasma cells. Complications include thrombosis ± occlusion, aneurysm, or rupture. They heal with focal replacement of media and elastica. The pathogenesis is poorly understood in most of these, and they will be discussed individually later in the course.
- C. Classification based on vessel size (with some typical features of presentation):
 - 1. Large arteries: Takayasu, Giant Cell, rheumatoid, ankylosing spondylitis.
 - a. Giant Cell (Temporal) Arteritis: Cranial arteries. Older patients. Associated with polymyalgia. Cerebral and ocular ischemia. Temporal artery biopsy. Corticosteroid therapy is dramatic.
 - b. Takayasu Arteritis. Most commonly aorta. Young Asian women. "Pulseless disease."
 - 2. Medium arteries: PAN, Kawasaki, Wegener's, Churg-Strauss, rheumatoid, SLE



- a. Polyarteritis nodosa. Acute and healing lesions coexist. Renal and cardiac involvement especially. Middle-aged men especially.
- b. Kawasaki - Infants and young children, Japan especially. Coronary arteries, sudden cardiac death. "Mucocutaneous lymph node syndrome".
- 3. Small vessel: serum sickness, H-S purpura, cryoglobulinemia, drug-induced angiitis
 - a. Generalized: Microscopic polyarteritis
 - b. Cutaneous (chiefly): Henoch - Schönlein purpura; Erythema nodosum.
 - c. Respiratory tract : Wegener's
 - d. With lots of eosinophils: Löffler's.
 - e. With granulomas: Churg-Strauss and Wegner's.

Vessel sizes typically involved in the vasculitides:



III. ARTERIOSCLEROSIS

Arteriosclerosis refers to stiffening of arterial walls ("hardening of the arteries"), and can be due to changes in the intima, media, or adventitia. The stiffening is caused by hyperplasia of cells, increased extracellular matrix, deposition of proteins, or mineralization. In many forms of arteriosclerosis, the stiffening is due to a wound healing response to chronic injury to the blood vessel wall. Often the stiffening is associated with stenosis of the vessel lumen, but aneurysm can also occur.



The various forms of arteriosclerosis cause more disease and death in western civilization than lesions of any other system, by far. The vast majority of these lesions are avoidable, or at least readily delayed.

- A. Forms of Arteriosclerosis (Stiffening of arterial wall, often with stenosis)
 - 1. Atherosclerosis: A type of arteriosclerosis involving larger arteries with lipid deposition and inflammation.
 - 2. Arteriosclerosis of vascular interventions: Intimal or medial thickening in response to angioplasty, stents, anastomosis, or autologous grafts.
 - 3. Graft arteriosclerosis: Due to immunologic injury to arteries in non-autologous organ transplants.
 - 4. Arteriolosclerosis: Sclerosis of small arteries and arterioles, usually due to hypertension or diabetes.
 - a. Hyaline arteriolosclerosis due to deposition of plasma proteins and extracellular matrix in the wall (in elderly and hypertensives)
 - b. Hyperplastic arteriolosclerosis (onion-skinning) due to smooth muscle hyperplasia (in severe hypertension. DBP>120 mmHg).
 - 5. "Medial" arteriosclerosis: Due to disease of the media without significant accompanying intimal pathology:
 - a. Fibrosis, calcification (e.g. Moenckeberg);
 - b. Muscular hypertrophy (hypertension);
 - c. Protein deposits (amyloidosis, diabetes, advanced age)

IV. ATHEROSCLEROSIS

Atherosclerosis is the primary cause of heart disease, stroke, and kidney disease, causing more than 50% of deaths in our country. It is a chronic disease that has a complicated multifactorial etiology with a variable presentation.

Hyperlipidemia, inflammation, and thrombosis are key mechanisms in vascular injury and repair, which underlie atherosclerosis. You will see we've begun to appreciate the roles of many contributing mechanistic factors including: fluid forces, lipid oxidation, endothelial activation, endothelial adhesion molecules, lymphocyte and macrophage recruitment, growth factors, and cytokines.

There have been many efforts to establish other causative agents, including elevations of homocysteine, but the most important factors in atherosclerosis continue to be the "classic" ones: serum lipid levels, hypertension, diabetes, smoking, family history, age, and male sex.



- A. Major Factors in Atherogenesis (Cardinal Risk Factors):
 - 1. Hyperlipidemia (total Cholesterol > 200mg%; elevated LDL/HDL)
 - 2. Hypertension
 - 3. Diabetes (Types 1 and 2)
 - 4. Smoking
 - 5. Family History
 - 6. Age
 - 7. Male Sex
- B. Other Independent Factors:
 - 1. Homocysteine (plasma level > 12 uM)
 - 2. Inflammation markers (such as C-reactive protein or IL6; although it arguable whether this is merely a marker of disease)
- C. The Injury and Repair Hypothesis:
 - 1. Endothelial injury is caused by combinations of:
 - a. Hyperlipidemia
 - b. Hypertension
 - c. Local Hemodynamic Factors
 - d. Smoking
 - e. Homocysteine
 - f. Cyclosporin and other drugs
 - g. Immune Reactions (Transplant, Systemic Sclerosis)
 - h. Radiation Damage
 - 2. Intimal hyperplasia is a wound healing response to endothelial injury.
 - 3. Elevated lipids (i.e. unless very low) lead to lipid insudation into the intimal wound healing, and a cycle of lipid injury to endothelium and lipid deposition.
- D. Natural History of Fatty Streak:
 - 1. Endothelial stress, injury (multifactorial), and activation
 - 2. Oxidized phospholipid trapped in subendothelium
 - 3. Monocyte transmigration and foam cell formation
 - 4. Release of chemokines by foam cells.
 - 5. More endothelial activation.
 - 6. More monocyte and lymphocyte recruitment.



E. Role of Endothelium:

1. A selective semipermeable barrier of relatively quiescent cells.
2. Integration of sensory and effector functions
3. Regulates thrombosis, inflammation, vascular tone, and vascular cell growth
4. Vulnerable to injury from common agents like smoking, abnormal serum lipids, homocysteine levels, etc.
5. Localization of atherosclerotic lesions due to pressure, flow rate, turbulence

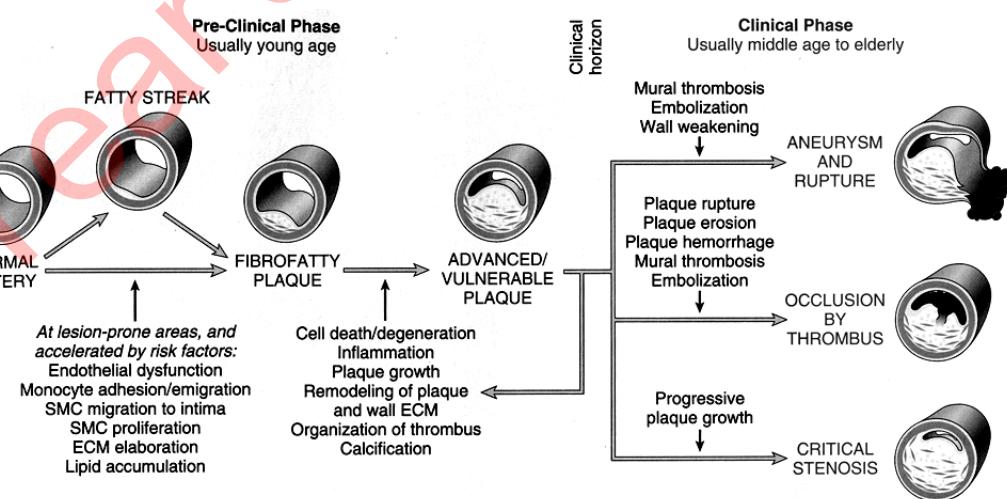
F. Lipid Deposition in Intima:

1. Small LDL particles can pass across injured endothelium
2. Atherosclerosis is associated with abnormal serum lipid levels and lipid metabolism [high LDL, low HDL, lipoprotein(a), and lipid oxidation]
3. Reduction of ischemic events by LDL-lowering Rx, and HDL elevation Rx
4. Atheromas regress with aggressive lipid lowering

G. Inflammatory Elements:

1. Atherosclerosis is associated with elevated serum levels of IL6, C-Reactive Protein, Serum Amyloid A and other acute phase proteins
2. Reactive T lymphocytes, monocytes are present within lesions.

H. Progression of Atherosclerotic lesions:



- I. Role of Thrombosis
 - 1. Thrombosis is a regular feature of ulcerated plaques, and organization of mural thrombi may contribute to bursts of plaque thickening.
 - 2. Sudden ischemic events are due to thrombosis at sites of atherosclerotic plaque degeneration (Plaque rupture or erosion).
 - 3. "Vulnerable" plaques, which are more likely to rupture, have thin fibrous caps over large lipid-laden intimal deposits.
 - 4. Increases in platelet reactivity, fibrinogen, vWF, and PAI-1 are associated with more acute ischemic events, due to more occlusive thrombi.
 - 5. Women have more vasospasm and plaque erosion, and less plaque rupture, than men.
 - 6. Therapeutic anticoagulation reduces ischemic events.
- J. Stabilization and regression:
 - 1. Atherosclerosis is a dynamic balance of progression and resolution.
 - 2. Removal of risk factors can slow progression, and convert vulnerable plaques to stable plaques.
 - 3. Aggressive lipid lowering can decrease plaque thickness.
- K. Consequences and Complications:
 - 1. Fixed Stenosis: critical narrowing with malfunction or atrophy of supplied tissues. If tissue demand for oxygen goes up and supply of oxygen cannot, this can lead to ischemia or infarction (e.g. angina or subendocardial myocardial infarction, respectively).
 - 2. Plaque rupture: atherosclerotic plaque ruptures causing immediate thrombosis due to blood mixing with thrombogenic atheromatous debris. Most common cause of myocardial infarction and unstable angina (at rest).
 - 3. Embolization of atherosclerotic debris or mural thrombus.
 - 4. Dissection: blood enters intimal defect under pressure and splits tissue planes, often in the media.
 - 5. Aneurysm +/- rupture with hemorrhage
- L. Management:
 - 1. Decrease Risk Factors that are controllable.
 - a. Stop Smoking
 - b. Control Plasma Cholesterol/Lipoproteins
 - c. Control Hypertension



- d. Exercise
 - e. Decrease Obesity (particularly intra-abdominal fat)
 - f. Control Diabetes (esp. Type II)
2. Preventive Medicines:
 - a. Aspirin (and maybe Clopidogrel, which blocks platelet ADP receptor) prevents thrombosis.
 - b. Statins improve lipoprotein profile and possibly decrease inflammation in atheromas.
 - c. Antihypertensives.
 3. Therapeutic options during acute ischemic syndromes:
 - a. Fibrinolytics (Streptokinase or tPA),
 - b. Antiplatelet agents (anti-lib/IIa, aspirin, clopidogrel, and dipyridamole) Interventional Cardiology: angioplasty, atherectomy & stents

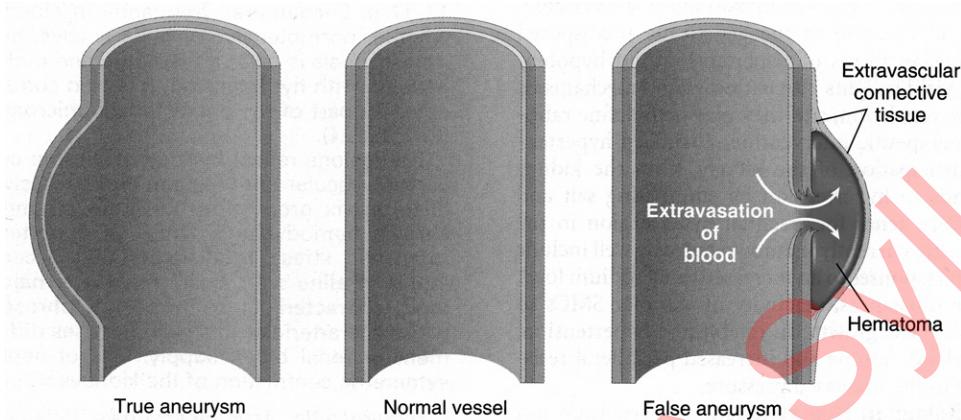
V. DISEASES OF THE AORTA

- A. Aneurysms: Most often in the infrarenal aorta. Medical management is recommended for small aneurysms. Surgical management is recommended for larger diameter ones, which are at risk for catastrophic rupture.
- B. Dissections:
 1. Associated with diseases that weaken the wall:
 - a. Atherosclerosis
 - b. Marfan, Ehler-Danlos and other matrix protein abnormalities.
 - c. Hypertension
 - d. Aortic Valve disease
 2. Classifications:
 - a. DeBakey (Types I-III): Old system
 - b. Stanford (Types A & B): Stanford A originates within or proximal to the aortic arch and usually requires surgery; Stanford B originates after the arch and can usually be managed medically.
 3. Intimal tear usually connects with a dissection plane along outer 2/3 of medial layer. Usually presents with chest pain, sometimes described as "ripping."
 4. Complications include hemorrhage, rupture, compression of nearby viscera, and branch occlusion, leading to the associated signs and symptoms.

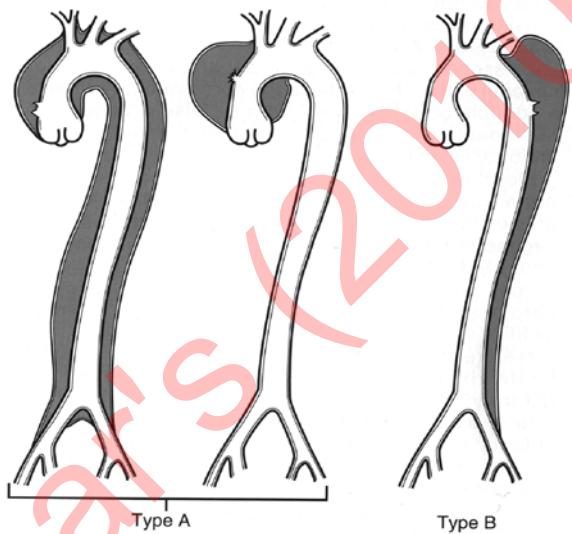


C. Rupture:

Note: A “false aneurysm” is really a contained perivascular hematoma that communicates with the lumen and mimics an aneurysm.



Aortic Dissections Stanford Types A and B:



THROMBOSIS, EMBOLISM, AND INFARCTION

Required Reading: Robbins and Cotran Pathologic Basis of Disease. 8th edition, [pp. 115-129](#).

I. INTRODUCTION

Vascular diseases can involve blood vessels of all sizes throughout the body. Some of the consequences of these diseases are due to local changes around the blood vessel, such as edema and hemorrhage, while other consequences are due to changes in tissue perfusion. The most common cause of severe morbidity and mortality in our society is inadequate tissue perfusion due to arterial lesions, causing heart attacks, strokes, pulmonary emboli, renal failure and blindness. As a final common pathway, inadequate tissue perfusion is usually the ultimate cause of death.

All tissues require nourishment; hence any may be affected by changes in the blood vessels meant to supply them. In this lecture we will cover obstructions from components of the blood, while obstructions from changes in the vessel wall will be covered more in the second lecture.

Mechanisms of Impaired Blood Flow:

- A. Obstruction from a component in the blood:
 - 1. Embolus: something circulating in the blood that can occlude a vessel.
 - 2. Thrombus: pathologic coagulated blood arising inside a blood vessel.
- B. Obstruction from changes in the vessel wall:
 - 1. Atherosclerosis
 - 2. Proliferative arteriosclerosis
 - 3. Dissection
 - 4. Vasospasm
- C. External compression:
 - 1. Tumor
 - 2. Torsion
 - 3. Increased tissue pressure
 - 4. Increased pressure on body parts (e.g. pressure sores or tourniquet)



- D. Disruption of a blood vessel
 - 1. Incision (cut)
 - 2. Laceration (traumatic tear)
 - 3. Avulsion (pulled off)

II. THROMBOSIS

A HEMOSTATIC PLUG is a physiologic plug of coagulated blood that stops blood loss. The steps in hemostasis have negative regulators in the blood and blood vessel wall that limit the extent of propagation, preventing excessive vascular occlusion. A THROMBUS is a pathologic intravascular plug of coagulated blood caused by combinations of vessel wall abnormalities, blood hypercoagulability, or abnormal blood flow (Virchow's Triad). Thrombosis may either partially occlude a vessel (MURAL THROMBUS) or totally block it (OCCLUSIVE THROMBUS). A HEMATOMA is coagulated extravascular blood that is in tissue, while CLOT is a coagulated collection of blood present in a body cavity or topologically outside your body.

A. Varieties of blood coagulation:

Hemostatic Plug	Thrombus	Hematoma*	Blood Clot
From blood coagulation at site of trauma	From blood coagulation at site of vascular pathology	From blood loss into tissues	From blood loss to outside the body or into a body cavity
Associated with blood vessel wall	Associated with blood vessel wall	Extravascular but in tissue	Ex vivo or in a cavity.
Tightly adherent	Adherent projecting into lumen	Surrounded by tissue	Non-adherent
Physiologic Response	Pathologic	Pathologic	
Layered, part of vessel wall healing	Layered	Homogeneous at first, then resorbed from edges	Homogeneous, red

*Or other blood extravasations: Hemorrhage, Bruise, Ecchymosis, Purpura, Petechiae...

B. Steps in Hemostasis:

- 1. Vasoconstriction mediated by stimulation of vascular smooth muscle by peripheral nerves and factors released by platelets.
- 2. Primary Hemostasis mediated by initial platelet deposition on exposed extracellular matrix.
- 3. Secondary Hemostasis mediated by the coagulation cascade with formation of thrombin and fibrin.



4. Resolution with cessation of hemostatic cascades and lysis of loosely adherent platelets and fibrin. This is abnormal in Thrombosis, leading to pathologic amounts of coagulation in the lumen.
- C. Virchow's Triad (Factors Predisposing to Thrombosis):
1. Changes in the vessel wall.
 2. Changes in the pattern of blood flow.
 3. Changes in the constituents of blood.

III. EMBOLISM

EMBOLISM: A partial or complete obstruction of some part of the vascular system by any mass carried there in the circulation. The transported material is an embolus. The most frequent type of embolus is a detached thrombus.

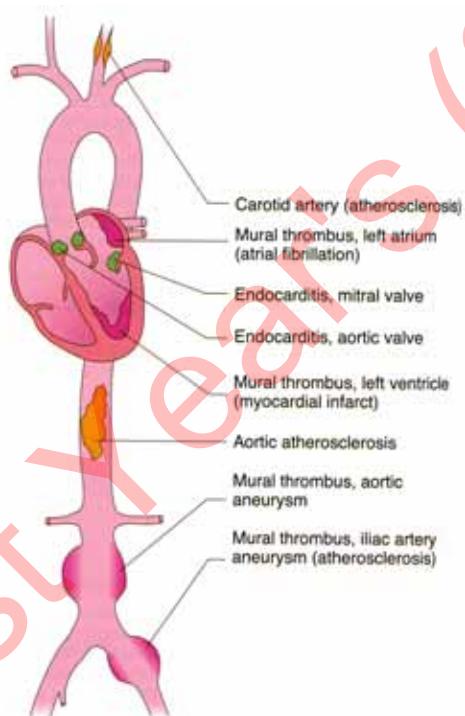
- A. Types of emboli: Emboli are classified as solid (detached thrombi, tissue fragments, clumps of tumor cells, etc.), liquid (fat globules) or gaseous. They may be bland or infected. They may be venous, arterial or lymphatic. A paradoxical embolus is one which arises in the venous circulation but enters the arterial or vice versa, through an Arterio-Venous (A-V) fistula or septal defect in the heart.
1. Pulmonary embolism: Originate commonly from thrombi in veins of lower extremities, pelvis and right heart. These range from tiny, involving arterioles, to massive, involving the main pulmonary artery or its major branches. The possible effects of pulmonary embolism include sudden death, infarction, or hemorrhage of the lung. Chronic embolization can lead to pulmonary hypertension.
 2. Systemic arterial emboli: Are usually derived from mural thrombi in the left atrium or left ventricle, vegetations on mitral or aortic valves, atheromatous plaques or aortic aneurysms. Vascular occlusions are most frequent in the spleen, kidneys, brain, bowel, heart, and lower extremities, leading to infarction.
 3. Fat embolism: The most common cause of fat embolism is bone trauma, e.g. fractured femur, but may occur in adipose tissue contusions, burns or decompression sickness with embolization to pulmonary vessels.
 4. Amniotic fluid embolism: An uncommon complication of childbirth which results in embolism of epithelial squamous cells, mucus and lanugo hairs to pulmonary vessels of the mother.



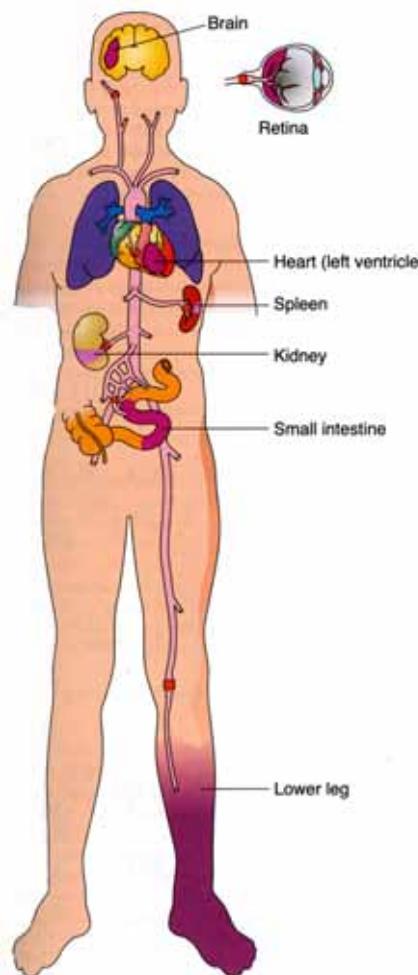
5. Air embolism: Pulmonary air embolism occurs when air is sucked into thoracic veins (at negative pressures during inspiration) as a result of cannulation, surgery or injury. The effect depends on the amount: 100-150 cc is required to produce death in an adult. Mechanism of death is blockage of right ventricular outflow. Systemic air embolism occurs when air enters the left-sided circulation during penetrating wounds, surgery, etc. In life this is manifested by bubbles in retinal vessels, skin mottling and tongue pallor. Decompression sickness ("bends") is due to gas emboli created by desaturation bubbles of nitrogen gas.
6. Other types of embolism: Placental fragments, clumps of tumor cells, bacteria, parasites, foreign bodies, bullets, shrapnel, barium sulfate (from radiology), catheter tips, etc., all may inadvertently enter the blood stream and become emboli. Some emboli are created purposely in arteries supplying tumors or vascular malformations by interventional radiologists using thrombogenic material.

B. Arterial Embolism:

Sources:



Infarcts:



IV. ISCHEMIA

Tissues receiving insufficient perfusion are said to be ISCHEMIC (G. Ischo to keep back haima blood). In contrast, HYPOXIA refers to insufficient oxygen supply, which is often due to ischemia, but may also be due to poorly oxygenated blood, etc. Those tissues with higher metabolic rate, like renal tubules and myocardium, are more vulnerable to damage during ischemia, as are those with only terminal vasculature. Tissues with COLLATERAL supply (dual circulation) and/or low metabolic rate, e.g. fibrous tissue, are less vulnerable.

Severe and sudden ischemia causes rapid cell death (NECROSIS), with relatively good morphologic preservation initially, called COAGULATIVE NECROSIS. The process is called INFARCTION, and the lesion itself, an INFARCT (e.g. heart attack or stroke). Slower and lesser degrees of ischemia may cause pain (e.g. angina pectoris), malfunction, (myocardial stunning with heart failure or transient renal failure) and, if prolonged, ATROPHY.

Restoration of blood flow (REPERFUSION) may paradoxically cause additional tissue injury by liberation of oxygen radicals. Removal of individually injured cells is accomplished by an orderly program of cell death, APOPTOSIS.

INFARCTS are irreversible and heal, given time, by phagocytosis of cell debris, regeneration, and fibrosis. The loss of tissue, amount of tissue regeneration possible, and size/location of SCAR determine the long-term effect of the lesion. Stunning and atrophy are largely reversible.

Morphology of Infarcts: Infarcts may be recent or old, bland or infected (septic). The shape of infarcts depends on the distribution of tissue downstream from the occlude vessel. They are often wedge-shaped with the wide base towards the periphery of the organ. In some organs, such as the heart, the pattern is more irregular. Infarcts are usually pale but may become hemorrhagic if there is either a minor collateral circulation (e.g., lung) or reperfusion after irreversible damage has been done. When an infarct extends to a serosal surface, it is covered by fibrinous (fibrin-containing) exudate initially, which may then cause fibrous (collagen-containing) adhesions as it heals.

In most infarcts, inflammatory cells are noted in the periphery of large lesions, because that is where the remaining arterial circulation allows delivery of leukocytes. In the first few days neutrophils predominate, and then macrophages and fibroblasts appear until the lesion is replaced by fibrosis (scar). Old infarcts tend to be pale, shrunken and depressed beneath the surface of the organ.



Clinical effects of infarcts: The most obvious effects are loss of function consistent with the amount of an organ that is compromised. Edema of the surrounding tissues can cause severe problems when the tissue compartment is constrained, such as in stroke or compartments of the extremities. Pain is a common acute manifestation of infarction. Fever and leukocytosis (rise in circulating white cells) are common. Bleeding may occur from mucosal surfaces of infarcted organs, such as hematuria (blood in urine), hemoptysis (blood in sputum), and intestinal bleeding from renal, lung, and bowel infarcts respectively.

Last Year's (2010) Syllabus



CARDIAC REFLEXES

PHYSIOLOGY BASIC PRINCIPLES - CARDIAC REFLEXES

The purpose of this session is to review the various reflex mechanisms that regulate cardiovascular function. The cardiovascular system is responsible for transporting nutrients, oxygen, carbon dioxide and non-useable metabolic products between various organs in the body. The demands on the cardiovascular system vary greatly during a "normal day" for most of us. Getting out of bed in the morning requires major changes in the cardiovascular system. The lecture will primarily focus on the autonomic nervous system and its role in regulating cardiac function. In addition, some mechanisms responsible for local regulation of blood flow in peripheral vessels will be discussed. After reviewing the basic circuitry for regulating cardiac function, we will ask members of the class to help demonstrate cardiovascular responses to minor physiologic stress. The lecture will be organized as follows:

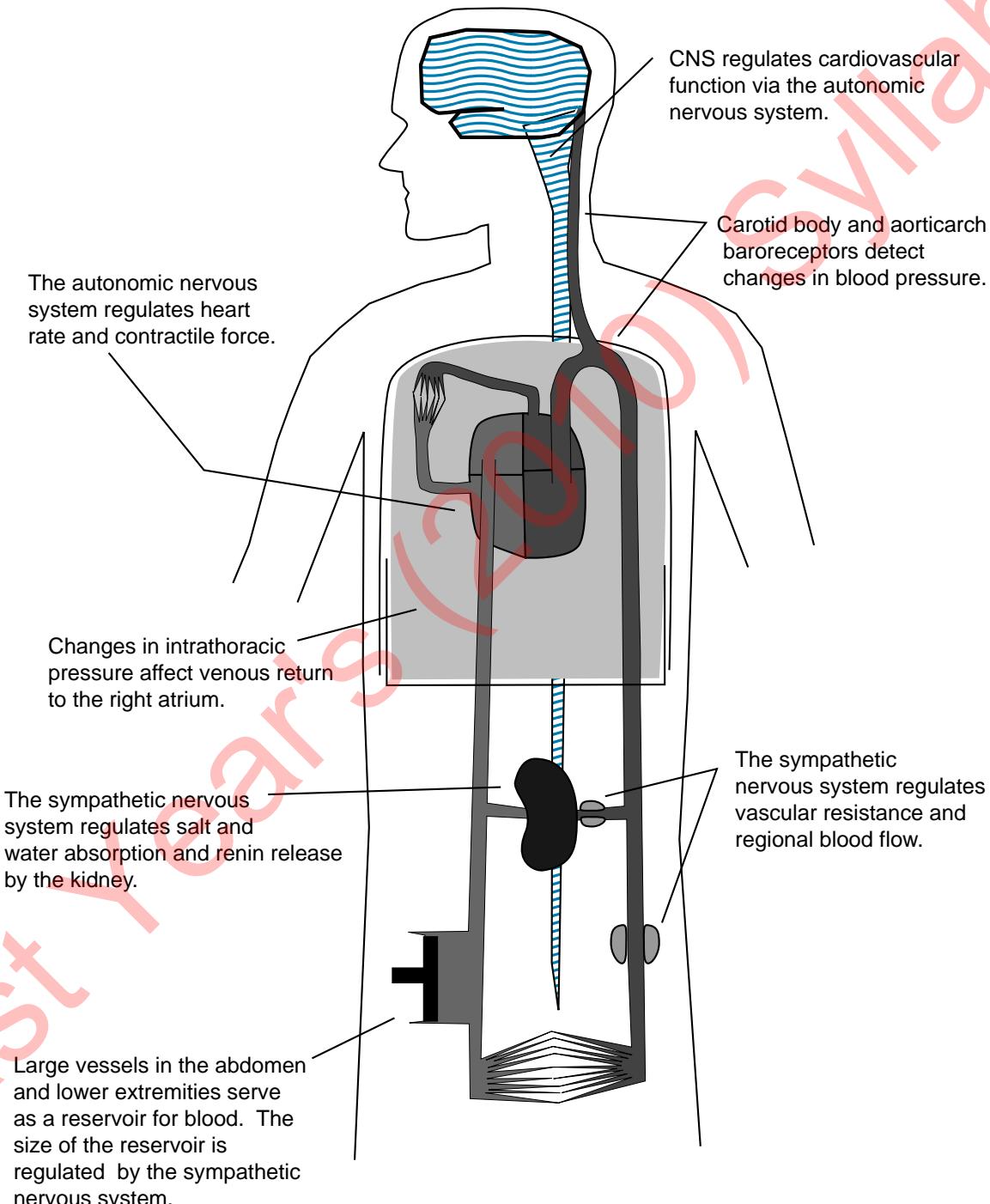
1. Cardiovascular System
2. Parasympathetic Nervous System
3. Sympathetic Nervous System
4. Receptors and Effector Systems
 - a. Receptor Subtypes
 - b. Effector Systems
 - c. Receptor Regulation
5. Sensory Pathways
 - a. Baroreceptors
 - 1) Carotid Sinus
 - b. Chemoreceptors
6. Methods to Assess Autonomic Function in Patients
7. Cardiac Reflexes in Health and Disease

I. CARDIOVASCULAR SYSTEM

- A. The cardiovascular system is a relatively simple circuit (diagrammed below). Cardiac output (the volume of blood pumped by the heart per minute) is varied by altering the heart rate or the volume of blood pumped during contraction. The heart rate is controlled by the autonomic nervous system and will be discussed below. The volume of blood pumped during each beat is determined by several factors: 1- The volume of blood delivered to the heart. The venous system serves as a reservoir of blood. The autonomic nervous system can regulate delivery of the blood from

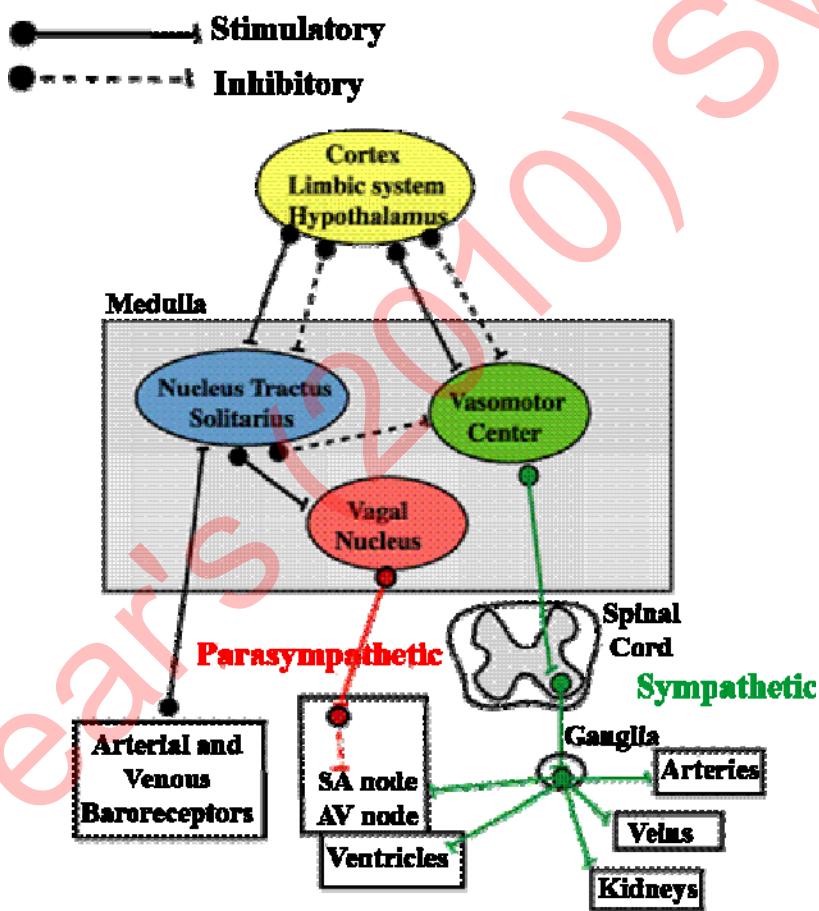


large veins to the heart. 2- The strength of contraction of the heart muscle. The autonomic nervous system can direct cardiac myocytes to change the strength of contraction. 3- The resistance to the flow of blood through the arteries. When resistance is high, the ventricle cannot empty completely and therefore delivers less volume per contraction. Arterial resistance is also regulated by the autonomic nervous system.



II. THE AUTONOMIC NERVOUS SYSTEM

- A. The central nervous system receives information about the performance of the cardiovascular system from several sources. The information is processed at several levels in the central nervous system, but the final integration is accomplished in the dorsal motor nucleus of the vagus, and the vasomotor center located in the medulla and the lower third of the pons. Adjustments in cardiovascular function are made via sympathetic and parasympathetic modulation of the heart rate, and cardiac contractility, as well as sympathetic modulation of arterial resistance, venous capacitance, and renal function.
- B. The basic circuitry is illustrated in the following figures.



- C. The autonomic nervous system consists of the sympathetic and parasympathetic nervous systems. Primary centers for control of cardiac function are found in the medulla. The vasomotor center controls the sympathetic output to the heart and blood vessels. Parasympathetic innervation of the heart originates in the dorsal motor nucleus of the vagus. Under conditions of normal cardiovascular function both sympathetic and parasympathetic



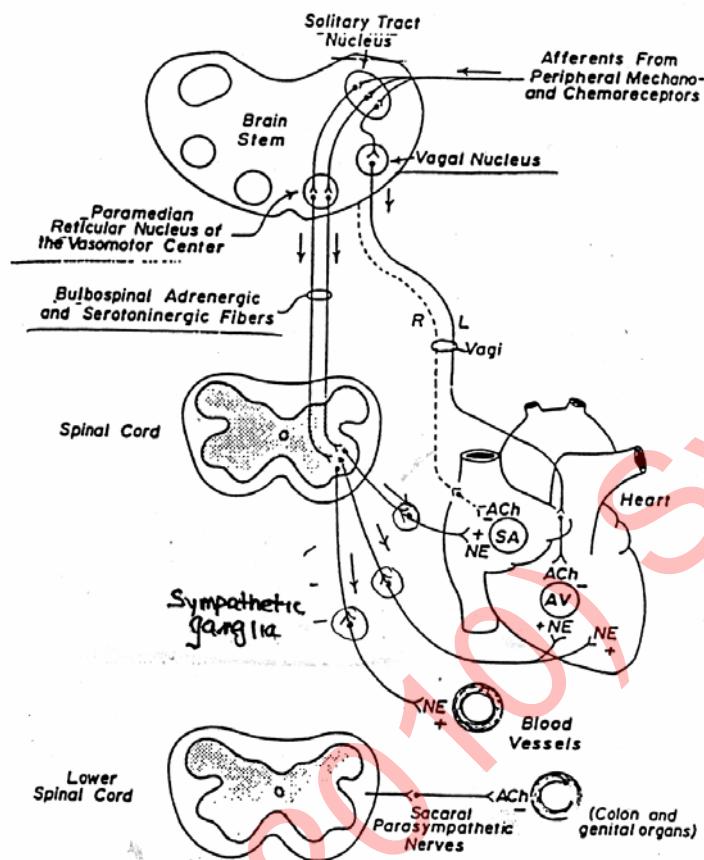
nervous systems are active. Modulation of function is accomplished by either increasing or decreasing the basal level of activity to specific organs.

- D. Higher levels of central nervous system control over cardiovascular function arise in the cerebral cortex, limbic system and the hypothalamus. These centers exert control over cardiovascular function by modulating the activity of the medullary centers.
- E. Spinal reflex circuits exist for the sympathetic nervous system. Some sympathetic control is preserved in patients with low cervical cord transections.

III. PARASYMPATHETIC SYSTEM

- A. Preganglionic fibers from the vagus nerve synapse within cardiac tissue and the short postganglionic fibers innervate the SA node, cardiac conduction tissue, vessels and muscle. Stimulation of vagal fibers innervating the heart produces a decrease in the rate of impulse generation in the SA node, a slowing of conduction within the AV node, and a mild decrease in cardiac contractility. The right vagus has a stronger influence on the SA node and the left vagus has a stronger influence on the AV node. Acetylcholine released by parasympathetic nerves around blood vessels causes vasodilatation, primarily by indirect mechanisms: acetylcholine induces the release of endothelium derived relaxation factor (EDRF or NO) from endothelium; acetylcholine also inhibits release of catecholamines from sympathetic nerve terminals. Acetylcholine released from postganglionic vagal fibers is rapidly degraded by acetylcholinesterase.





IV. SYMPATHETIC SYSTEM

- A. Sympathetic nerves originate in the intermediolateral columns of the lower cervical and upper thoracic spinal cord. The preganglionic fibers synapse in the sympathetic ganglia which lie adjacent to the vertebral column. Postganglionic fibers from sympathetic nerves innervate the SA node, conduction tissue and muscle, as well as the walls of arteries and veins. The adrenal medulla is a specialized sympathetic ganglion that releases epinephrine and norepinephrine into the systemic circulation. The neurotransmitter released from the sympathetic nerve terminal is primarily norepinephrine while both epinephrine and norepinephrine are released from the adrenal medulla. As discussed below, specific adrenergic receptor subtypes are more responsive to epinephrine while others are more responsive to norepinephrine. Increased sympathetic tone increases impulse generation in the SA node, increases the rate of impulse conduction in the AV node and the conduction system, and increases the contractility of cardiac myocytes.



Renal Nerve Stimulation Frequency (Hz)	Renin Secretion Rate	UNaV	GFR	RBF
0.25	No effect on basal, augments RSR mediated by nonneural stimuli	0	0	0
0.50	Increased without changing UNaV, GFR or RBF	0	0	0
1.00	Increased with decreased UNaV without changing GFR or RBF	↓	0	0
2.50	Increased with decreased UNaV, GFR and RBF	↓	↓	↓

- B. Most of the sympathetic nerves going to the heart either synapse in, or pass through the stellate ganglia (fusion of the last cervical and first thoracic). The right stellate ganglion has a greater effect on heart rate and the left has a greater effect on contractility. Stellate ganglion ablation has been used to treat a type of ventricular tachycardia called torsade de pointes (the long QT syndrome).
- C. Most of the resistance and capacitance vessels to skin, skeletal muscle and viscera are richly innervated by sympathetic nerves. Release of norepinephrine from sympathetic nerve terminals in these vessels leads to vasoconstriction through alpha 1 adrenergic receptors; however, during exercise, circulating epinephrine released from the adrenal medulla activates beta 2 receptors in skeletal muscle vessels leading to dilatation of these vessels. Cerebral, coronary and pulmonary vessels are poorly innervated and are poorly responsive to sympathetic stimulation. Under maximal sympathetic stimulation, blood flow to the brain, heart and lungs is preserved at the expense of other organs.



- D. The kidneys are richly innervated by sympathetic nerves. Catecholamines modulate renal blood flow, fluid and electrolyte balance and renin release.

V. RECEPTORS AND EFFECTOR SYSTEMS IN TARGET TISSUES

- A. Activation of the sympathetic nervous system under severe stress such as the fight or flight response, or strenuous, prolonged physical exertion leads to a generalized release of catecholamines (predominantly norepinephrine) from all sympathetic nerve terminals throughout the body as well as a release of catecholamines from the adrenal gland into the circulation. Nevertheless, each tissue has a specific response to these catecholamines. For example, blood vessels in skeletal muscle dilate to increase blood flow to muscles, while blood vessels in the abdominal viscera constrict, diverting blood from intestines.
- B. This organ and tissue specific response to catecholamine release is accomplished by structural and functional diversity in the family of adrenergic receptors that respond to catecholamines. Similar diversity exists in the family of muscarinic receptors that respond to acetylcholine.
- C. Muscarinic and adrenergic receptors are structurally and functionally similar plasma membrane receptors that form the interface between the autonomic nervous system and the cardiovascular system. They have seven membrane spanning domains. Activation of the receptor by neurotransmitter leads to the activation of a membrane associated GTP binding protein (G protein). The activated G protein goes on to modulate one or more cellular enzymes or ion channels.

VI. RECEPTOR SUBTYPES

- A. There are 9 subtypes of adrenergic receptors (Alpha 1a, b and c, Alpha 2 a, b and c, Beta 1, Beta 2 and Beta 3) and 5 subtypes of muscarinic receptors (m1-m5).
- B. The precise physiologic role of each receptor subtype is not yet known; however, some general functional properties can be summarized as follows:
1. Alpha 1 adrenergic receptors are found on smooth muscle cells of both capacitance and resistance vessels. Stimulation of these receptors leads to vasoconstriction resulting in an increase in peripheral vascular resistance, an increase in systemic blood pressure, and an increase in venous return to the heart. Alpha 1 receptors are also found on cardiac myocytes where stimulation leads to an increase in contractility. There is experimental evidence that



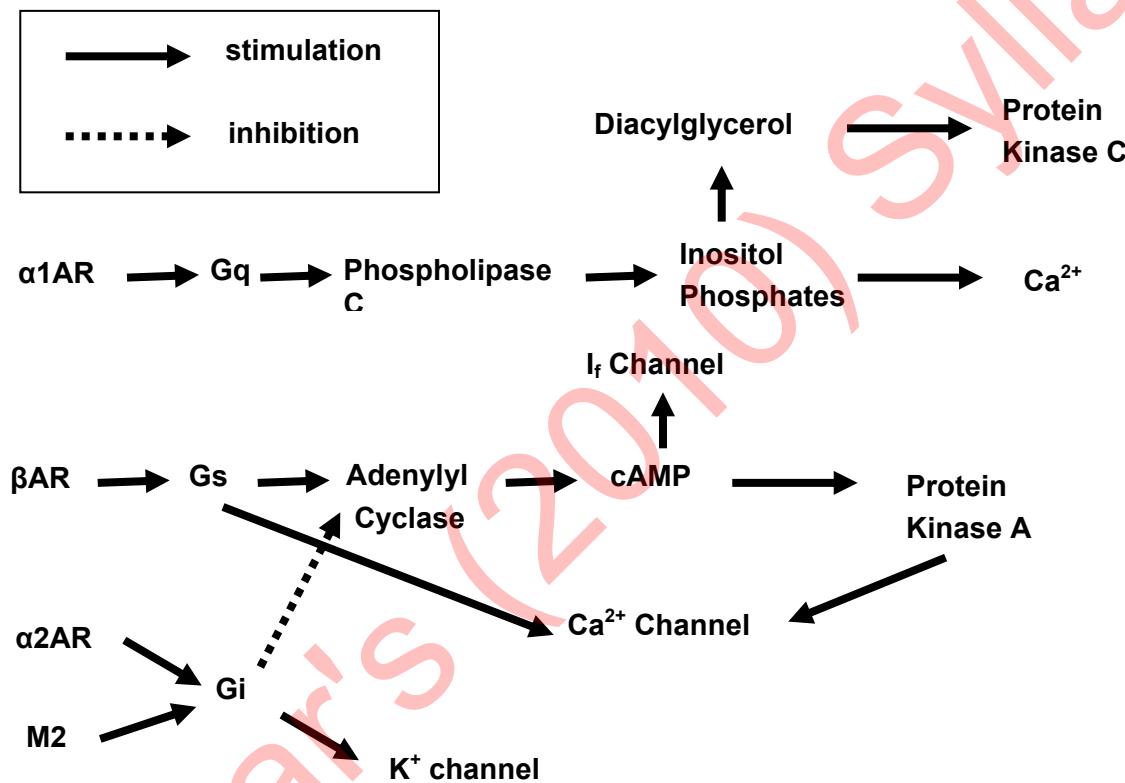
- prolonged stimulation of alpha 1 receptors on cardiac myocytes can lead to myocyte hypertrophy. The predominant effect of alpha 1 receptor stimulation (by phenylephrine) is an increase in blood pressure.
2. Alpha 2 adrenergic receptors are found throughout the sympathetic nervous system. Stimulation of alpha 2 adrenergic receptors in the brainstem vasomotor center leads to a decrease in sympathetic tone. Stimulation of alpha 2 receptors at the end of postganglionic sympathetic nerve terminals leads to an inhibition of neurotransmitter release. Alpha 2 receptors are found in some vascular beds (such as the intestines) and activation of these receptors leads to vasoconstriction. Alpha 2 receptors are found on endothelial cells in some vascular beds. Stimulation of these receptors induces the release of EDRF (NO) resulting in vasodilatation. Alpha 2 receptors are also found in the kidney where they regulate sodium and water excretion. Alpha 2 receptors have a higher affinity for epinephrine than do alpha 1 receptors, and are therefore more responsive to catecholamines released into the circulation from the adrenal medulla. The predominant effect of alpha 2 receptor stimulation (by clonidine) is a decrease in heart rate and blood pressure.
 3. Beta 1 and beta 2 receptors are found in cardiac conduction tissue and myocytes. Both are believed to influence heart rate and contractility; however, beta 1 receptors are thought to mediate most of the beta receptor effects in the heart. Chronic stimulation of cardiac beta receptors may produce structural changes in heart muscle resulting in heart failure (cardiomyopathy). The predominant effect of beta 1 receptor stimulation (by isoproterenol) is tachycardia and increased contractility.
 4. Beta 2 receptors are found in blood vessels in skeletal muscles where they mediate vasodilatation. Beta 2 receptors in the kidney may be involved in the regulation of fluid and electrolyte excretion. Beta 2 receptors have a higher affinity for epinephrine than do beta 1 receptors, and are therefore more responsive to catecholamines released into the circulation from the adrenal medulla. The predominant effect of beta 2 receptor stimulation (by isoproterenol) is a decrease in blood pressure.



5. m₂ muscarinic receptors are found in cardiac muscle, pacemaker and conduction tissue. Stimulation of these receptors leads to a slowing of impulse formation, a slowing of impulse conduction, and a mild decrease in cardiac contractility. The predominant effect of m₂ receptor inhibition (by atropine) is tachycardia.

VII. EFFECTOR SYSTEMS

- A. The receptors and the cellular effector systems modulated by the receptors are summarized below (simplified).



VIII. RECEPTOR REGULATION

- A. The function of both adrenergic and muscarinic receptors are subject to both transcriptional and posttranslational regulation. Chronic stimulation leads to loss of receptor number and function. Mechanisms for some of these processes involve changes in the transcription of receptor genes, changes in mRNA stability and phosphorylation of receptors by specific cytosolic kinases. The process of desensitization is probably required for normal physiologic function. However, in certain disease states such as heart failure, loss of beta-1 receptor function due to desensitization by high levels of circulating catecholamines may contribute to poor ventricular function. Furthermore, desensitization limits the effectiveness of certain drugs which act as agonists at adrenergic and muscarinic receptors. In the case of the alpha 2 receptor, there is a rapid attenuation to the antihypertensive effects of clonidine, probably by down regulation of alpha 2 receptors in the vasomotor center. If clonidine is suddenly withdrawn, the reduction in the number of alpha 2 receptors results in an increase in vasoconstrictor tone and a rise in blood pressure over pretreatment levels.

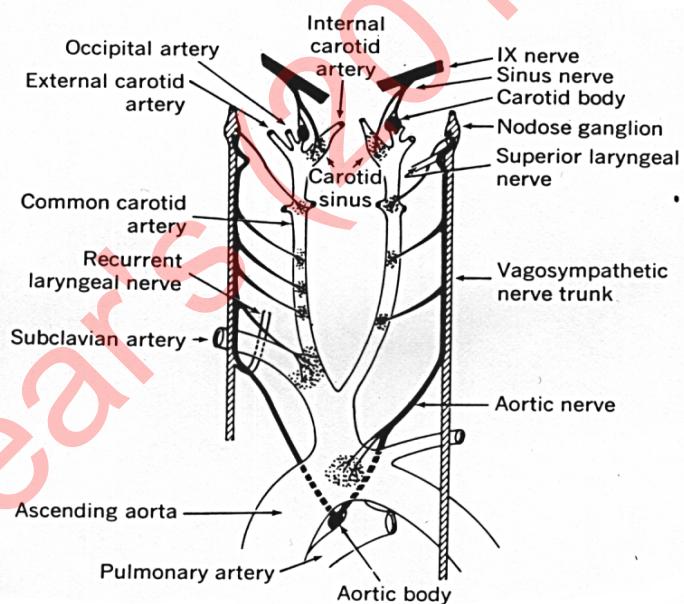


Fig. 42-1. Diagrammatic representation of location and innervation of baroreceptors and chemoreceptors of aortic and carotid regions in cat and dog.^{4,7,8} Baroreceptor areas are indicated by stippling. Nerves and arteries are labeled.



IX. SENSORY SYSTEMS

- A. Sensory input is derived from several different types of specialized mechanoreceptors designed to respond to changes in blood pressure (high pressure baroreceptors), vascular volume (low pressure baroreceptors), as well as chemoreceptors capable of responding to changes in chemical factors such as pH, pO_2 and pCO_2 which reflect the ability of cardiovascular system to deliver oxygen and remove waste. Sensory impulses are carried predominantly by the vagus nerve to the solitary tract nucleus in the medulla.

X. MECHANORECEPTORS

- A. Baroreceptors found in the carotid artery and the aortic arch have been well characterized and respond to changes in blood pressure. There is also evidence for baroreceptors in the great veins, the right atrium, and the ventricles. These receptors are responsive to changes in vascular volume. Furthermore, there are receptors in the lungs and pleura that may also be responsive to intravascular volume. Baroreceptor nerve endings are located in the adventitia and monitor arterial pressure by detecting changes in the diameter of elastic arteries. The frequency of impulses from these baroreceptors is related to the absolute diameter of the artery and the rate of increase in diameter. Pulsatile flow produces more impulses than nonpulsatile flow. After a prolonged period of increased blood pressure the baroreceptors adapt to a new "set point".



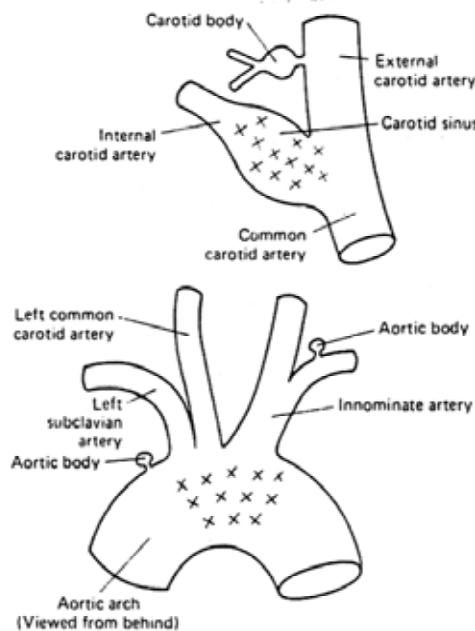


Figure 31-5. Baroreceptor areas in carotid sinus and aortic arch. The Xs identify sites where receptors are located.

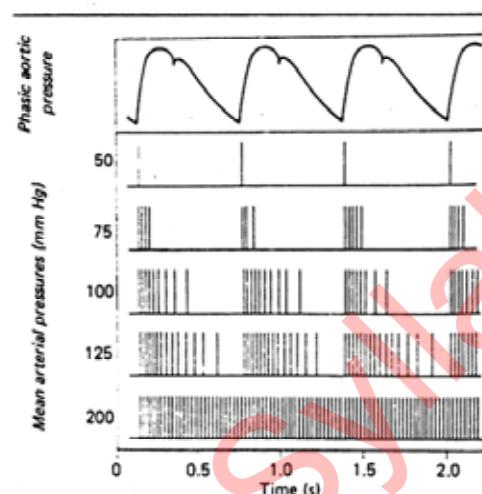


Figure 31-6. Discharges (vertical lines) in a single afferent nerve fiber from the carotid sinus at various arterial pressures, plotted against changes in aortic pressure with time. (Reproduced, with permission, from Berne RM, Levy MN: *Cardiovascular Physiology*. 3rd ed. Mosby, 1977.)

XI. CAROTID SINUS

- A. The carotid sinus is perhaps the most important baroreceptor to remember for several reasons: 1- It probably is the most important monitor of systemic blood pressure (pressure perfusing the brain); 2- Its function can easily be assessed by the clinician; 3- It can be used to diagnose and treat several arrhythmias; and 4- It can function abnormally and lead to syncope. The carotid sinus is located in the internal carotid artery just distal to the bifurcation. Mechanical stimulation of the carotid sinus by manual pressure (Carotid sinus massage) is interpreted by the vasomotor center as a sudden increase in blood pressure leading to an increase in vagal tone to the SA and AV nodes, and a decrease in sympathetic tone to resistance and capacitance vessels.

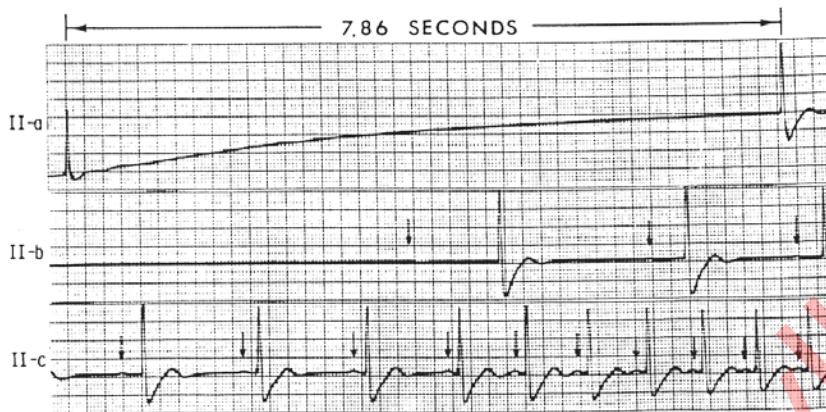


- B. Various responses of cardiac arrhythmias to carotid sinus stimulation (Table 16-1):

Arrhythmia	Response
Sinus tachycardia	1. Transient slowing of sinus (atrial) rate 2. Varying degree A-V block (less common)
Atrial tachycardia	1. Termination of arrhythmia 2. No response 3. Slowing of ventricular rate because of increased A-V block (less common) 4. Increased atrial rate because of increased A-V Block
Atrial fibrillation or flutter	Slowing of ventricular rate because of increased A-V block
A-V junctional tachycardia	1. Termination of arrhythmia
Paroxysmal	2. No response
Nonparoxysmal	No response
Ventricular tachyarrhythmias	No response (rare exceptions)
WPW syndrome	Response varies
Parasystole	Response varies
Digitalis intoxication	Carotid sinus stimulation not recommended
Hypersensitive individuals	Carotid sinus stimulation not recommended
C.	Atherosclerosis impairs the sensitivity of baroreceptors by reducing the compliance of the artery. This may in part explain the tendency for orthostatic hypotension (a symptomatic fall in blood pressure when going from a supine to a standing position) in the elderly.



D. Carotid Sinus Hypersensitivity:



1. This is a condition where mild increases in external pressure around the carotid sinus, such as might be caused by a tight shirt collar, can produce marked bradycardia and often syncope. This is often associated with tumors of the neck, prior neck surgery or radiation to the neck. The ECG rhythm strip below is from a patient with carotid sinus hypersensitivity.

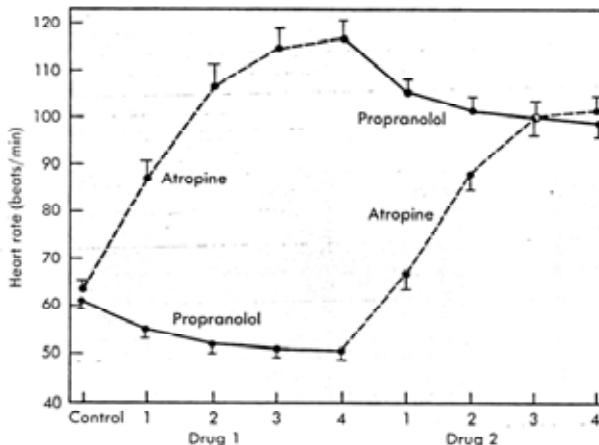
XII. CHEMORECEPTORS

Chemoreceptors are located adjacent to the carotid and aortic baroreceptors. These structures respond to a decrease in pO₂ or an increase in pCO₂. The reflex response to activation of chemoreceptors includes an increase in vagal tone to the heart and an increase in sympathetic tone to the peripheral vascular beds. These adjustments maximize perfusion of the heart and brain.

XIII. SUMMARY

- A. In a healthy subject most of the minor adjustments made in heart rate, for example from supine to standing to walking, are made by the parasympathetic nervous system. These adjustments are made by withdrawing parasympathetic tone to increase the heart rate. In contrast, changes in blood pressure are mediated primarily by the sympathetic nervous system. In general, the parasympathetic nervous system responds more rapidly to a change in body position than the sympathetic nervous system. The relative importance of the parasympathetic nervous system in regulating resting heart rate is illustrated on the following page.





■ The effects of four equal doses of atropine (0.04 mg/kg total) and of propranolol (0.2 mg/kg total) on the heart rate of 10 healthy young men (mean age, 21.9 years). In half of the trials, atropine was given first (*top curve*); in the other half, propranolol was given first (*bottom curve*). (Redrawn from Katona, P.G., McLean, M., Dighton, D.H., and Guz, A.: J. Appl. Physiol. 52:1652, 1982.)

- B. As the level of physical activity increases, the sympathetic nervous system becomes more influential. Adjustments in heart rate from resting to a normal walk are primarily accomplished by withdrawal of vagal tone, however further increases in heart rate require an increase in sympathetic tone. Catecholamines released from the adrenal medulla into the circulation and from sympathetic nerve terminals act on beta 2 receptors in skeletal muscle resistance vessels, and alone with local factors produced by muscles, lead to vasodilatation and enhance blood flow to muscles. At the same time, blood flow to the abdominal viscera including the kidneys is reduced. Furthermore, catecholamines activate receptors in renal tubules resulting in an enhanced reabsorption of salt and water. Thus, the autonomic nervous system makes the appropriate adjustments in cardiovascular function to optimize fuel and oxygen delivery to muscles, heart and brain.
- C. The autonomic nervous system is also critical for preserving vital functions in response to injury involving a large loss of an individual's blood volume. In the extreme case, blood flow to viscera, skin and muscles is severely reduced to preserve perfusion of the brain heart and lungs. In addition, catecholamines acting at alpha 2 receptors in spinal nerves have an analgesic effect. A summary of these responses is given below.



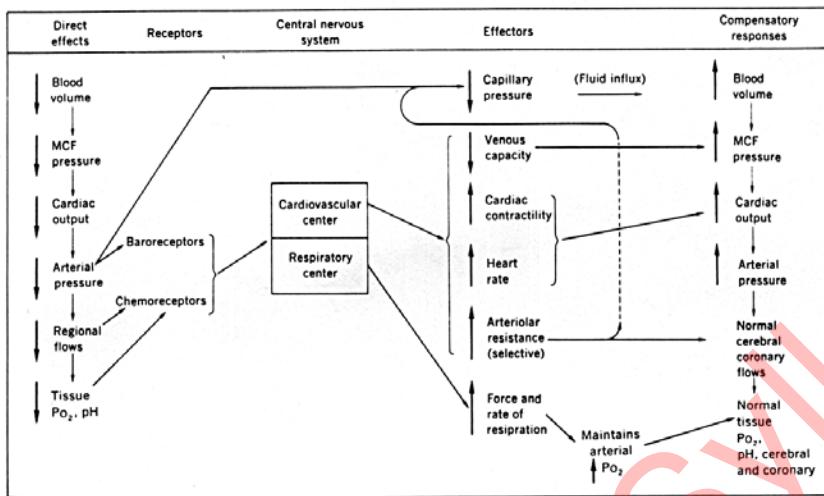


Fig. 42-14. Schematic summary of responses to hemorrhage. MCF pressure = mean circulatory filling pressure (p. 957). Compensatory responses tend to counteract direct effects of hemorrhage. Release of antidiuretic and adrenal cortical hormones is not included in diagram.

XIV. METHODS TO ASSESS AUTONOMIC FUNCTION

- A. During this session I will ask members of the group to help me demonstrate the normal function of the autonomic nervous system. The following tests are normally used to evaluate patients thought to have autonomic dysfunction. Perhaps the most common cause of autonomic dysfunction is diabetes. These tests are safe, simple and can be performed with equipment readily available in the clinic.
- B. Valsalva Maneuver: Subject sits quietly and then blows into a mouthpiece attached to a manometer to achieve a pressure of 40 mmHg for 15 s. There are four phases to the Valsalva maneuver. During phase 1 intrathoracic pressure augments ventricular pressure leading to a brief increase in arterial pressure. During phase 2 the increase in intrathoracic pressure reduces the flow of venous blood to the heart resulting in a drop in blood pressure cardiac output and therefore a drop in blood pressure. Phase 3 begins immediately after release of intrathoracic pressure resulting in a further drop in blood pressure. As a result of the reduced blood pressure during phase 2 and 3, the baroreceptor activity is reduced leading to an increase in sympathetic tone and a subsequent increase in heart rate and arterial resistance. During phase 4, there is an increase in blood flow to the heart. This combined with the increased peripheral resistance and increased contractility leads to a rapid increase in blood pressure and activation of baroreceptors leading to a decrease in sympathetic tone and an increase in vagal tone with a subsequent drop in heart rate. The Valsalva maneuver therefore tests all components of the autonomic system: afferent, parasympathetic and sympathetic.



- C. The typical response to a Valsalva is shown below.
1. The Valsalva ratio is the ratio of the longest R-R interval shortly after the maneuver to the shortest R-R interval during the maneuver.

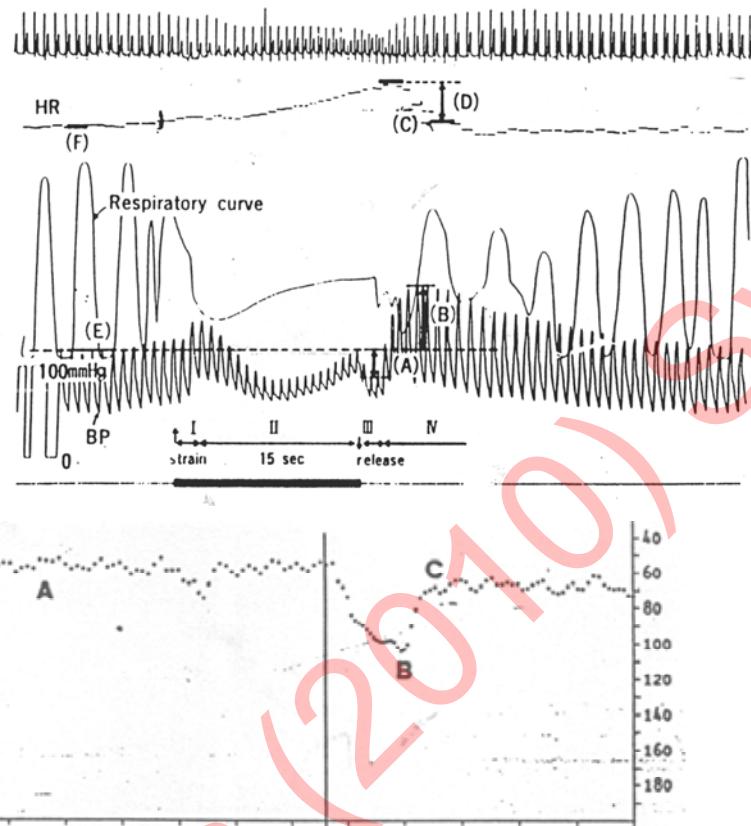


Fig. 4. The instantaneous heart rate response (beats min^{-1}) in active orthostatic test. The vertical line (S) shows the moment of standing up. Max/min ratio = length of the R-R interval (ms) at point C divided by length of the R-R interval at point B. IIHR = the instantaneous heart rate (beats min^{-1}) at point B minus that at point A.

- D. Heart rate and blood pressure response to standing:
1. The subject lies quietly for 5 minutes then stands up unaided. While supine the cardiovascular system no longer has to work against gravity and adapts to a reduced work load by decreasing peripheral resistance and increasing venous capacitance. Upon standing there is a transient drop in blood pressure (usually less than 10 mmHg) due to a decrease in venous return as blood pools in the legs. The immediate response is a decrease in parasympathetic tone resulting in an immediate increase in heart rate and an increase in sympathetic tone to resistance and capacitance vessels. In normal individuals there is an increase in heart rate that reaches a maximum at about the 15th beat after standing. This is followed by a normalization of blood pressure and a relative bradycardia that reaches a maximum



around the 30 th beat. The 30:15 ratio is the ratio of the longest R-R interval around the 30th beat to the shortest R-R interval around the 15th beat.

- E. Heart rate response to deep breathing: The subject sits quietly and breaths deeply and evenly at a rate of 6/min. The maximum and minimum rates during each breathing cycle are determined from the R-R intervals and the average difference is determined from three successive cycles.

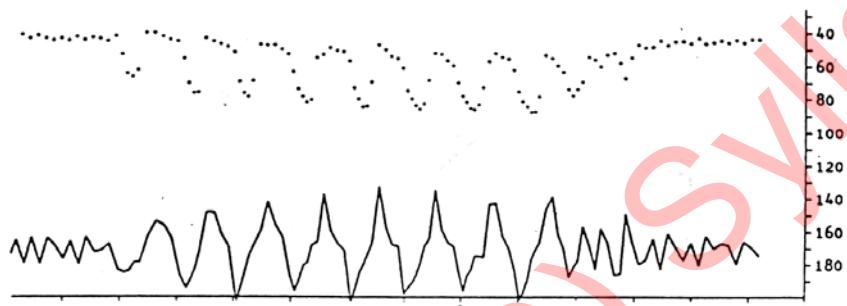


Fig. 3. The instantaneous heart rate response (beats min^{-1}) in deep breathing test. The respiration signal (lower curve) reflects the phase of respiration (downwards, inspiration; upwards, expiration).

- F. Blood pressure response to hand grip: Hand grip is maintained at 30% of maximum voluntary contraction for up to 5 min. The blood pressure is measured each minute. The difference between the diastolic blood pressure just before release of hand grip and just before starting is the response.

Results of cardiovascular autonomic function tests in normal subjects

Test	Measurement	No. of subjects		Age range (yr)	Mean \pm SD	Range	Relation to age	Previously defined values			
		All	Male					Normal	Borderline	Abnormal	
Valsalva maneuver	Valsalva ratio	135	92	43	16–69	1.75 ± 0.39	1.22–2.87	$r = 0.2$ (NS)	≥ 1.21	1.11–1.20	≤ 1.10
Lying to standing heart rate response	30:15 ratio	111	73	38	16–69	1.29 ± 0.17	1.00–1.79	$r = -0.49$ ($P < 0.001$)	≥ 1.04	1.01–1.03	≤ 1.00
Heart rate response to deep breathing	Maximum-minimum heart rate (beats/min)	71	39	32	16–65	31 ± 9	12–53	$r = -0.57$ ($P < 0.001$)	≥ 15	11–14	≤ 10
Postural blood pressure change	Fall in systolic BP (mmHg)	73	40	33	16–65	-1 ± 8	+30–15	$r = 0.16$ (NS)	≤ 10	11–29	≥ 30
Sustained handgrip test	Rise in diastolic BP (mmHg)	139	79	60	16–69	Men 34 ± 10 Women 25 ± 8	17–64 12–52	$r = 0.02$ (NS) $r = -0.35$ ($P < 0.05$)	≥ 16	11–15	≤ 10



AUTONOMIC DRUGS OVERVIEW II

Reading assignment: Katzung (10th ed.), Chapter 6

LEARNING OBJECTIVES:

- A. Continue to learn the tissue responses that follow autonomic nerve stimulation and the receptors that mediate the responses.
- B. Learn the local synaptic feedback mechanisms that regulate (1) neurotransmitter release from autonomic nerve endings and (2) responsiveness of post-synaptic cells to neurotransmitter.
- C. Learn the feedback mechanisms that control systemic blood pressure. Understand why some drugs elicit both direct and reflex effects.

I. TOPICS

- A. Responses to autonomic stimulation
- B. Feedback at the synapse
- C. Reflex control of blood pressure



Last Year's (2010) Syllabus

ECG Small Groups

I. ELECTROCARDIOGRAMS

A. Essential concepts:

1. ECG records extracellular electrical currents that result from asymmetries in membrane potential between 2 regions in the heart (e.g. one region depolarized and another polarized). Therefore when all myocytes are at the same potential (either all depolarized or all repolarized) the ECG signal will be at baseline.
2. The size of a structure affects whether or not depolarization is seen on surface ECG (you don't see small structures such as the SA or AV nodes or His bundle).

B. Normal ECG:

1. Every P wave should be followed by a QRS complex.

P wave = atrial depolarization

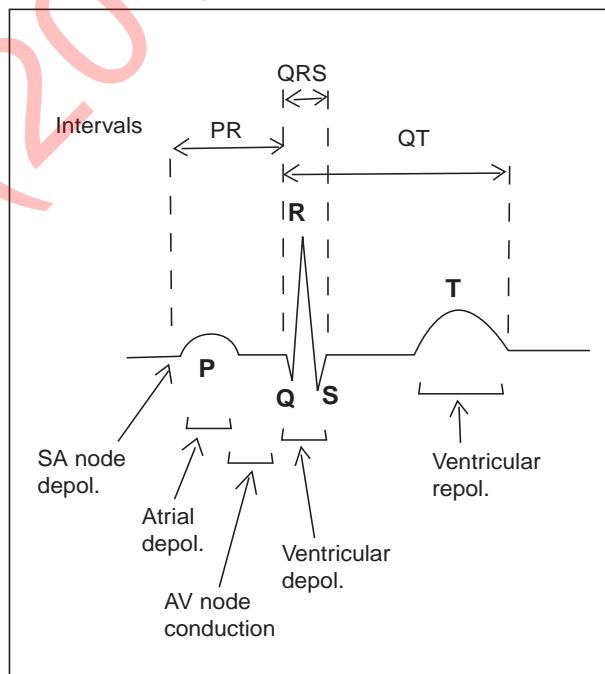
Atrial repolarization is obscured by QRS

PR interval should be between 0.15 and 0.2 seconds.

2. The duration of the QRS complex should be less than 3 small boxes (0.12 seconds) QRS complex =

ventricular dipolarization.

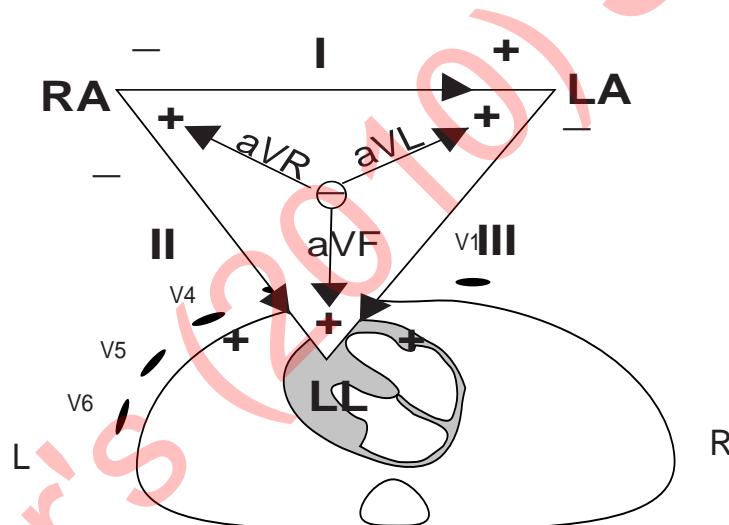
The Q wave is defined as a downward deflection at the beginning of the QRS complex. It is never preceded by an upward deflection (an R wave). An S wave is a downward deflection that is preceded by an R wave. QRS complexes don't need to have all elements (Q, R, S).



3. The ST segment corresponds with ventricular contraction and the plateau phase of the action potential.



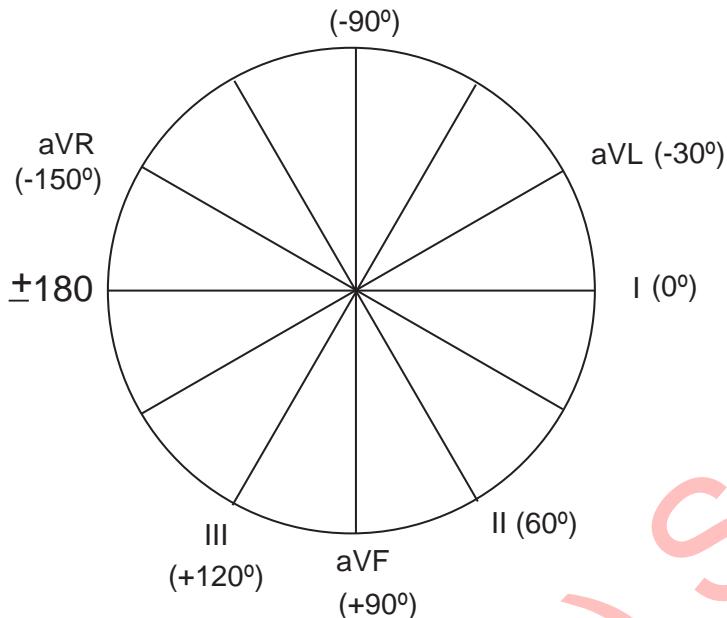
4. The T wave normally is in the same direction as the QRS complex because ventricular depolarization proceeds from endocardium to epicardium while repolarization proceeds from epicardium to endocardium.
 5. The QT interval depends on heart rate. A rough rule-of-thumb is that the QT interval should be less than half of the R-R interval.
 6. Heart rate: determine the number of large squares between two QRS complexes (the R-R interval). The rate = $300/\text{R-R interval}$ (in number of squares).
- C. Standard EKG leads:
1. Limb leads look at frontal plane:
Einthoven bipolar leads: I, II, III
Augmented unipolar leads: aVR, aVL, aVF



Cross section looking from head towards feet

2. Chest leads look at horizontal plane: V1, V2, V3, V4, V5, V6





D. QRS Axis:

1. Vectors are used to indicate the magnitude and direction of depolarization. The QRS complex is the sum of all depolarization vectors over time. A positive QRS complex in a lead means that the sum of all vectors is moving in the direction of that lead.
2. The QRS axis is a reflection of the direction of depolarization and provides information about the position of the heart in the chest, the relative thickness of the ventricles, previous infarction and abnormalities in the conduction system.
3. To determine the axis, inspect the limb leads and find the lead with the smallest QRS (called the isoelectric lead). The QRS axis will be perpendicular to this lead. For example if the QRS in lead I is small (isoelectric) and positive in lead aVF, the axis will be close to 90°.
4. The normal axis is -30° to $+90^\circ$ (it varies with age). Left axis deviation is from -30° to -90° . Right axis deviation is from 90° to 180° . Extreme left axis deviation is from -90° to 180° .



Last Year's (2010) Syllabus

Autonomic Drugs: Cholinomimetic Drugs

Reading assignment: Katzung (10th ed), Ch. 7

LEARNING OBJECTIVES:

- A. Continue to learn the tissue distribution of nicotinic cholinergic receptors and muscarinic cholinergic receptors and the responses that occur following administration of an agonist.
- B. Understand how drugs may influence the action of acetylcholine, producing beneficial an/or undesirable effects.
- C. Learn the catalytic cycle of acetylcholinesterase and the pharmacology of drugs that inhibit the enzyme.
- D. Understand why the issue of drug selectivity (or lack thereof) affects the clinical use of the drugs discussed in this session.

TOPICS

- A. Cholinergic receptor agonists
- B. Inhibitors of acetylcholinesterase
- C. Pralidoxime



Last Year's (2010) Syllabus

CARDIAC MUSCLE MECHANICS

OBJECTIVES

- A. Definition of actin-myosin sliding filament model.
- B. Understanding of the relationship between this model and the Frank-Starling effect.
- C. Understanding of the two major mechanisms governing cardiac performance:
 - 1. Frank-Starling effect
 - 2. Changes in contractility
- D. Understanding the Force-Length relationship in papillary muscle.
- E. Understanding the Force-Velocity relationship in papillary muscle.
- F. Translation of papillary muscle Physiology to intact heart:
 - 1. Pressure-Volume Loop

I. OVERVIEW

- A. A number of indices have been developed to describe the performance of cardiac muscle. Such studies have been carried out on strips of isolated heart muscle in a muscle bath in vitro. A common preparation used is the right ventricular papillary muscle of small animals. The parallel fiber arrangement of the papillary muscle avoids the problems of complex geometry and fiber direction in the intact heart. The various indices which have been developed reflect the two basic mechanical properties of heart muscle: its ability to shorten and to develop force.
- B. Cardiac muscle performance can be altered by two major mechanisms. The first is by starting at a different initial muscle length. This phenomenon is often referred to as the Frank-Starling mechanism. The second mechanism is by changing the contractile state of the muscle. For example, catecholamines (i.e. adrenaline) increase cardiac contractile state.
- C. In the intact heart, the performance of the heart is primarily determined by four variables: preload, afterload, contractile state, and heart rate.
 - 1. Preload as defined in isolated heart muscle studies, is the resting force stretching the muscle to a given initial length. Changes in the resting force or length of the muscle, therefore, are often used as indicators of changes in preload.



2. Afterload is defined in isolated heart muscle studies as the additional force the heart has to generate in order to shorten. In terms of the intact heart, the afterload is analogous to the aortic pressure, since the left ventricle must generate that pressure before it can eject blood.
3. Contractile state refers to the vigor of contraction. When loading conditions are kept constant, it is often measured as a change in the velocity of shortening or in the rate of force development.

II. STRUCTURE-FUNCTION RELATIONSHIPS

- A. Atrial function can be categorized into three components. During ventricular systole, the A-V valves are closed; thus, the atria collect blood from the veins and serve as a reservoir. During early diastole, the atria empty their contents into the ventricle and then serve as a conduit for continuing blood flow into the ventricles during mid-diastole. In late diastole, atrial contraction ejects another portion of blood into the ventricles just prior to ventricular contraction.
- B. The two ventricles are anatomically suited to their different tasks (Figure 1). The right ventricle is a thin-walled volume pump which ejects blood both by shortening of the free wall and compression of the chamber (bellows action). This mechanism is ideally suited to efficiently eject a large volume of blood against the low pressure system found in the pulmonary artery. The left ventricle is a thick-walled pressure pump which ejects blood primarily by overall constriction of the chamber although there is some shortening of the apex to base. Thus, the left ventricle is well-adapted to eject blood against the high pressure found in the aorta.

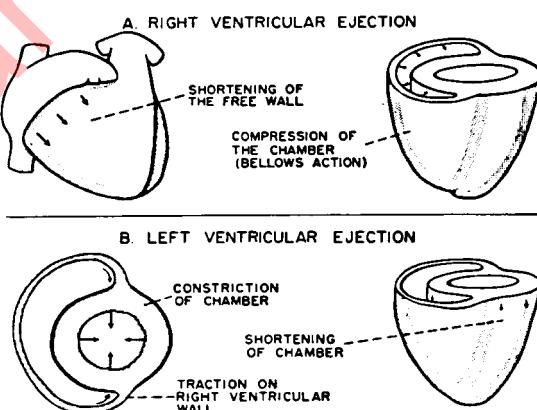


Figure 1: Primary mechanisms of right and left ventricular ejection. Reproduced from Cardiovascular Dynamics, Rushmer, ed., W.B. Saunders Co., Philadelphia, 1976, p 92.



- C. The microscopic structure of the myocardium is illustrated in the syllabus section on Excitation-Contraction coupling and is schematized in Figure 2. A myocardial cell or fiber is bounded by intercalated discs and has a single, centrally placed nucleus. A fiber is made up of numerous fibrils. Each fibril is a long train of individual sarcomeres.
- D. Numerous mitochondria exist in cardiac muscle because of the continual requirement for oxygen and oxidative phosphorylation. A transverse tubular system (T system) represents an invagination of the sarcolemma (membrane surrounding the cell) and transmits the electrical signal on the surface into the cell. A longitudinal tubular system (sarcoplasmic reticulum) is involved in calcium release and uptake with each contraction.

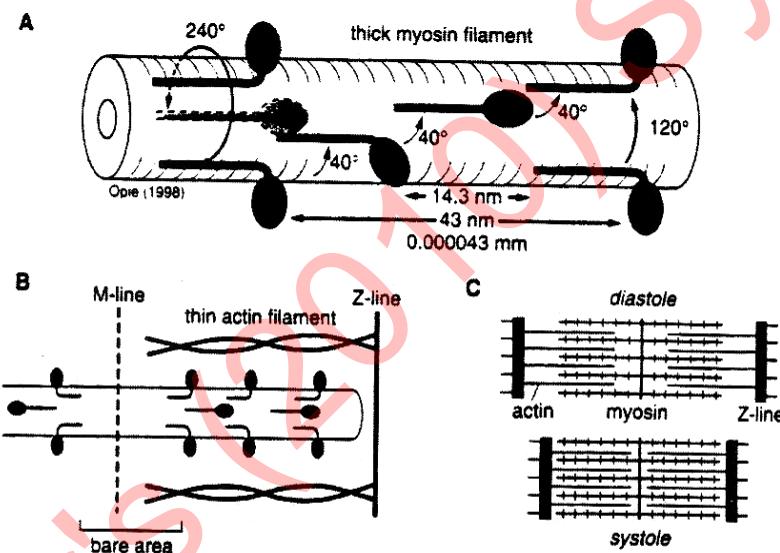


Plate 1. Sarcomere structure. (A) Relationship of thick myosin and thin actin filaments to sarcomere structure. The thickness of the thick filament is only relative because the length/width proportion is approximately 100:1. The heads emerge in groups of three and shift their positions by 40 degrees in succession. Thus, nine rows of about 16 heads each are placed in a line on the surface of each arm of the bipolar filament. (B) About 300 myosin heads come off at right angles to the body (150 heads to each side of the M line). (C) Compared with diastole, there is increased overlap of actin and myosin during systole, so that the Z lines move together during contraction.

Figure 2: (L. Opie, The Heart. Plate 1.)

- E. A sarcomere is about 2.2 microns long and is bounded by Z lines. The thin actin filaments (1.0 microns long) are attached to the Z lines, while the thick myosin filaments (1.5 microns long) are in the center of the sarcomere. Cross-bridges between actin and myosin filaments are formed with each contraction. On light microscopy, the A band refers to the myosin bands, whereas the I band refers to the region of actin filaments between two A bands. The M line is a specialized thickening of the myosin filaments at the center of the sarcomere, which helps maintain the hexagonal lattice arrangement of the myosin.



- F. The thin actin filaments have an attachment site for the myosin cross-bridge, thus activating myosin activity. Since ATP is the energy source for contraction, the myosin ATPase activity releases energy at the cross-bridge site, which produces force and shortening. The troponin-tropomyosin complex on the actin filament inhibits actin-myosin interaction. Calcium binds to troponin C to release this inhibition, uncovering the cross-bridge on the actin filament and initiating contraction (Figure 3).

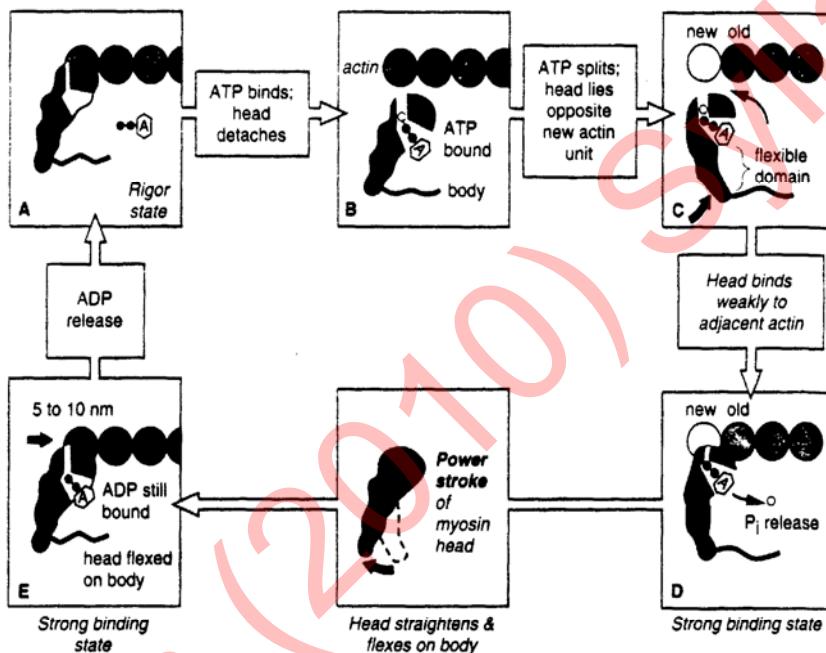


Plate 5. Crossbridge cycling model of Rayment et al. (1993) incorporating features of models of Eisenberg and Hill (*Science* 1985;227:293–309) and Lynn and Taylor (1971), with additional changes proposed by the present author. The Rayment model is based on electron density mapping of conformational changes in the myosin head. On the myosin head there is an ATP (nucleotide) binding pocket. Starting with the rigor state, binding of ATP to the binding pocket opens the cleft, and the previously strong binding state becomes a weak binding state (B). The ATP is split by the myosin ATPase and the head changes configuration (C). Next, the binding pocket closes around its base to induce further conformational changes to occur which, in turn, further closes the cleft, so that there is strong binding of myosin to actin. The result is that the affinity of myosin for Pi decreases, so that Pi is extruded, which results in a further molecular change in the myosin head to initiate the power stroke. The myosin head flexes to assume the rigor state once again. In the process, ADP is released so that the binding pocket becomes vacant. The open binding pocket is now ready to receive ATP to reinitiate the crossbridge cycle. (The increasing spatial separation between actin and myosin as contraction occurs is not shown.)

Figure 3: Schematic representation of the myosin-actin-ATP Interaction(L. Opie, The Heart, Plate 5)

- G. Several structural differences between skeletal and cardiac muscle are listed in Table I and relate to physiological differences in their function, as discussed below. Because the heart depends on the availability of oxygen from beat to beat, it has far more mitochondria than skeletal muscle, which can develop an oxygen debt. On the other hand, skeletal muscle contraction depends



primarily on intracellular stores of calcium, which are contained in a much more extensive sarcoplasmic reticulum than is found in heart muscle. Experimentally, if one removes the source of external calcium from skeletal muscle, contraction is little affected. On the other hand, removing the external source of calcium from cardiac muscle reduces contractile function rapidly. The passive length-tension properties of skeletal muscle are less stiff than cardiac muscle. Since the length of skeletal muscle is usually fixed in the body by attachment to bone, they cannot be stretched out beyond their optimum length. Thus, they do not require a stiff passive length tension relation to prevent overstretching. In *in vitro* experiments, however, it is easier to passively stretch skeletal muscle than cardiac muscle. Stretching heart muscle, however, does not stretch sarcomeres much beyond about 2.5 microns. This increased stiffness of cardiac muscle presumably relates to an increased collagen content.

Table 1. Differences between cardiac and skeletal muscle.

	<u>Skeletal</u>	<u>Heart</u>
Mitochondria	+	++
Sarcoplasmic Reticulum	++	+
Resting Force at L max	Low	High
Number of Sarcomeres in overstretched muscle	>2.2	2.2
Tetanus	Yes	No
Intercalated Discs	No	Yes
Contraction	Graded	All or none

- H. Skeletal muscle contraction can be tetanic and sustained when stimulated by a train of electrical stimuli. On the other hand, cardiac muscle responds only to a single stimulus and has a long refractory period before it responds again to another stimulus. Thus, cardiac muscle is characterized by a twitch contraction, whereas skeletal muscle can contract tetanically. Furthermore, cardiac muscle contraction is all or none and cannot be graded (by recruitment of additional motor units) as can skeletal muscle. There is a predictable relationship between sarcomere length at the onset of contraction and the amount of force developed by the muscle. Classical studies in skeletal muscle suggest that the developed force is related to the degree of overlap of thin and thick filaments (Figure 4). In skeletal muscle, the optimum force development occurs at approximately 2 to 2.2 microns. As muscle is stretched beyond this point, there is less overlap between thin and thick filaments and thus less opportunity for crossbridges to form. Developed force falls accordingly. At muscle lengths shorter than 1.9 microns, the thin actin filaments cross through the center



of the sarcomere and apparently interfere with each other in development of cross-bridges. This has been postulated as the primary mechanism for the reduction in force at shorter muscle lengths.

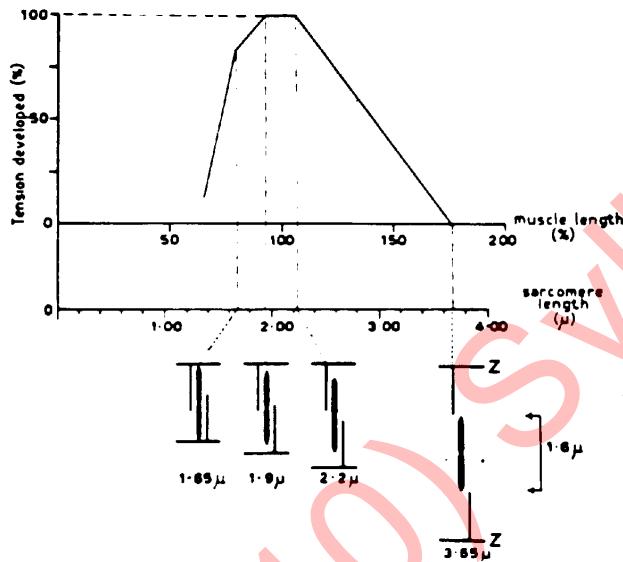


Figure 4: Classical relation between the force of development of skeletal muscle and the overlap of thin and thick filaments.
Reproduced from Hanson J, Lowy J: Molecular basis of contractility in muscle. Brit Med Bull 21:264-271, 1965.

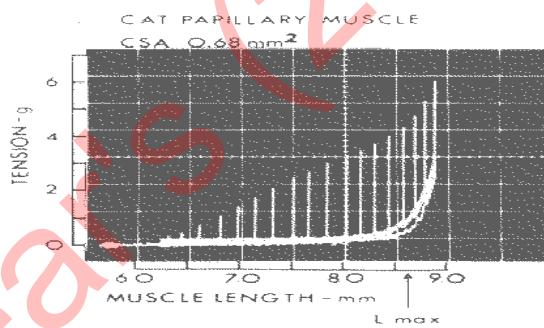


Figure 5: Representative series of isometric contractions in a cat papillary muscle studied in vitro in a muscle bath. Contractions are superimposed on a memory oscilloscope and then photographed with a Polaroid picture. The lower line represents the passive length-tension curve of the muscle at that length.
CSA = Cross-sectional area

- I. Cardiac muscle is relatively stiff as one tries to stretch it out to longer muscle lengths. The resting and developed force at a series of muscle lengths are shown in Figure 5 in a representative experiment. At longer lengths, the resting force (bottom line) rises abruptly because of the stiffness of the muscle. Note that as length increases, the force developed by the muscle (height of vertical lines) progressively increases until one reaches the L max point,



which represents the maximum developed force of the muscle. Beyond that length, developed force (height of vertical lines) is reduced. Figure 6 plots representative resting and developed length-force relations of cardiac muscle. The developed force rises to a peak at the length designated L_{max} and then declines. The resting force rises relatively slowly at shorter lengths but as one approaches and passes L_{max} , there is an abrupt rise in resting force along its exponential passive length-force curve. The simple addition of resting and developed force is the total force which is a relatively straight line over much of its course.

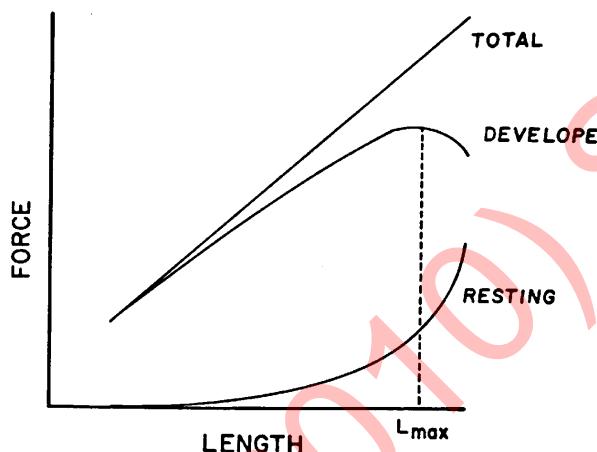


Figure 6: Resting and developed force-length curves as obtained in isolated heart muscle. The addition of resting and developed force determines the total force line.

- J. The relation between myocardial and sarcomere lengths and the passive and active length-force curves of cardiac muscle are illustrated in Figure 7. At a sarcomere length of 2.2 microns, there is an optimal overlap of thin and thick filaments, thus optimizing the formation of cross-bridges. There are few cross-bridges at the center of the myosin filament in the vicinity of the M line so that the ends of the opposite actin filaments are slightly separated. At longer lengths in skeletal muscle the sarcomeres are pulled out slightly and force is reduced due to fewer cross-bridges formed. Because the passive length-tension relation is so stiff, however, it is difficult to pull cardiac muscle sarcomeres out much beyond 2.5 microns. The reduction in force at small sarcomere lengths presumably relates to the cross-over of actin filaments through the middle of the sarcomere, which interfere with each other. The region between 1.9 and 2.2 is presumably the normal physiological range of sarcomere lengths.



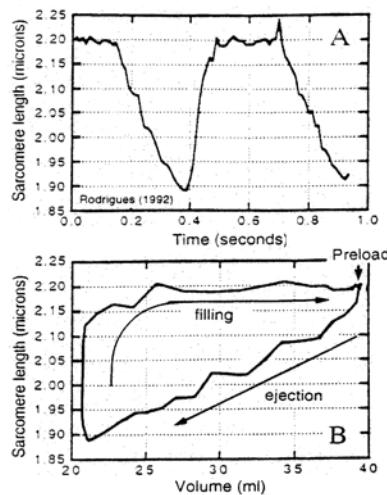


FIG. 12-7. Changes in sarcomere length during a typical cardiac contraction-relaxation cycle in the intact dog heart. Top panel shows that during diastole the sarcomere length is 2.2 μm , reducing to 1.90 μm during systole. Bottom right panel relates sarcomere length to LV volume. Starting at the top right, the preload is the maximum sarcomere length just before the onset of contraction. Then ejection decreases the LV volume, in this case by about half. Sarcomere length decreases from 2.20 to 1.90 μm . Then, during the rapid phase of filling (see Fig. 12-22), the sarcomere length increases from 1.90 to 2.15 μm , to be followed by the phase of constant sarcomere length (diastasis). Modified from Rodriguez et al. (1992).

Figure 7A: (L. Opie FIG. 12-7)

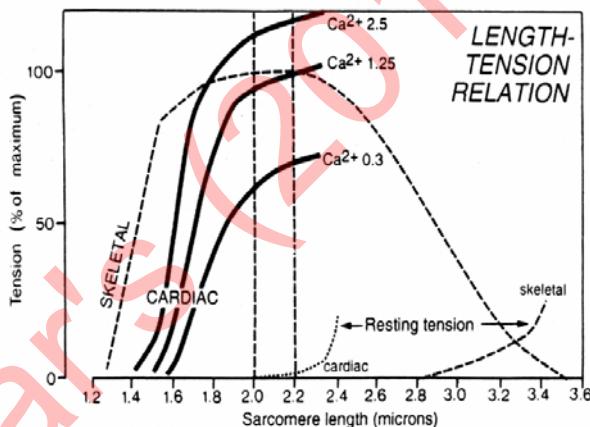


FIG. 12-6. Effect of sarcomere length on tension. The relationship between sarcomere lengths and tension for cardiac muscle in comparison with skeletal muscle. Note (i) the effect of increasing calcium ion concentration and (ii) the absence of any decrease of tension at maximal sarcomere lengths, so that there is no basis for the descending limb of the Starling curve. Recent sophisticated laser-diffraction techniques invalidate previous curves based on apparent sarcomere length-tension relationships of imperfect papillary muscle preparations. For data on failing human heart, see Holubarsch et al. (1996).

Figure 7B: Relationship between myocardial sarcomere length and the passive and active length-tension curves of isolated muscle (L. Opie FIG 12-6)



- K. Although classical studies have suggested that the active length-tension curve of cardiac muscle is due entirely to the changing relationship of cross-bridge overlap, some studies have suggested that another factor (length-dependent activation) may be important. Figure 7 illustrates one piece of information suggesting this possibility. If one plots the relative force development of both skeletal and cardiac muscle, one might expect that they would be identical curves since the overlap of thin and thick filaments would be the same at different muscle lengths. The cardiac muscle curve, however, falls far inside the skeletal muscle curve at shorter muscle lengths. One interpretation of this data is that there is decreasing activation of the twitch contraction of cardiac muscle at shorter lengths, as compared to the tetanic contraction of skeletal muscle. Thus, the active length-tension curve of cardiac muscle may be due in part to this length-dependent activation, in addition to the overlap of thin and thick filaments.

III. ISOMETRIC CONTRACTION

- A. When studying isolated heart muscle in the laboratory, the standard contraction is the isometric contraction, where the ends of the muscle are fixed so that muscle length remains constant. When activated, the muscle develops force but cannot shorten. The characteristic force versus time twitch for such a contraction is shown in Figure 8. The resting force of the muscle is the preload, the additional force which is developed represents the afterload. Other quantitative measures of the twitch contraction include the maximum rate of force development ($\max \frac{dF}{dt}$) which is the maximum slope of the ascending portion of the curve, and the time-to-peak force which is the time from the onset of contraction to peak force.

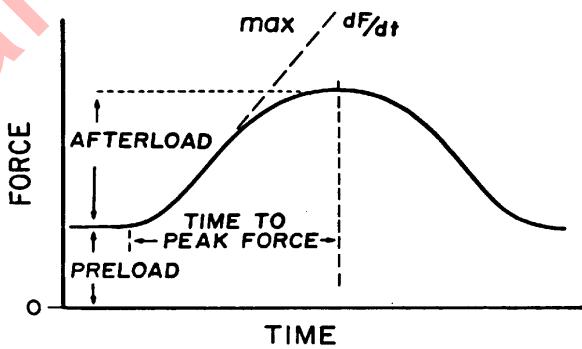


Figure 8: Isometric contraction of cardiac muscle. See text for details.



- B. If one keeps preload constant and increases the contractility of the muscle by adding certain drugs such as the catecholamines, the alteration in the time course of contraction is shown in Figure 9. The control contraction is at the bottom and the contraction produced by the addition of a catecholamine, at the top. Note that there was an increase in force development and rate of force development together with a more rapid relaxation and a shorter time-to-peak force. These are the characteristic changes seen with an increase in contractile state.

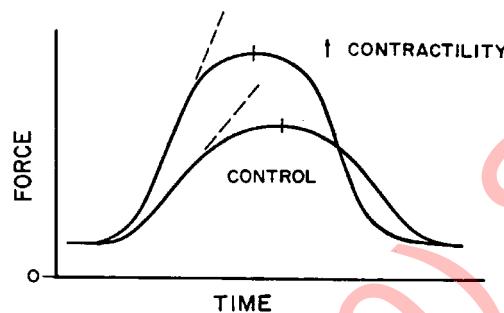


Figure 9: Alteration in the isometric contraction of isolated cardiac muscle following an increase in contractile state.

- C. An increase in both force development and maximum rate of force development usually occur when contractile state is changed. By convention, the maximum rate of force development is the preferable index of contractile state. This higher rate of force development goes along with increases in enzyme activity.
- D. A number of interventions alter contractility. Those which increase contractility are called positive inotropic interventions, whereas those which decrease contractility are called negative inotropic interventions. Those factors which alter contractility are listed in Table 2. In general, most factors which enhance contractile state do so by increasing calcium availability to the myofilaments.

Table 2. Effects of different inotropic interventions.

Factors which increase contractile state:	Factors which decrease contractile state:
Incr. Calcium	Decr. Heart rate
Incr. Heart rate	Incr. parasympathetic tone
Incr. sympathetic tone	Beta adrenergic receptor blockade
Incr. catecholamines (endogenous)	Calcium-channel blockade
Sympathetic amines (dopamine, dobutamine, etc.)	Anti-arrhythmic drugs (Quinidine, Procainamide, etc.)
Glucagon	Hypoxia
Hyperthyroidism	Acidosis
Paired electrical stimulation	Cardiac hypertrophy
Digitalis compounds	Heart Failure



- E. Increasing heart rate increases contractility by making more calcium available to the myocardium due to the increased number of depolarizations. The relationship between the rate of contraction and the force developed is termed the force interval relation. In most mammalian species an increase in heart rate will increase cardiac contractility (Figure 10).



Figure 10: Isometric twitches of cardiac muscle (B) An increase in stimulation frequency increases contractile state. In: Handbook of Physiology. I. The Cardiovascular System, Berne RM, ed., Am Physiol Soc, Bethesda, MD, 1979, p 476

- F. Many different interventions increase contractility, but there is a limit to which contractility can be increased. This has been referred to as the ceiling of contractility. Thus, if contractility is increased by one intervention, a second intervention will have a lesser effect as one approaches the ceiling of contractility.

IV. ISOTONIC CONTRACTION

- A. Use Figure 11a as a way to understand Figure 11b. Both demonstrate the same principles; Figure 11a is just simpler and in one dimension.

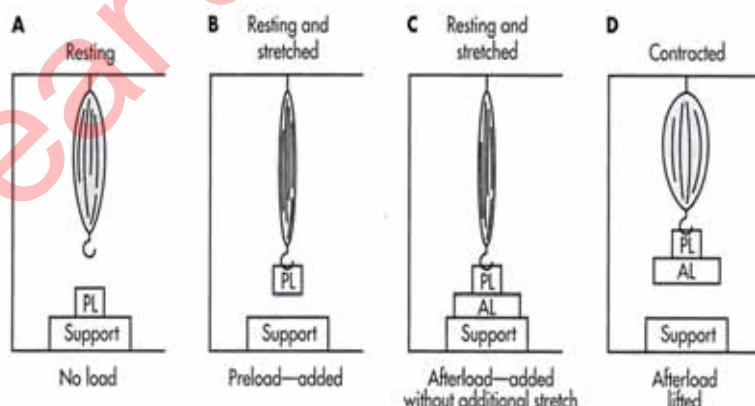


Figure 3-7 ■ Preload and afterload in a papillary muscle. A, Resting stage—in the intact heart just before opening of the AV valves. B, Preload—in the intact heart at the end of ventricular filling. C, Supported preload plus afterload—in the intact heart just before opening of the aortic valve. D, Lifting preload plus afterload—in the intact heart ventricular ejection with a decrease in ventricular volume. PL, Preload; AL, afterload; $PL + AL$ = total load.



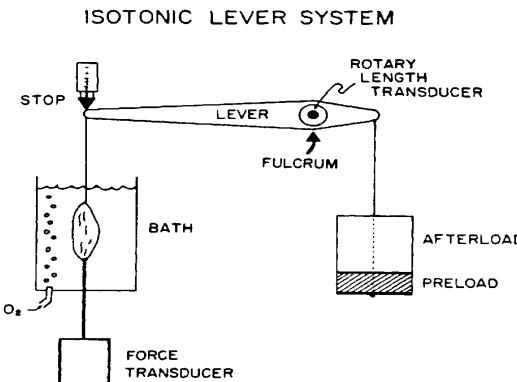


Figure 11b: Schematic diagram of the isotonic lever system used to study afterloaded isotonic contractions in isolated cardiac muscle.

- B. Figure 11b shows a schematic diagram of the kind of lever system used to obtain tonic contractions in isolated heart muscle. The force transducer is fixed and measures the force at the end of the muscle. The other end of the muscle is attached by a thread to the tip of a lever system which rotates around a fulcrum. When the stop at the upper left is raised out of the way, any load placed on the right-hand side of the lever will stretch the muscle to a length appropriate to its resting length-tension relation. By definition, this is the preload. The relative length of the lever arms are used appropriately to calculate the correct preload. With the preload in place and the muscle stretched to an initial length, the stop is then slowly lowered until it just touches the upper left-hand portion of the lever. When any additional load (afterload) is placed on the right-hand side of the lever, the lever can no longer stretch the muscle any further since it is prevented from doing so by the stop. Thus, the muscle does not sense this additional load until it starts to contract. Force rises until the developed force matches the afterload, at which point force remains constant (isotonic) while the muscle shortens. The slope of the shortening trace is the velocity of shortening for that particular load. If one alters the afterload over a wide range, the series of contractions which occur are superimposed in Figure 13



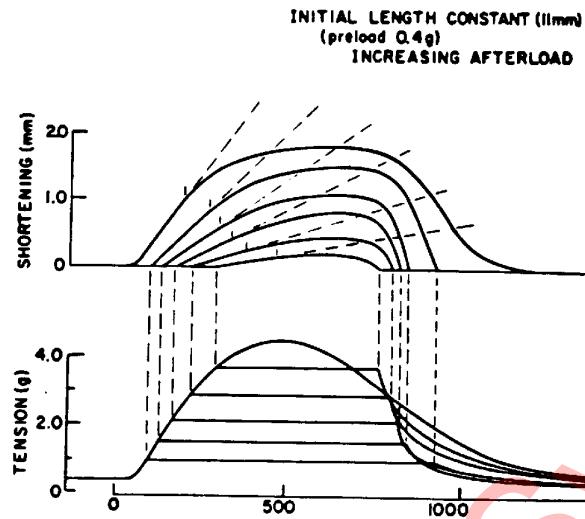


Figure 13: Series of superimposed isotonic afterloaded contractions.
Reproduced from Mechanisms of Contraction of the Normal and Failing Heart,
Braunwald E, Ross J Jr, Sonnenblick EW, eds., Little, Brown & Co, Boston,
1968, p.36.

- C. The dashed lines between the shortening and tension traces connect the corresponding traces for each contraction. As the afterload is increased, both the distance shortened and the velocity of shortening are reduced. The relation between the load and the distance the muscle shortens is shown in a representative muscle in Figure 14. It is clear from this figure that one way to increase muscle shortening is to reduce the load which the muscle has to lift. (This is the basic principle underlying the use of afterload reducing therapy with vasodilator drugs in patients with congestive heart failure. Reduction of the afterload increases the cardiac output to the body, and can ameliorate some of the signs and symptoms of heart failure.)

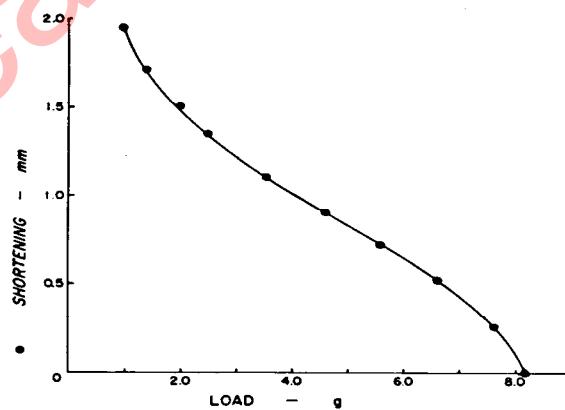


Figure 14: Relationship between load and distance shortened in a sequence of isotonic afterloaded contractions in an isolated papillary muscle with a single preload. Note that the curve will shift to the right with increase preload.



- D. If one takes the values for velocity of shortening and loading from each of the individual contractions and replots them as a force-velocity relation, the general relationship is a hyperbolic curve (Figure 15). The position of the curve is changed both by increases in muscle length (preload) and by increases in contractility. Figure 15A shows the alterations in the curve which occur as one progressively increases muscle length. The lower left-hand curve is at a short muscle length while the two right-hand curves reflect data obtained at longer muscle lengths. Note the increase in force development as one moves up the ascending limb of the length-tension curve. (See Figs. 5, 6.)
- E. If one extrapolates the force-velocity relation to the zero axis, one obtains V_{max} , the theoretical maximum velocity of shortening. (See Fig. 15.) Note that V_{max} remains relatively constant with changes in muscle length even though there are considerable increases in force development. On the other hand, an increase in contractility at a given initial muscle length produces a relatively symmetrical shift of the force-velocity relation up and to the right with an increase in both V_{max} and developed force (Fig. 15B.) Thus, V_{max} has been proposed as an index of contractility, since it is relatively unchanged by changes in preload but is shifted upwards by an increase in contractile state.

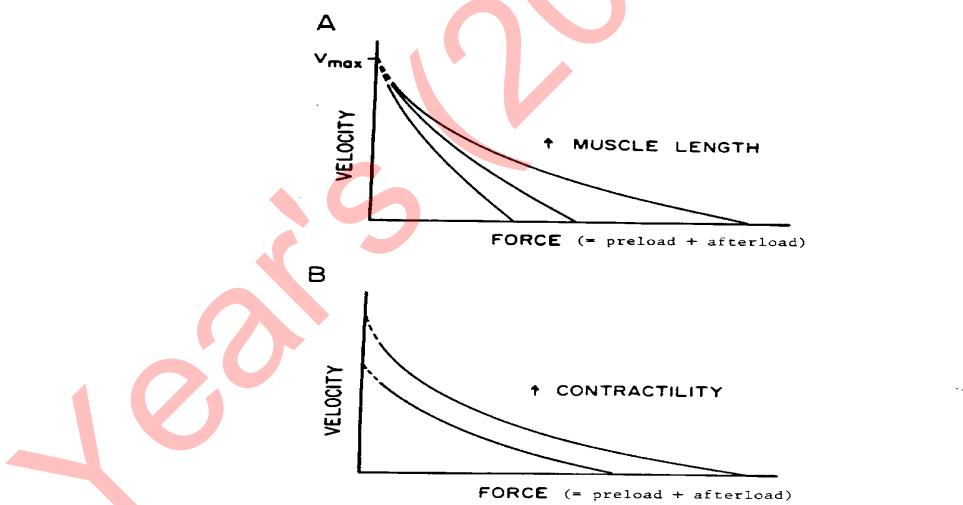


Figure 15: (A) Representative force-velocity relations in isolated heart muscle obtained at three different initial muscle lengths. (B) Representative change in the force-velocity relation following an increase in contractile state.



- F. Another useful relationship is that which exists between length and force during isometric and isotonic contractions, as illustrated in Fig. 16. The resting length-tension relation and the total force line are similar to those previously illustrated in Figs 5 and 6. For example, an isometric contraction beginning at point A would show a rise in force to point B. An isotonic contraction beginning at point E with the same total load (preload plus afterload) would follow the course EFB. E to F represents force development prior to shortening and F to B represents shortening while the force remains constant (isotonic). Similarly, an isotonic contraction beginning at point C (with the same total load) would follow the course CDFB. Note that all of these contractions ended at the same point, B, on the total force line regardless of whether the contraction was isometric (AB) or isotonic (EFB or CDB). If one obtained a series of contractions with different preloads and afterloads, the end-point of contraction would always be on the total force line. Thus, the total force line represents an important marker of the contractile abilities of heart muscle.

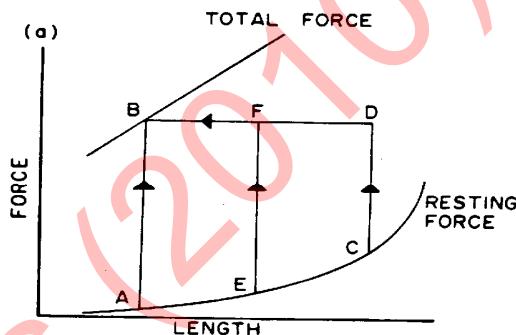


Figure 16: Relationship between force and length with both isometric and isotonic contractions. See text for details. Note: Total load (preload + afterload) remains constant.

** Note: The important concept in this lecture is the length/force relationship. Much of the material that follows this point touches on concepts that will be presented more fully in subsequent lectures (e.g., PV loops are the topic on the next set of lectures). Read through the rest of the notes, but don't be discouraged if everything isn't clear just yet. Table 3 is very important for understanding why we are belaboring the length/force relationship. **

- G. An analogous sequence of events happens in the intact heart when one plots pressure against volume. Figure 17 shows a representative pressure-volume relation during one contraction cycle of the left ventricle. Beginning at point A, the mitral valve opens and blood flows into the ventricle along the passive pressure-volume relation. Atrial contraction brings the ventricle to point B at end-diastole. During the initial portion of contraction



(isovolumic systole), pressure rises without a change in volume until the aortic valve opens at point C. The ventricle then ejects blood with a rise and fall of aortic pressure until the aortic valve closes at point D.

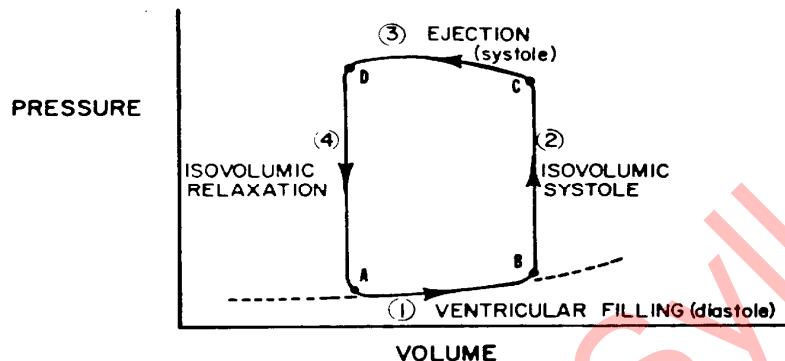


Figure 17: Representative pressure-volume loop of the left ventricle during a single cardiac cycle.

- H. Pressure then falls without a change in volume until the mitral valve can open again to allow blood to fill the ventricle (point A). This counter-clockwise loop represents the contraction pattern of the left ventricle with each cycle. By definition, the area inside this loop equals the stroke work done by the heart with each contraction.
- I. Figure 18 illustrates changes in the pressure-volume loop with changes in preload and afterload. In an experimental animal, if one can clamp the aorta to prevent ejection of blood, the ventricle will develop pressure up to a point and then relax. A series of contractions (with different aortic pressures) define the isovolumic pressure line. This line is analogous to the total force line in isolated heart muscle (Figure 6). Also illustrated in Figure 18 are three regular contractions (a, b and c) which begin at different preloads and have different afterloads. Note, however, that the upper left-hand corner of each loop ends on the isovolumic pressure line. Thus, this line represents the end-point of contraction for both isovolumic and ejecting beats. Furthermore, this line is also independent of preload and afterload.

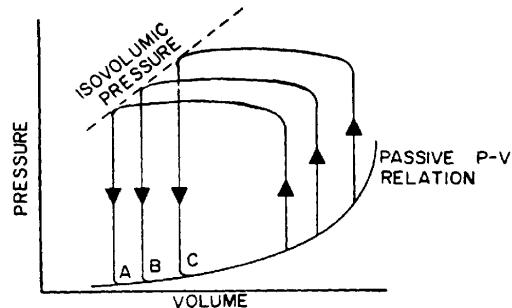


Figure 18: Alterations in the pressure-volume loop of the left ventricle with alterations in preload and afterload. Note that the upper left-hand corner of each loop ends on the isovolumic pressure line.

- J. The only intervention which changes the isovolumic pressure line is an increase in contractile state which would shift the line up and to the left in a similar manner to that which would occur with the total force line in isolated heart muscle. Figure 19 shows two representative contraction cycles where preload and afterload have been kept constant but contractile state has been increased. Contraction A is at the lower contractile state and contraction B is at the higher contractile state. The increase in contractile state shifts the isovolumic pressure line up and to the left. Note that there is a resultant increase in stroke volume (the width of the pressure-volume loop) due to the increase in contractile state.

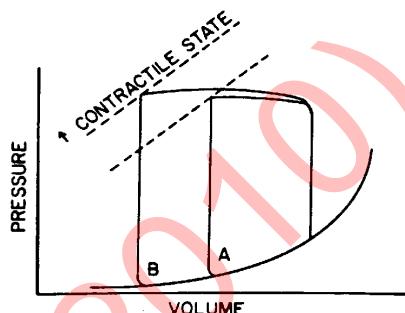


Figure 19: Alterations in the pressure-volume loop of the left ventricle following a change in contractile state. Preload and afterload have been kept constant. Loop A is the control loop and Loop B is following an increase in contractile state. The isovolumic pressure line is shifted up and to the left by the increase in contractile state.

V. INDICES OF CONTRACTILITY

- A. The two major ways of increasing cardiac performance are by increasing initial muscle length (preload) and/or by increasing contractility. An ideal index of contractility, therefore, would be one which is not changed by a change in initial muscle length but is altered only by an increase in contractility. The three indices of contractility which we have discussed are (1) maximum rate of force development ($\text{max } dF/dt$), (2) V_{max} , and (3) total force line. At a constant preload in the isometrically contracting muscle, $\text{max } dF/dt$ is an excellent index of contractile state when testing the effects of different drugs. However, $\text{max } dF/dt$ does change somewhat with changes in preload, so that it is not totally specific for contractile state alone. The same is true for V_{max} which is altered substantially by changes in contractility and slightly by changes in preload. On the other hand, the total force line is more specific for changes only in contractile state.



VI. APPLICATION OF MUSCLE MECHANICS TO THE INTACT HEART

- A. Table 3 has paired some of the analogous terms which are used in isolated heart muscle and in the intact heart. Some of these comparisons are briefly discussed below. In isolated heart muscle we measure force, whereas in the intact heart we measure intraventricular pressure. Force in the wall of the heart is related to pressure by the Laplace relation, a simplified form of which is shown in the table.

Table 3. Application of muscle mechanics to intact heart.

<u>ISOLATED MUSCLE</u>	<u>INTACT HEART</u>
1. Force (F) is related by the Laplace relation to	→ Pressure (P)
$F = PR$	A - cross sectional area
$A = 2h$	R - radius
	h - wall thickness
2. Passive length-tension curve relation	→ Passive pressure-volume
3. Preload	→ LVEDP
4. Afterload	→ Aortic pressure
5. Active length-tension curve	→ Ventricular function curve
6. Distance shortened	→ Ejection fraction (EF)
7. Total Force Line (pressure volume loop)	→ Stroke volume
8. Max dF/dt	→ Isovolumic pressure line
9. Stimulation frequency	→ Max dP/dt
10. Isometric force-velocity relations	→ Heart rate
	→ Isovolumic force-velocity relations

- B. The passive length-tension curve of isolated muscle and the passive pressure volume relation of the left ventricle are both exponential curves which resist further lengthening at higher force or pressure. The term preload refers to the initial load stretching isolated heart muscle prior to contraction. In the intact left ventricle, left ventricular end-diastolic pressure (LVEDP) represents the pressure in the ventricle just prior to contraction and is thus an index of the preload. In isolated heart muscle, the afterload refers to the additional load above the preload which the muscle has to match in order to shorten. In an analogous way, the aortic pressure represents the pressure that must be developed by the left ventricle before it can open the aortic valve and eject blood.
- C. The active length-tension curve has a somewhat similar shape to the ventricular function curve illustrated in Figure 20. This representation of ventricular performance plots some measure of LV performance, such as stroke work or stroke volume, as a function of the left atrial pressure, which is frequently measured by



a catheter in the pulmonary capillary wedge position. These pressures represent the diastolic filling pressure of the left ventricle, and thus are an index of preload. Note that there is a rising portion to this curve with optimum performance occurring at a LV filling pressure of 15-20 mmHg. A normal left atrial pressure is generally less than 12 mmHg, so that the heart is normally working on the ascending limb of the left ventricular function curve.

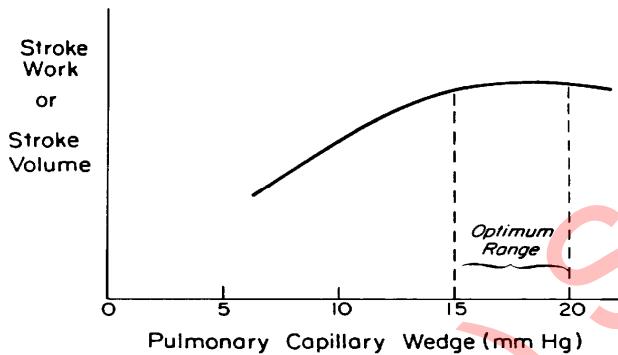


Figure 20: Representative ventricular function curve of patients. The pulmonary capillary wedge pressure is an approximation of the left atrial pressure (and therefore of left ventricular end-diastolic pressure).

- D. Another useful index of left ventricular performance is the ejection fraction. By definition, the ejection fraction is the stroke volume divided by the end-diastolic volume. In principle, this is conceptually related to a ventricular function curve, as illustrated in Figure 21. By plotting stroke volume versus the end-diastolic volume, different curves of left ventricular performance are illustrated. The slope of the dashed line connecting points A, B and C on the three different curves to the origin is the ejection fraction (SV/EDV). A normal ejection fraction is approximately $2/3$. As left ventricular performance decreases, ejection fraction is reduced and the ventricular function curve is shifted down and to the right (A to B to C). The ejection fraction is one of the most useful single numbers for characterizing left ventricular performance (although it is load-dependent).



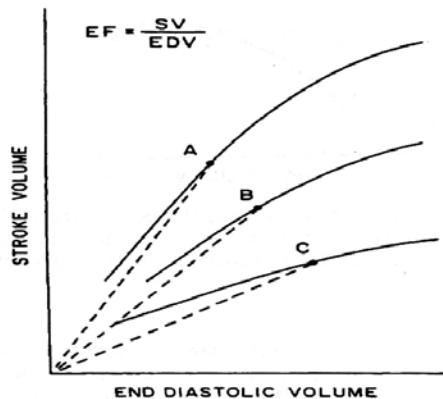


Figure 21: Three different ventricular function curves are illustrated. The ejection fraction is the slope of the dashed line connecting the origin to points A, B, and C on the three different curves. As the curves are progressively shifted down and to the right to a lower level of function, there is a decrease in the ejection fraction.

VII. COMPENSATORY MECHANISMS

- A. During the process of heart failure, there are three immediate compensatory mechanisms used to maintain cardiovascular compensation. These are (1) dilation (Frank-Starling mechanism), (2) sympathetic stimulation and an increase in circulating catecholamines, and (3) increased heart rate. The effect of two of these mechanisms on the ventricular function curve is shown in Figure 22. During the process of heart failure, the left ventricle has moved from point A on the normal curve down to point B on a depressed and failing curve. The heart dilates from B to C which produces a slight increase in stroke volume. The increase in circulating norepinephrine (NE) and epinephrine moves the patient from C to D so that stroke volume can be returned to a reasonable range, although at the expense of a larger volume. Since cardiac output is the product of stroke volume and heart rate, an increase in heart rate will also tend to maintain cardiac output when stroke volume is reduced.
- B. Chronic compensatory mechanisms include (1) hypertrophy, which occurs with both volume and pressure overload, and (2) increased extraction of oxygen from the blood. This latter effect increases oxygen delivery to body tissues at a given cardiac output.



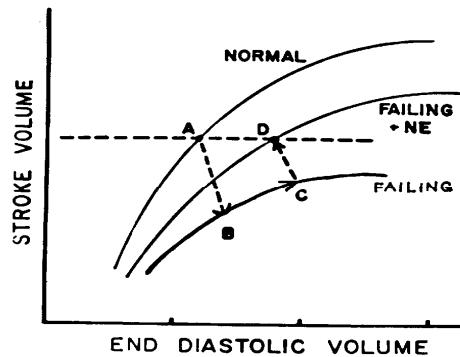


Figure 22: Acute compensatory mechanisms in heart failure. The patient begins at point A on a normal ventricular function curve and shifts down to point B with the development of heart failure. The heart dilates from B to C. An increase in circulating catecholamines shifts the curve back up to point D.

C. The responses of the ventricle to volume or pressure overload are shown in Figures 22 and 23. The passive-pressure volume relations of the ventricle are usually altered by pressure or volume overload (Fig. 23). In volume overload such as occurs with aortic or mitral valvular regurgitation, the ventricle tends to dilate and the curve is shifted to the right with an increase in compliance. In pressure overload such as occurs with aortic stenosis, the curve is often shifted to the left. The wall hypertrophies with a reduction in intraventricular volume (decreased compliance).

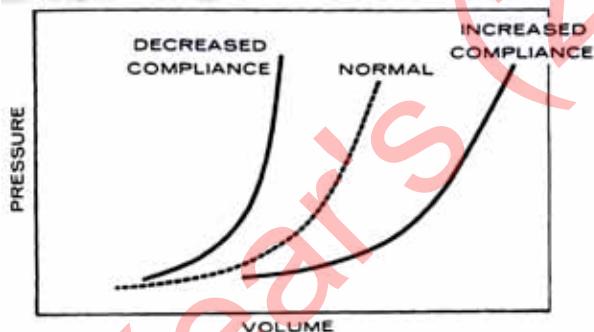


Figure 23: Changes in the passive-pressure volume relation of the ventricle in response to volume overload (increased compliance) and pressure overload (decreased compliance). See text for details. Compliance = dV/dP



VIII. VENTRICULAR RESERVE

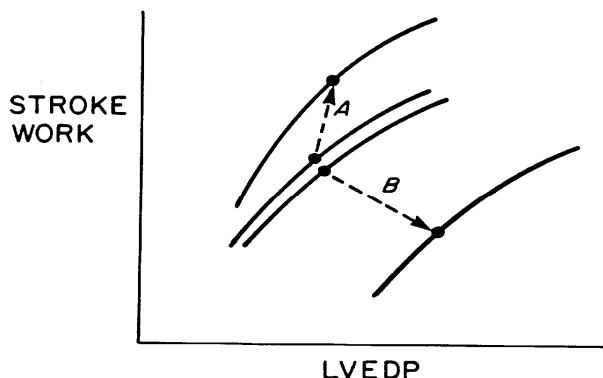


Figure 24: Alteration in the ventricular function curve in response to an increase in arterial pressure. Response A is a normal response and indicates good ventricular reserve. Patient B is an abnormal response indicating poor ventricular reserve. See text for details.

- A. An important principle relating to the onset of heart failure is that there may be preservation of ventricular function at rest although the reserve of the heart in response to stress or exercise is markedly reduced. This is illustrated schematically for two different patients in Figure 24. The lower curve of patient A is a control ventricular function curve. In response to an increase in arterial pressure, there is a tendency for stroke volume to be reduced because of the increased afterload. The ventricle, therefore, increases its contractility by responding to increased systemic and local norepinephrine secretion to maintain stroke volume. This results in a shift upward in function as shown by the dashed line (A) to the higher function curve. This represents a normal integrated response to an increase in arterial pressure in a compensated ventricle. The upper control curve of patient B has resting measurements similar to the resting measurements of patient A.
- B. In response to the same increase in arterial pressure, however, this patient has little reserve. Therefore, as afterload is increased, there is a reduction in left ventricular performance and cardiac dilation. This results in a marked shift of function down and to the right (dashed line), as illustrated. Thus, although resting measurements of performance were similar in the two patients, patient A had relatively normal ventricular reserve, whereas patient B had a marked reduction in ventricular reserve. Patient B, therefore, would probably also be limited by symptoms of shortness of breath and fatigue during exercise.



IX. MYOCARDIAL ENERGETICS

- A. ATP is the sole energy source for cardiac contraction, although creatine phosphate is a high energy phosphate which can interchange with ATP. It appears that some depletion of high energy phosphates may occur in heart failure, although this is probably not the cause of the heart failure. With the onset of ischemia, depletion of ATP is an important factor in the subsequent deterioration of cardiac performance.
- B. The oxygen consumption of the heart has an important relationship to pressure development and to shortening. As a general rule, pressure development requires more oxygen than does shortening. Therefore, increases in stroke volume require less of an increase in oxygen consumption than an increase in pressure development.
- C. The major determinants of myocardial oxygen consumption are: heart rate, left ventricular pressure, heart size, and contractile state. When any or all of these are increased, there is an increase in oxygen consumption. Minor determinants of oxygen consumption include the basal levels required to maintain cellular integrity, the minor cost of activation, and the direct metabolic effects of catecholamines.

X. SUMMARY

- A. Cardiac muscle can increase its performance by an increase in muscle length and/or an increase in contractile state. The primary determinants of myocardial performance are preload, afterload, contractile state, and heart rate. The increase in performance produced by an increase in muscle length probably relates to optimal overlap of cross-bridge formation. In addition, length-dependent activation may play a role in cardiac muscle. Cardiac muscle has a stiff passive length tension relation that prevents over distension of the muscle with increasing stretch.
- B. Isometric contraction of cardiac muscle occurs when the ends of the muscle are fixed. Maximum rate of force development ($\text{max } dF/dt$) is a good index of contractility during isometric contraction. During isotonic contraction, the muscle shortens against different afterloads. Both the distance shortened and the velocity of shortening are inversely related to the load against which the muscle shortens. The maximum velocity of shortening at zero load (V_{max} , a hypothetical extrapolation) is another index of contractility, since it is altered by changes in contractile state but is little affected by changes in initial muscle length.



- C. The total force line determined by isometric contractions in isolated heart muscle also represents the endpoint of contraction for all isotonic afterloaded contractions. Thus, the total force line is a good measure of the contractile ability of the heart. With an increase in contractile state, this line is shifted up and to the left. The application of this concept to the intact heart is represented by the pressure volume loop during ventricular contraction. The isovolumic pressure line likewise represents the contractile state of the heart independent of preload or afterload. An increase in contractile state shifts the isovolumic pressure line upwards and to the left. Two additional indices of contractile state in the intact heart include the ventricular function curve and the ejection fraction. The ventricular function curve plots some measure of left ventricular performance as a function of the preload or filling pressure. The ejection fraction (stroke volume divided by end-diastolic volume) is a single number which is representative of a given ventricular function curve.
- D. In certain pathological conditions such as hypoxia, ischemia and heart failure, there is a reduction in cardiac contractility. Various compensatory mechanisms are utilized during heart failure to maintain cardiovascular performance. These include dilation, sympathetic stimulation, an increase in circulating catecholamines and an increased heart rate. Chronic compensatory mechanisms include hypertrophy and an increased extraction of oxygen from the blood.

Clinical Correlation

A 50 year old man is admitted with acute myocardial infarction and severe left ventricular failure. On physical examination, it is noted that he has evidence of low cardiac output and peripheral vasoconstriction (cold, clammy extremities). After placement of catheters to measure hemodynamics, a vasodilator drug (nitroprusside) is given to reduce the afterload (peripheral vascular resistance). Cardiac output increases 50% with the administration of the vasodilator and the peripheral vasoconstriction disappears. The patient is also treated with diuretics to get rid of excess fluid. Over the next 24 hours, the patient becomes very hypotensive. Measurement of the pulmonary capillary wedge pressure (preload) shows it to be 7 mmHg. (An optimal filling pressure usually is 15-20 mmHg.) Accordingly, the patient is given volume intravenously, the filling pressure rises from 7 to 18 mmHg, and the hypotension disappears. Although arterial pressure and pulmonary capillary wedge are reasonable, the cardiac output is still low. Accordingly, the patient receives a catecholamine (dobutamine) to increase the contractile state of the remaining normal myocardium and the cardiac output is improved.

This patient illustrates how appropriate manipulation of preload, afterload, and contractile state can beneficially improve the hemodynamics of a patient with severe heart failure.



XI. STUDENT GOALS

- A. Be able to define and understand the two mechanisms whereby cardiac muscle increases its performance.
- B. Define and understand preload, afterload, contractile state, and heart rate.
- C. Understand the relationship between sarcomere length and the active length tension curve of striated muscle.
- D. Define and understand isometric contraction of cardiac muscle and how it is changed with an increase in cardiac contractility.
- E. Understand isotonic contraction and the relationship between force, velocity of shortening, and distance shortened.
- F. Understand the relationship between the total force line and isotonic contractions in cardiac muscle, and the isovolumic pressure line and ejecting contractions in the intact heart.
- G. Understand the pressure volume loop of the left ventricle and the different portions of the cardiac cycle.
- H. Understand the left ventricular function curve.
- I. Understand the relationship between ejection fraction and the ventricular function curve.
- J. Understand the physiologic changes that occur with the process of heart failure.
- K. Understand the acute and chronic compensatory mechanisms that help to offset some of the adverse effects of heart failure.
- L. Understand the principle of ventricular reserve and how it relates to patient symptoms.
- M. Understand the relationship between hemodynamic factors and myocardial oxygen consumption.

XII. REFERENCES

- A. Opie, L. The Heart. Chaps. 6,8,12. Raven.1998
- B. Braunwald, E. ed. Heart Disease, Chap. 12. W.B. Saunders 1997

XIII. DEFINITIONS

- A. Preload - the resting force stretching heart muscle to its initial length.
- B. Afterload - the additional force the heart has to generate in order to shorten.
- C. Contractility - the vigor of contraction as quantitated by different indices.



- D. Heart rate - number of contractions per minute.
- E. Myocardial cell or fiber - bounded by intercalated discs with a single, centrally placed nucleus.
- F. Sarcomere - fundamental unit of cardiac muscle contraction.
- G. Actin and Myosin - thin and thick filaments in a sarcomere.
- H. Isometric contraction - contraction of heart muscle with the ends fixed. This results in force development but no shortening.
- I. L max - the length of muscle at which developed force is maximum.
- J. Maximum rate of force development ($\text{max } dF/dt$ - during an isometric contraction, $\text{max } dF/dt$ is the maximum slope of the force versus time curve and is an index of contractility of heart muscle).
- K. Isotonic contraction - contraction obtained using lever system with preload and afterload. The muscle develops force to match the afterload and then shortens while force remains constant (isotonic).
- L. V max - when heart muscle performance is plotted as a force-velocity relation, V max represents the theoretical maximum velocity of shortening at zero load.
- M. Total force line - the sum of resting and developed force during a series of isometric contractions at different muscle lengths.
- N. Pressure volume loop - course of a single ventricular contraction obtained by plotting instantaneous pressure versus instantaneous volume throughout the contraction cycle.
- O. Ventricular function curve - some measure of ventricular performance such as stroke volume or stroke work is plotted as a function of preload, such as ventricular filling pressure.
- P. Frank-Starling mechanism:
1. isolated muscle - for the same inotropic state, an increase in resting length and resting force (preload) results in an increased force of contraction during stimulation.
 2. intact heart - for the same inotropic state, an increased end-diastolic volume and pressure (preload) results in an increased stroke volume. Thus, the Frank-Starling mechanism is responsible for the ascending limb of the ventricular function curve.
- Q. Ejection fraction - stroke volume divided by end-diastolic volume.
- R. Inotropic – Pertaining to the force of muscle contraction, particularly heart muscle. Inotropic agents increase the ability of heart muscle to contract.



Autonomic Drugs: Anticholinergic Drugs

Reading assignment: Katzung (10th ed), Ch. 8 & 27 (pp 424-436)

LEARNING OBJECTIVES:

- A. Learn the pharmacology of atropine. Understand the reason for its limited clinical usefulness. Understand the concept of "pharmacokinetic selectivity".
- B. Learn the pharmacologic effects of ganglionic-blocking drugs. Understand why they are obsolete clinically.
- C. Learn the pharmacology of d-tubocurarine and succinylcholine, drugs that relax skeletal muscle.
- D. Learn the action of botulinum toxin.

TOPICS

- A. Nicotinic receptor antagonists
 - 1. Ganglionic blockers
 - 2. Neuromuscular blockers
- B. Succinylcholine: a persistent agonist
- C. Muscarinic receptor antagonists



Last Year's (2010) Syllabus

ARRHYTHMIAS

LEARNING OBJECTIVES:

- A. To be able to describe basic mechanisms of arrhythmias.
- B. To be able to recognize P wave and QRS complex and describe characteristics and electrical origin of each.
- C. To be able to calculate intervals and heart rate on ECG.
- D. To be able to measure duration of PR, QRS, QT intervals on ECG and to understand how they relate to timing of electrical and mechanical events.
- E. To be able to identify common arrhythmias using a single lead ECG (including sinus bradycardia, sinus tachycardia, atrial tachycardia, atrial flutter, atrial fibrillation, supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation, premature atrial beats, and premature ventricular beats.)
- F. To be able to describe the mechanism, evaluation, and treatment of common arrhythmias including sinus bradycardia, sinus tachycardia, atrial tachycardia, atrial flutter, atrial fibrillation, supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation, premature atrial beats, premature ventricular beats.
- G. To be able to identify using a single lead ECG the presence of Wolff-Parkinson-White syndrome.
- H. To be able to describe the differential diagnosis of a beat or rhythm with a wide QRS complex.
- I. To be able to describe bundle branch block and functional bundle branch block (aberrancy).
- J. To be able to describe the differential diagnosis and appropriate evaluation of the patient with syncope.
- K. To be able to describe general function and indications for permanent pacemaker implantation.
- L. To be able to describe the general function and indications for implantable defibrillators.

TOPICS TO REVIEW FROM PHYSIOLOGY:

The conduction system, genesis of electrocardiogram, parts of the electrocardiogram (P, QRS), relation between electrical events and cardiac events such as valve opening, atrial and ventricular systole and diastole



TYPES OF RHYTHMS AND ARRHYTHMIAS

- A. Sinus Rhythm
- B. Abnormalities of Sinus Rhythm
 - 1. Sinus Bradycardia
 - 2. Sinus Tachycardia
- C. Atrial Arrhythmias
 - 1. Atrial Fibrillation
 - 2. Atrial Flutter
- D. Supraventricular Tachycardia
- E. Accessory Pathways and Wolff-Parkinson-White Syndrome
- F. Ventricular Arrhythmias
 - 1. Ventricular Tachycardia
 - 2. Ventricular Fibrillation
- G. Atrioventricular Block
 - 1. First Degree A-V Block
 - 2. Second Degree A-V Block
 - a. Mobitz Type I (Wenckebach Block)
 - b. Mobitz Type II
 - 3. Complete A-V Block (Third Degree)

DEFINITION OF ARRHYTHMIAS:

Arrhythmias are broadly defined to be abnormalities of cardiac rhythm.

I. MECHANISMS OF ARRHYTHMIAS

A. DISTURBANCES OF IMPULSE FORMATION:

The sinus node may transiently fail to create a sinus beat, a situation called sinus arrest. Sinus arrest may be due to changes with aging or fibrosis in the sinus node, damage to the sinus node blood supply, surgical injury, severe electrolyte abnormalities, or drugs (calcium channel blockers, beta receptor blockers).

B. ECTOPIC IMPULSE FORMATION

- 1. Ectopic beats may arise from the atrium, conduction system, and ventricle. While they generally are premature (before the normal sinus beat would ordinarily have occurred), there also a series of ectopic beats called an escape rhythm that occurs when the normal impulse does not occur at a fast enough rate. [It is important to note that ectopic beats may



- occur prematurely or when the sinus rhythm is not fast enough]
2. For example, in sinus arrest secondary pacemaker sites in the AV node, His Purkinje system, or the ventricle will begin to take over impulse formation. These secondary pacemakers have intrinsic rates that are significantly slower than the sinus node and are normally suppressed by the sinus node.
 3. Premature ectopic beats are generally due to abnormal automaticity or pacemaker activity, which can be caused by metabolic or electrolyte abnormalities. As discussed above, the SA node, AV node and His-Purkinje fibers have spontaneous depolarizing activity. (Figure 1). It can be caused by acute ischemia, drugs, chronic degenerative changes, inflammation, chronic ischemia or fibrosis.



Figure 1

Following a pause (in this case after cessation of a burst of pacing) early afterdepolarizations was recorded on monophasic action potential tracing giving rise to a premature ventricular complex.

4. Ectopic premature beats may also be caused by triggered activity, which is a term used to describe an arrhythmia caused by afterdepolarizations. Afterdepolarizations are caused by oscillatory changes of the membrane potential that depend on preceding electrical activity (needs a trigger). Hence, unlike automatic tachycardias, these arrhythmias are not self-initiating. There are two types of afterdepolarizations based on the timing of the afterdepolarizations with respect to repolarization,: (1) early afterdepolarizations which occur prior to completion of repolarization, and (2) late afterdepolarizations, which occur following full repolarization. It should be kept in mind that this categorization is an oversimplification of a very complex group of arrhythmias exhibiting a full spectrum of afterdepolarizations occurring anywhere within and after repolarization, and that the disorder can be attributed to disturbances of several ion channels. The one common theme of these arrhythmias is their dependence on a prior depolarization. Triggered arrhythmias may respond to beta blockers or calcium-channel blockers.



- a. Early afterdepolarizations: This activity, typically occurring during phase 2 and 3 of repolarization, can be caused by any intervention in which inward (depolarizing) current exceeds outward (repolarizing) current. The problem is believed to be in the reduction of outward current. Reduced potassium conductance can be caused by some potassium-blocking drugs (quinidine, sotalol). Some people are born with a defective K- or Na-channel. When such oscillatory activity reaches threshold potential it can cause a premature contraction (Figure 1) or a burst of tachycardia.

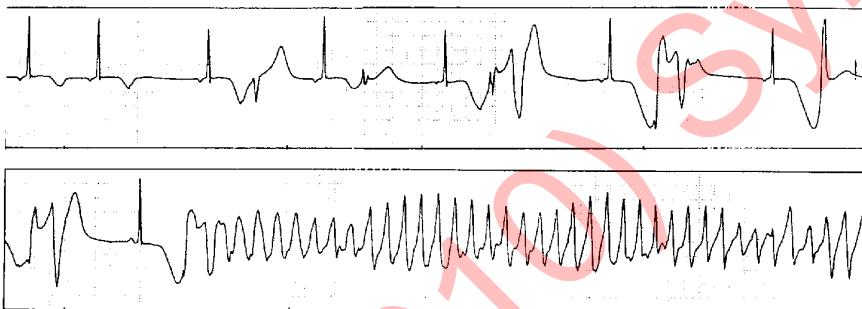


Figure 2

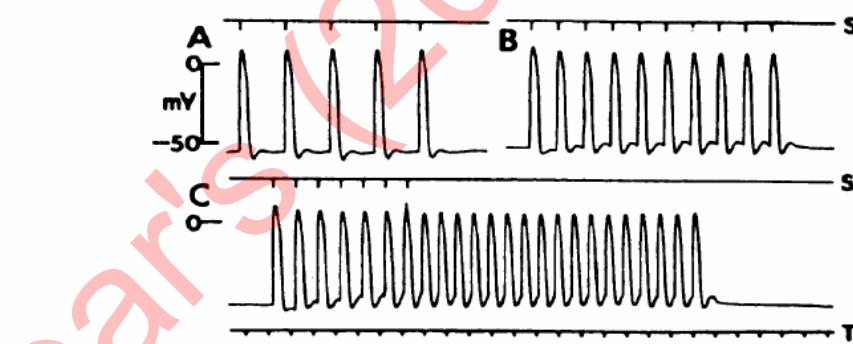
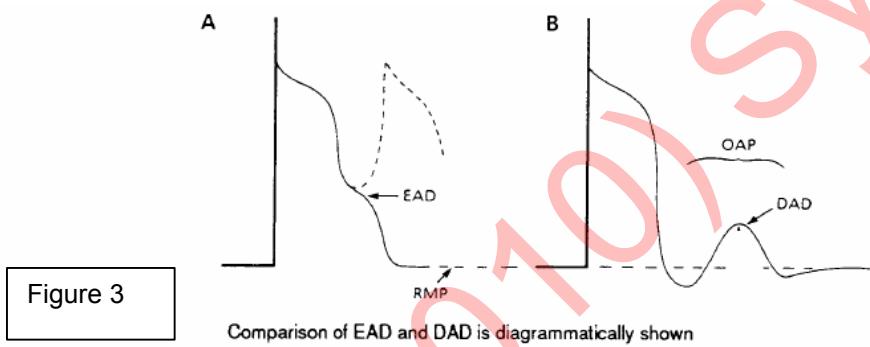
An example of a pause-dependent long-QT and polymorphic VT in a patient on quinidine (a drug that blocks Na^+ and K^+ channels). Note the bizarre and long QT interval following the pause.

One clinical entity seems to fit this mechanism, the polymorphic ventricular tachycardia known as torsade de pointes (twisting of the points) (Figure 2). This entity is also known as the Long QT Syndrome because it is typically associated with a long QT pattern. Because the occurrence of afterdepolarization is not uniform throughout the ventricle, the delay in repolarization causes unpredictable, chaotic dispersion of recovery, resulting in reentry with a constantly moving pattern. Hence the ECG picture is a polymorphic type of ventricular tachycardia. This arrhythmia is commonly drug-induced (quinidine and other antiarrhythmics) or due to electrolyte abnormalities (hypokalemia and/or hypomagnesemia). There are also inherited forms of the Long QT Syndrome due to mutations in potassium or sodium channels. These arrhythmias may be life-threatening.

- b. Delayed afterdepolarizations: This abnormality, which was first noted in the setting of digitalis toxicity, is believed to be due to excess in intracellular calcium causing abnormal inward current. Digitalis, by blocking the Na^+/K^+ pump causes an increase in

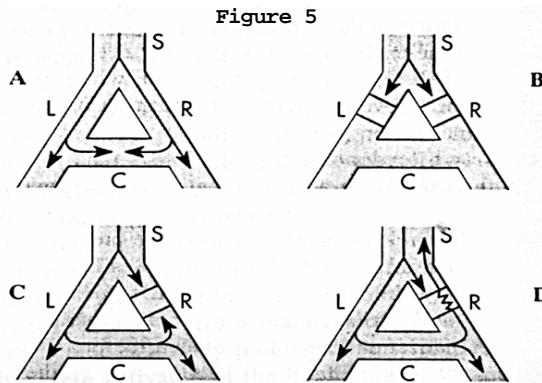


intracellular Na^+ , which in turn increases intracellular Ca^{++} through the $\text{Na}^+ \text{-Ca}^{++}$ exchange mechanism. The increased level of intracellular Ca^{++} is believed to alter membrane permeability allowing inward movement of mostly Na^+ ions. Increased intracellular Ca^{++} can also be caused by catecholamines, which are known to enhance conductance through L-type Ca^{++} channels. Unlike early afterdepolarizations, the magnitude of delayed afterdepolarizations increases with higher rates of preceding depolarizations (Figure 3) because with increasing frequency of depolarization, there is an accumulation of intracellular Ca^{++} .



Shown here is a transmembrane recording from a Purkinje cell recovering from ischemia. The preparation was stimulated at increasing rates from A to C, resulting in an increase in the amplitude of DAD which finally reached threshold potential and initiated triggered rhythm.





The role of unidirectional block in reentry. In **A**, an excitation wave traveling down a single bundle (**S**) of fibers continues down the left (**L**) and right (**R**) branches. The depolarization wave enters the connecting branch (**C**) from both ends and is extinguished at the zone of collision. In **B**, the wave is blocked in the **L** and **R** branches. In **C**, bidirectional block exists in branch **R**. In **D**, unidirectional block exists in branch **R**. The antegrade impulse is blocked, but the retrograde impulse is conducted through and reenters bundle **S**.

- c. Reentry: Reentry is by far this is the most common type of arrhythmia in the clinical setting, and because of its self-sustaining characteristics. It simply requires the presence of conduction disparity between tissue sites whereby an area of slower conduction would initially block a premature impulse and later allow it to reenter, setting up a self-sustaining loop (Figure 5). Conduction disparity can occur under normal conditions (dual AV nodal pathways) from congenital anomalies (accessory pathways as in Wolf-Parkinson-White syndrome) or precipitated by drug effect or ionic imbalance. It should be noted that the conduction delay or block may not necessarily be created by a fixed, structural abnormality. A simple disparity of conduction due to physiologic or pathologic anisotropy is sufficient to cause reentry. More commonly, areas of slow conduction occur as a result of tissue pathology, such as heterogeneity in areas of healed myocardial infarction or cellular hypertrophy and fibrosis from cardiomyopathy. The latter conditions are usually present in patients with reduced left ventricular function and the arrhythmia is frequently fatal. It is estimated that sudden death from fatal ventricular tachycardia and/or fibrillation affects over 400,000 people in the U.S. yearly. Reentry can occur at any site in the heart. Atrial reentry arrhythmia includes atrial flutter. In atrial fibrillation (AF), the most common clinical arrhythmia, there is not one specific reentrant pathway but rather



a changing series of reentrant wavefronts. Ventricular reentry arrhythmias include ventricular tachycardia (VT). As in atrial fibrillation, in ventricular fibrillation (VF), there are multiple reentrant wavefronts occurring throughout the ventricular myocardium. Ventricular tachycardia and ventricular fibrillation are the most "malignant arrhythmias." In the group of arrhythmias classified under the common term "paroxysmal supraventricular tachycardia" (PSVT), reentry is the most common mechanism, usually either within the AV node (AV nodal reentrant tachycardia AVNRT) or involving an accessory pathway (AV reciprocating tachycardia, AVRT). To effectively treat reentry arrhythmia, the slow conduction should be corrected or the alternate pathway eliminated or both. So far, available antiarrhythmic drugs have disappointing efficacy. This should really not surprise anyone because drugs that are aimed at blocking any of the ionic channels may actually make the situation worse. Beta blockers and calcium-channel blockers have limited effect on the atrial and ventricular myocardium. The Na⁺-channel blockers may further slow conduction (and not surprisingly, some are indeed "proarrhythmic"). K⁺-channel blockers offer some promise because by prolonging recovery, they may terminate reentry. For supraventricular tachycardias, the definitive therapy usually requires the elimination (ablation) of the alternate pathway or key elements of the reentry circuit. The most effective immediate therapy for life threatening reentrant ventricular tachycardias is electrical cardioversion. By using a large transthoracic voltage it is possible to depolarize the entire heart muscle and thereby abolishing discrepancies in conduction that are essential for reentry.

Some of the commonly encountered reentry arrhythmias that constitute distinct clinical entities and will be discussed below.

II. RHYTHM DISTURBANCES

A. Sinus Rhythm

The sino-atrial (SA) or sinus node generates an electrical impulse that spreads throughout the heart, producing a constant rhythm. This is called the Sinus Rhythm, occurring at rates from 60 to 100 beats per minute.



These rates are arbitrarily designated as the normal range. The rate of the sinus node impulse formation is influenced by sympathetic and parasympathetic regulation.

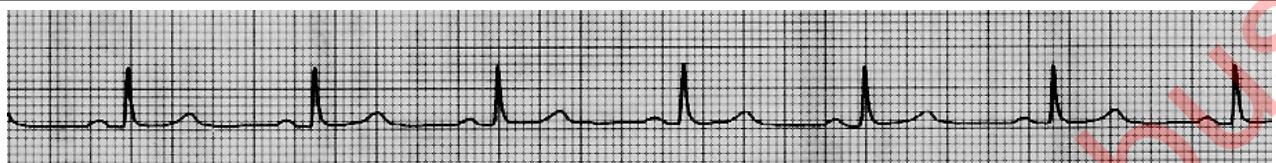


Figure 6. Normal Sinus Rhythm. The rate shown here is between 60-75 beats per minute.



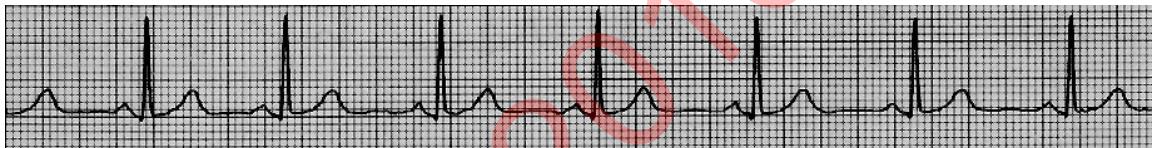
Self Study Question #1

Normal sinus rhythm occurs at rates from _____ to _____ beats per minute.



Answer: 60 to 100.

Identify the P-Wave, QRS complex, and T-wave in the following EKG



B. Abnormalities of Sinus Rhythm

Two abnormalities of sinus rhythm are sinus bradycardia and sinus tachycardia.

1. Sinus bradycardia occurs when the sinus rhythm falls below 60 beats per minute. While described as an arrhythmia, sinus bradycardia frequently occurs normally during sleep, in young adults and in athletes. When the rates are extremely slow or pauses greater than 3.0 seconds occur while awake, sinus node dysfunction is likely present. This may result in symptoms of lightheadedness and loss of consciousness, and may require a permanent pacemaker (see therapy section below).

Sinus Bradycardia: < 60 beats per minute

2. Sinus tachycardia occurs when the sinus rhythm is greater than 100 beats per minute. The sinus rate usually increases gradually as sympathetic stimulation increases. Therefore, causes for sinus tachycardia should be investigated, but by itself does not require treatment in most situations.



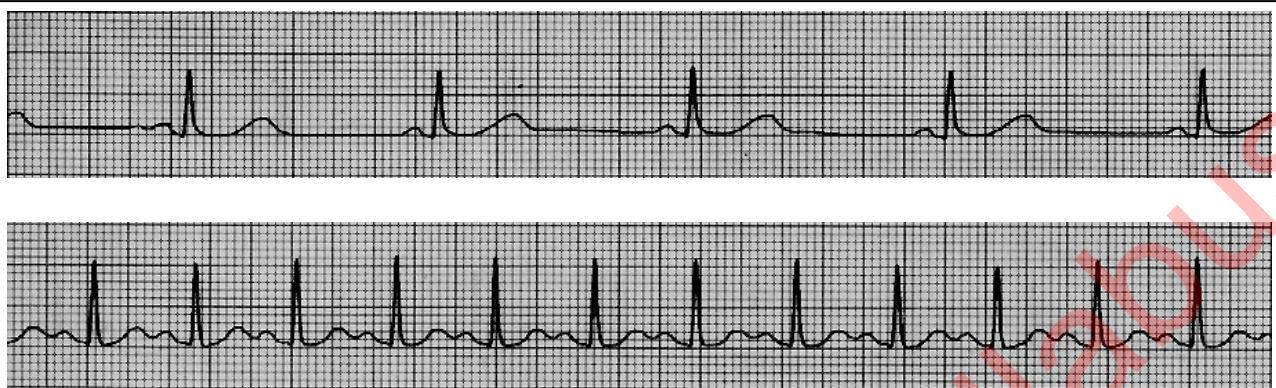


Figure 7. Sinus Bradycardia (above) and Tachycardia (below). With bradycardia, the rate of the sinus impulses falls below 60 beats per minute. The tracing below illustrates tachycardia, with a rate of 121 beats per minute.

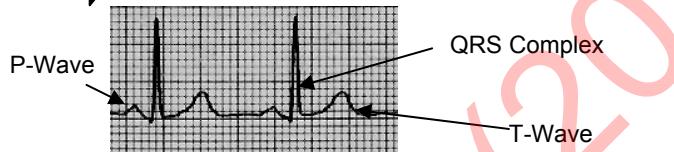


Study Question #2

As sympathetic stimulation increases, sinus _____ can occur.
With excess parasympathetic stimulation, sinus _____ can occur.



Answer: (from #1)



Answer: (from #2) tachycardia, bradycardia In terms of rate, sinus bradycardia < normal sinus rhythm < sinus tachycardia.

Atrial Arrhythmia

Atrial Fibrillation

III. ATRIAL FLUTTER

- A. Atrial Fibrillation occurs when there is rapid chaotic disorganized electrical activity in the atria due to multiple wavefronts. This random electrical activity originates from within the atria only, not from other parts of the heart. Atrial fibrillation is not due to a single reentrant circuit (see below). The atrial activity occurs at rapid rates varying between 300 and 600 beats per minute. Since the A-V node does not play an obligate role in the perpetuation of the atrial fibrillation, even though vagal maneuvers or adenosine will block conduction via the A-V node transiently, they will not terminate the rhythm.



Atrial fibrillation occurs when there is rapid chaotic disorganized electrical activity in the atria. Not due to single reentrant circuit. Rates of 300-600 beats per minute seen.

In multiple locations in the atria, there are wavefronts that activate different parts of the atria. Therefore, there are no true P-waves, only many irregular deflections or “bumps” on an EKG. Only some of the impulses travel from the atria to the ventricles via the A-V node. Impulses bombard the A-V node at an irregular rate and the A-V node only permits some of these impulses to travel to the ventricles. This can result in a ventricular rhythm that is also irregular.

Atrial fibrillation may occur in patients with enlargement of the atria associated with increased atrial pressures. Atrial fibrillation may be associated with hyperthyroidism, congestive heart failure, and increased age.

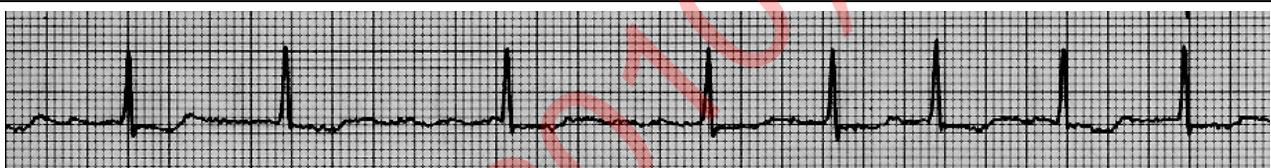


Figure 8. Atrial Fibrillation. The absence of an identifiable P-wave is a characteristic of atrial fibrillation.

Because of the multiple electrical wavefronts occurring during atrial fibrillation, the coordinated contraction of the atrium immediately preceding ventricular contraction is absent. Atrial contraction in sinus rhythm, sometimes called “an atrial kick” provides an additional blood volume to the ventricles and results in an increase in cardiac output of between 10-25%. The absence of atrial contraction may lead to “stagnation” of blood in the atria, potentially causing blood clots, which may embolize to the brain and other parts of the body. Atrial fibrillation is an important cause of stroke, particularly in patients with heart failure, hypertension, or increasing age.

Study Question #3

Where are the P-waves in the above tracing?

What is the rate?

→ Answer: (from #3) With atrial fibrillation, there are no discernible P-waves.

The atrial rate is said to be between 300-600 beats per minute.



What is more useful to know is the ventricular rate, which can be calculated by measuring the time between the QRS complexes.

- B. Atrial Flutter occurs when there is reentry within one or both atria. Reentry (see above) creates an electrical wavefront to move in a circular path through the atria so that each wave is identical to the next wave. This results in a repetitive appearance of the atrial activity on the EKG. The EKG in atrial flutter is described as having a "sawtooth" appearance that is regular. This appearance is most notable in the inferior EKG leads: II, III, and aVF. The atrial rate is commonly 300 beats per minute usually from 250 to 350 beats per minute. As in atrial fibrillation, in atrial flutter, the A-V node does not play an obligate role in the perpetuation of the atrial rhythm. Thus, vagal stimuli or adenosine (that transiently blocks conduction through the A-V node) will not terminate atrial flutter.

Atrial Fibrillation vs. Atrial Flutter

- Atrial flutter is caused by a single reentrant circuit
- Atrial fibrillation is caused by multiple wavefronts
- Atrial flutter has a characteristic "sawtooth" pattern while atrial fibrillation has a non-repetitive "wavy" appearance
- The ventricular complexes in atrial flutter may be somewhat regular while they are usually quite irregular in atrial fibrillation



Figure 9



- C. Supraventricular Tachycardia is a term used to describe arrhythmias in which impulse conduction begins above the ventricles (hence supraventricular) and then travels via the A-V node through the rest of the conduction system. These tachycardias have atrial rates, which usually range from 150-250 beats per minute and have ventricular rates, which may be the same or less depending on the arrhythmia's mechanism. Remember, atrial flutters have rates ranging from 250-350 beats per minute, and atrial fibrillation have rates ranging from 300-600 beats per minute

ATRIAL RATES	
Atrial Fibrillation: 300-600 beats per min	
Atrial Flutter:	250-350 beats per min
	Supraventricular
Tachycardia:	150-250 beats per min

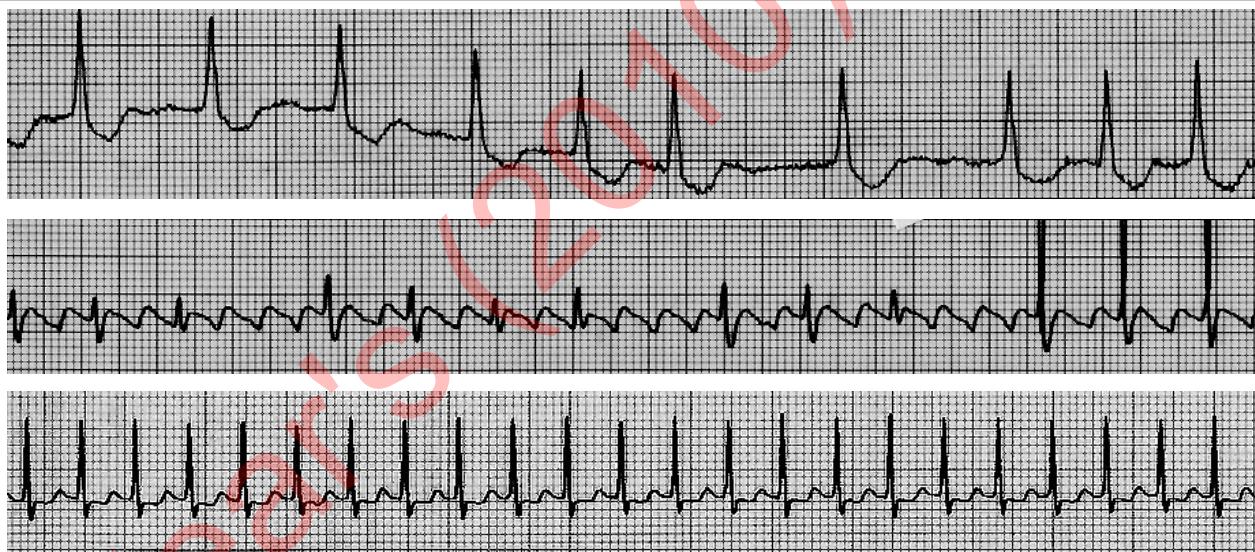


Figure 10. Atrial Fibrillation (top), Atrial Flutter (middle), and Supraventricular Tachycardia (bottom).

1. Atrial fibrillation is irregular due to multiple wavefronts in the atria, and is not due to a single reentrant circuit.
2. Atrial flutter is due to a reentrant circuit in the atria, causing a repetitive saw toothed pattern.
3. Supraventricular tachycardias are most commonly caused by reentrant circuits involving the A-V node and in some cases also an accessory pathway.

1. There are three general causes of supraventricular tachycardias:
 - a. A-V nodal reentry, which results from a circuit of reentry within and around the A-V node itself. A reentrant rhythm is caused by a self-sustaining



- electrical circuit that repeatedly depolarizes a region of cardiac tissue.
- b. A-V reciprocating tachycardia utilizing an accessory pathway. Conduction occurs from the atria, through the A-V node to the ventricles, and then back to the atria via an accessory pathway. (See section on Accessory Pathways and Wolff-Parkinson-White syndrome below).
 - c. Ectopic atrial tachycardia. This is a less common cause of supraventricular tachycardia, which primarily occurs due to abnormal automaticity from a site within the atria.

Study Question #5



Supraventricular tachycardias generally have rates ranging above _____ beats per minute, and less than _____ beats per minute.

What are the types of supraventricular tachycardias?



Answer: (from #3) With atrial fibrillation, there are no discernible P-waves.

The atrial rate is said to be between 300-600 beats per minute.

What is more useful to know is the ventricular rate, which can be calculated by measuring the time between the QRS complexes.

IV. ACCESSORY PATHWAYS AND WOLFF-PARKINSON-WHITE SYNDROME

Accessory Pathways

Wolff-Parkinson-White Syndrome

Treatments

- A. Accessory Pathways are connections between the atrium and the ventricles in the A-V groove along either the mitral or tricuspid annuli. Some accessory pathways can conduct both antegrade (from atrium to ventricle) and retrograde (from ventricle to atrium). Many accessory pathways can only conduct retrograde. Accessory pathways that conduct antegrade are more similar to myocardial tissue than A-V nodal tissue. What this means is that when the heart rate increases, the refractory period of the bypass tract may actually decrease as the atrial rate increases. Normally in the absence of an antegradely conducting accessory pathway, as the atrial rate increases, the refractory period of the A-V node increases.



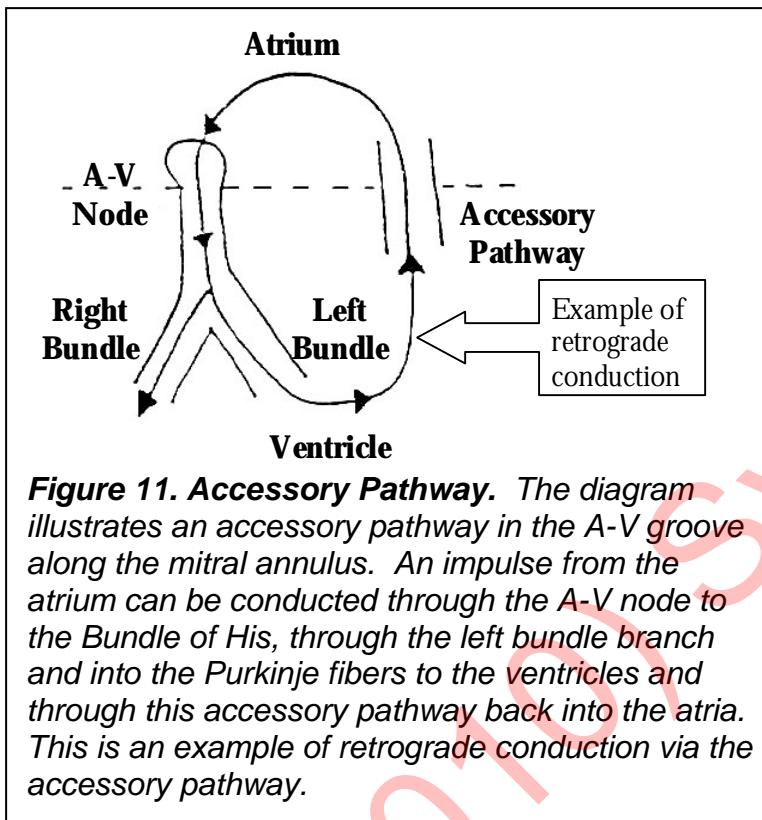


Figure 11. Accessory Pathway. The diagram illustrates an accessory pathway in the A-V groove along the mitral annulus. An impulse from the atrium can be conducted through the A-V node to the Bundle of His, through the left bundle branch and into the Purkinje fibers to the ventricles and through this accessory pathway back into the atria. This is an example of retrograde conduction via the accessory pathway.



Study Question #6

What direction is antegrade? Retrograde?



Answer: Antegrade—from atria to ventricle. Retrograde—from ventricles to atria.

- B. Wolff-Parkinson-White Syndrome (WPW) occurs in patients having accessory pathways with both antegrade and retrograde conduction. Conduction antegrade (from atrium to ventricle) via the accessory pathway may result in conduction the ventricles earlier than via the slowly conducting A-V node. Antegrade conduction results in a portion of the ventricles before normal depolarization occurs. Therefore, the P-R interval appears shortened, while the QRS complex appears lengthened. What results is a slur on the upstroke of the QRS complex called a delta wave. (Patients with an accessory pathway which only conducts retrograde do not have a delta wave on the ECG. These patients are referred to as having a concealed accessory pathway since it is not visible as a delta wave on the ECG). This indicates that there is an accessory pathway that can conduct antegrade from the atrium to the ventricles. With the presence of a delta wave, the PR interval (which reflects the conduction from atrium to ventricle) therefore is shorter than usual (< 0.12 seconds).



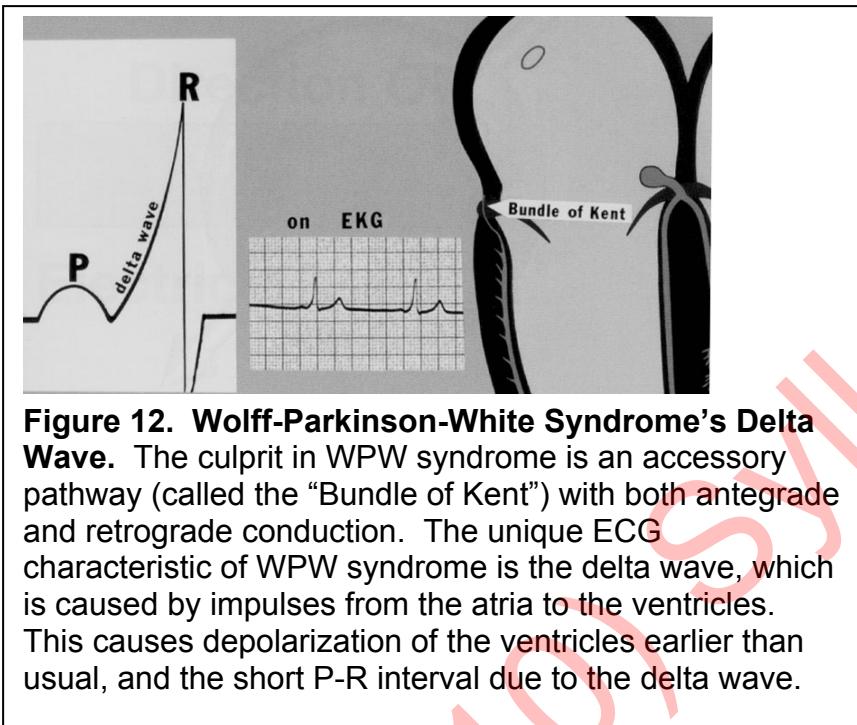


Figure 12. Wolff-Parkinson-White Syndrome's Delta Wave. The culprit in WPW syndrome is an accessory pathway (called the "Bundle of Kent") with both antegrade and retrograde conduction. The unique ECG characteristic of WPW syndrome is the delta wave, which is caused by impulses from the atria to the ventricles. This causes depolarization of the ventricles earlier than usual, and the short P-R interval due to the delta wave.

The most common arrhythmia in WPW syndrome is A-V reciprocating tachycardia. Here, conduction is from the atrium to the ventricles via the A-V node to the His bundle, and then goes from the ventricles to the atria via the retrograde accessory pathway, restimulating the atria (see Figure 6 above).

Some patients have accessory pathways with extremely short refractory periods, permitting much more rapid conduction to the ventricles than in patients without Wolff-Parkinson-White Syndrome. These rates may approach 300 beats per minute and result in collapse or ventricular fibrillation (see below).



Figure 13. Wolff-Parkinson-White Syndrome. The characteristic delta wave is seen in the tracing above that is indicative of this syndrome.

- C. Treatments for WPW Syndrome or other arrhythmias associated with accessory pathways include drug therapy and radiofrequency catheter ablation.



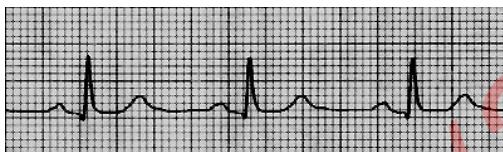
1. Type 1A or 1C or III drugs may be used to treat patients with Wolff-Parkinson-White syndrome also in combination with beta-receptor antagonists to prevent catecholamine reversal of the effects of these antiarrhythmic drugs. Sole therapy with agents that block the A-V node should be avoided.
 - a. Type 1A: Procainamide, Quinidine, Disopyramide
 - b. Type 1C: Flecainide, Propafenone
 - c. Type III: Amiodarone, Sotalol, Dofetilide
2. Radiofrequency Catheter Ablation is a non-surgical technique that uses a catheter that creates small burns at the site of the accessory pathway or arrhythmic site. This prevents accessory pathway conduction that causes the patient's arrhythmias. Radiofrequency catheter ablation cures more than 90% of patients with WPW.

Study Question #7



Patients with WPW syndrome have both _____ and _____ conduction pathways. This results in a _____ wave on their QRS complexes.

Identify the tracing with Wolff-Parkinson-White Syndrome.



Answer: antegrade and retrograde, delta.

The EKG tracing on the right has WPW Syndrome.

V. VENTRICULAR ARRHYTHMIAS

Ventricular Tachycardia

Ventricular Fibrillation

A.

Wide Complex Tachycardia is a rapid rhythm with ventricular rates greater than 100 beats per minute with a QRS complex greater than 0.12 seconds. The mechanism of such a rhythm is most commonly either ventricular tachycardia, a rhythm starting in the ventricles, or a supraventricular arrhythmia starting in the atria but conducting down only one bundle branch because of the rapid rates. The increase in QRS duration, typically due to block in one of the two bundle branches, occurs with rapid atrial rates and is called functional bundle branch block or aberrancy. In such cases the QRS is not wide at slow rates but becomes wide when one bundle branch becomes refractory, permitting conduction down only one bundle branch.



The narrow QRS duration normally seen in the absence of bundle branch block originates from the rapid conduction via the His-Purkinje system that nearly simultaneously carries the electrical wavefront to most parts of the ventricles. When the impulse is blocked in one of the bundle branches, the rest of ventricles are activated slowly.

The wide complex tachycardia must be due to a ventricular tachycardia (origin in the ventricles) or a supraventricular tachycardia with aberrancy.

- B. Ventricular Tachycardia is characterized by a wide QRS typically 0.14 seconds or greater in width with a rapid rate, typically 150 to 250 beats per minute. Most commonly there is no evidence of atrial activity preceding each QRS complex. Ventricular tachycardia may be either monomorphic, having the same appearance for each complex (most common), or polymorphic, different appearances for each QRS complex. The most common mechanism is reentry, which usually is the result of a prior myocardial infarction. A tachycardia with wide QRS complex may be either ventricular tachycardia or a supraventricular rhythm with functional bundle branch block (also called aberrancy). [It is important to recognize that a wide QRS complex may be ventricular tachycardia.]

Ventricular tachycardia frequently results in a decrease in blood pressure of varying degrees. If the ventricular tachycardia is sustained and does not terminate by itself, it is usually considered to be serious and life-threatening. [It is important to note that ventricular tachycardia may cause hypotension and be life-threatening. Therefore, it must be diagnosed and treated quickly.]

Some polymorphic ventricular tachycardias occur as the result of genetically based ion channel abnormalities. In such cases, the QT interval may be significantly prolonged, hence, the name long QT syndrome. Some drugs may cause such a prolongation of the QT and may result in polymorphic ventricular tachycardia. Many of the polymorphic ventricular tachycardias due to QT prolongation may have a twisting or turning appearance and are called torsade de pointes.



Ventricular Tachycardia

- Wide QRS—0.14 secs or greater
- Usually 150-250 bpm
- Most commonly no P waves
- QRS complexes either monomorphic or occasionally polymorphic
- Commonly due to reentry
- Life-threatening



Figure 14. Ventricular Tachycardia. Wide QRS complex tachycardia without clearly visible P-waves. May cause hypotension or lead to collapse. Considered life-threatening. [It is important to be able to recognize ventricular tachycardia]



Study Question #8

Which is more serious – supraventricular tachycardia or ventricular tachycardia?

What is the ventricular rate during ventricular tachycardia? How wide is the QRS complex?



Answer: ventricular tachycardia is more serious.

It is considered life-threatening.

Usually 150-250 bpm. QRS width is 0.14 seconds or greater.

C.

Ventricular Fibrillation results from a rapid (rates of 300-600 beats per minute), extremely irregular rhythm of the ventricles which prevents effective contraction of the ventricles. This gives an erratic appearance on the ECG without clearly recognizable QRS complexes. The failure to have an organized ventricular contraction during systole results in hypotension. If not treated, this rapidly results in death. Ventricular fibrillation must be immediately converted using an electrical shock to the chest. [It is important to be able to recognize ventricular fibrillation on ECG and to understand that it is immediately life-threatening.]



Ventricular Fibrillation

- 300-600 bpm
- Irregular, erratic ventricular rhythm
- No QRS, P, or T waves apparent.
- May be caused by myocardial ischemia or disturbances in electrolytes.

How is ventricular fibrillation caused? It is not caused by reentry.

Ventricular fibrillation may be caused by myocardial ischemia, disturbances in electrolytes, or occur in the setting of left ventricular dysfunction.



Study Question #9

Ventricular fibrillation has no __-waves, no __-waves, and no __-complexes.

How can ventricular fibrillation be recognized?

What is the treatment of ventricular fibrillation?



Answer: P or T-waves, nor QRS complexes.

Ventricular fibrillation is recognized by the absence of discrete QRS complexes and presence of irregular ventricular activity.

Ventricular fibrillation must be immediately treated with an electric shock to the chest.

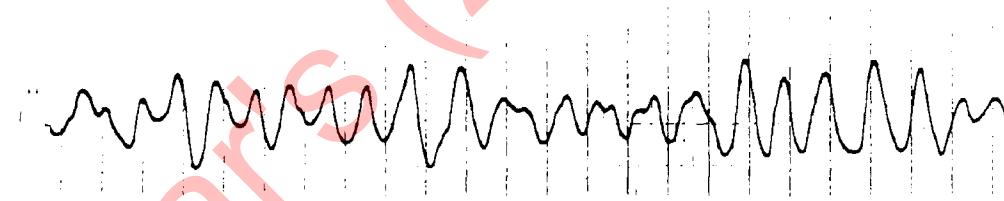


Figure 15.

VI. ATRIOVENTRICULAR BLOCK

First-Degree A-V Block

Second-Degree A-V Block

 Mobitz Type I (Wenckebach block)

 Mobitz Type II

Complete A-V Block (Third Degree)

A-V Block is a term used to refer to altered conduction through the A-V node and the His-Purkinje system. This can range from an increased conduction time from the atrium to the ventricle to complete absence of conduction from the atrium to the ventricle.



- A. First Degree A-V Block results from an increase in the conduction time from the atrium to the ventricle. It is identified on an ECG by a P-R interval greater than 0.2 seconds. The P-R interval includes the beginning of the P-wave up to the beginning of the Q of the QRS complex.



Figure 16. First Degree A-V Block. Measure the P-R interval. Remember, each small box is 0.04 seconds. Pick a P-wave and measure to the beginning of the following QRS complex. The PR interval in the above tracing is about 0.28 sec. or 280



Study Question #10

With first degree A-V block, conduction from the atrium to the ventricle is _____.

Pick which tracing has First Degree A-V Block.



Answer: delayed or prolonged.

The middle tracing has first degree A-V block.

Its P-R interval is about 0.32 second or 320 ms.

- B. Second Degree A-V Block occurs when intermittently one atrial beat fails to conduct from the atrium to the ventricle. (One P wave is not followed by a QRS complex) There are two kinds of second degree A-V block:

1. Mobitz Type I second degree A-V block (Wenckebach Block)—occurs when there is a progressive prolongation of the P-R interval before the atrial beat fails to conduct. For example, the P-R interval increases over two or three complexes, when on the fourth complex, a P wave will be seen without a subsequent QRS complex. This type of block usually occurs at the level of the A-V node rather than the His Purkinje system and is usually not an indication for permanent pacing, unless the patient is symptomatic with lightheadedness or loss of consciousness. [It is important to



be able to distinguish Type I from Type II based on an ECG and level of the block.]

Similarities & Differences between the Mobitz Types I and II

- In both Types I and II second degree A-V block, intermittently one P wave is not followed by a QRS complex.
- Type I (Wenckebach) – the P-R interval progressively increases before a P wave is not followed by a QRS complex. Usually at the level of the A-V node.
- Type II-the P-R interval is constant before a P-wave is not followed by a QRS complex.- Usually below the level of the His bundle.
- Type I block occurs *at the level of the A-V node*.
- Type II block occurs *below the level of the His bundle*.

2. Mobitz Type II—occurs when there is a constant P-R interval before the atrial beat fails to conduct. This is almost always associated with an underlying bundle branch block and occurs below the level of the His bundle and usually is an indication for permanent pacing.
 - a. 2:1 A- V block – when there are two P-waves for every QRS
 - b. 3:1 A-V Block – then there are three P-waves for every QRS complex

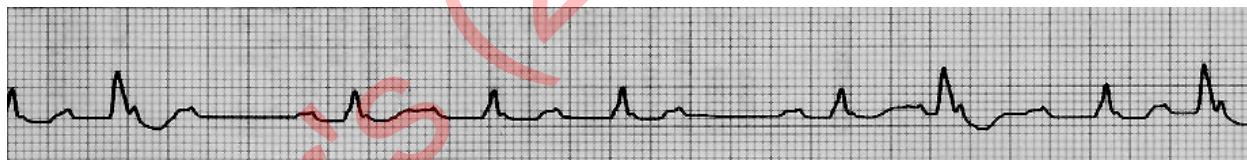
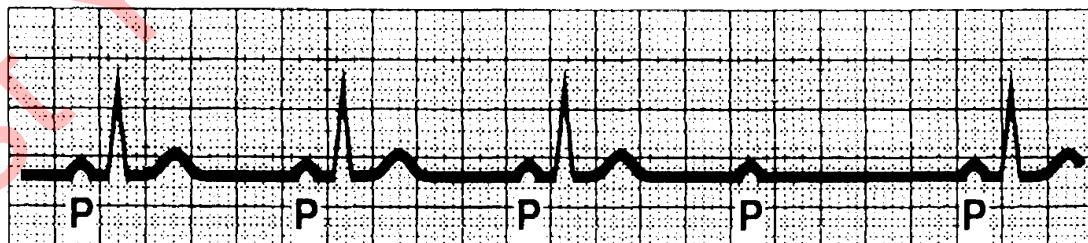


Figure 17. Second Degree A-V Block: Mobitz Type I (Wenckebach, above) and Mobitz Type II (below). For each tracing, observe the sequences that are encircled. In Mobitz Type I, the P-R interval increases with every beat until after one P-wave a QRS complex is dropped. In Mobitz Type II, the P-R interval remains constant, before the QRS complex is dropped.



Study Question # 11

Wenckebach block occurs at the level of _____ in the heart, while Mobitz Type II block occurs at _____.





Answer: The A-V node, a level below the His bundle.

- C. Complete A-V block (Third Degree) occurs when there is no conduction from the atria to the ventricles. The site of the block may be in the A-V node or in the His-Purkinje system. Even with complete A-V block, an escape rhythm occurs in order to maintain a ventricular rate. The escape rhythm is due to some automaticity of the His Purkinje system. The slow escape rhythm may compromise cerebral blood flow and result in syncope. Therefore, acquired complete A-V block usually necessitates permanent pacemaker implantation.

VII. SYNCOPES

The loss of consciousness, may be due to many cardiovascular and non-cardiovascular causes. Syncope may be caused by insufficient blood flow or nutrients to the brain. Insufficient blood flow may result from a decrease in blood pressure or cardiac output. Most episodes of syncope are due to a cardiovascular cause. Neurologic disorders such as seizures are usually considered separately but the patient's cardiac syncope may present with tonic-clonic motions that suggest seizure activity but are secondary to cerebral hypoperfusion usually due to hypotension. Many common causes of syncope may include: 1) bradyarrhythmias, 2) supraventricular or ventricular tachyarrhythmias, 3) neurally mediated or neurocardiogenic causes, 4) orthostatic hypotension, 5 other causes of hypotension, 6) psychogenic causes. The unifying mechanism for non-psychogenic causes is hypotension resulting in cerebral hypoperfusion.

Bradyarrhythmias may result in syncope since the heart rate may not be adequate to maintain cardiac output and cerebral perfusion.

Tachyarrhythmias may result in hypotension because the excessive heart rates do not permit adequate ventricular filling and thus stroke volume.

Neurally mediated or neurocardiogenic syncope occurs as the result of excessive parasympathetic activity and sympathetic withdrawal, resulting in bradycardia and peripheral vasodilatation. This may be triggered by emotion, sight of blood, pain, acute decrease in ventricular diastolic volume due to venous blood pooling, or no clear precipitation. It is felt that an initial sympathetic surge may initiate a sequence of events including excessive parasympathetic activity and subsequent sympathetic withdrawal. In addition, a decrease in ventricular volume or excessive myocardial contractility may result in the reflex consisting of increased parasympathetic activity and sympathetic withdrawal. Treatment of neurocardiogenic syncope may be pharmacologic, beginning with agents which expand volume or with beta-receptor antagonists, which may be effective in blocking the initial sympathetic surge and excessive myocardial contractility. It is important to avoid volume depletion. In some cases, a test called head-up tilt table test, in which the patient lies on a



table which is positioned at 60 to 90 degrees tilt, may reproduce the relative bradycardia and hypotension of the neutrally mediated syncope by causing the stimulus of decreased ventricular volume due to venous pooling of blood.

Orthostatic hypotension may occur as the result of volume depletion or disorders of autonomic regulation of vascular tone resulting in excessive peripheral vasodilatation.

The most important issue in determining the approach to the patient with syncope is the presence of structural heart disease. The etiologies of syncope range from the relatively benign disorders such as neutrally mediated syncope to life-threatening ventricular arrhythmias. When a patient has evidence of structural heart disease, it is important to consider ventricular tachyarrhythmias as possible causes of syncope since they may be life-threatening. A special procedure called an electrophysiologic study (EP study) may be used to determine the likelihood of a ventricular arrhythmia in such patients. For patients without structural heart disease, ECG monitoring may help define the etiology of the syncope.

A. Treatment of Bradyarrhythmias

The common indication for the treatment of bradyarrhythmias are symptoms such as syncope or near syncope, fatigue, or congestive heart failure which may result from excessively slow rates.

Neurological and cardiovascular characteristics of the patient make the rate and duration of bradycardia which results in syncope variable. Permanent pacemaker implantation is the treatment for symptomatic bradycardia. Pauses greater than 3.0 seconds while awake even in the absence of symptoms may sometimes be considered an indication for permanent pacing. Permanent pacemakers are also usually implanted for Mobitz Type II Second degree A-V block and complete A-V block. No pharmacologic therapy is commonly used to treat bradyarrhythmias which otherwise would be treated with pacemakers.

B. Treatment of Supraventricular Tachyarrhythmias

Supraventricular tachycardias which utilize the A-V node as an obligate part of the reentrant circuit (A-V nodal reentrant tachycardia or A-V reciprocating tachycardia utilizing an accessory pathway or bypass tract) may be acutely treated with vagal maneuvers such as carotid sinus massage or Valsalva maneuver or with intravenous medications which block A-V nodal conduction. The drug of first choice is adenosine while other agents such as beta-adrenergic receptor antagonists and calcium channel antagonists verapamil or diltiazem may also be effective. Arrhythmias that result in hypotension should be immediately treated with cardioversion.



For chronic therapy, patients with frequent highly symptomatic episodes of supraventricular tachyarrhythmias without Wolff-Parkinson-White syndrome may usually be treated with A-V nodal blocking agents alone. Radiofrequency catheter ablation, a technique in which a small amount of energy is delivered via a thin tube advanced from an artery or vein to the exact region of the heart responsible for the arrhythmia. The energy creates a very small (several millimeters) "burn"-like lesion in the myocardial tissue responsible for the arrhythmia. This technique is useful for most supraventricular arrhythmias.

In patients with Wolff-Parkinson-White syndrome, Type IA, IC, or III antiarrhythmic drugs may be used, sometimes in conjunction with beta-receptor antagonists to prevent catecholamine reversal of many of these drug effects. Radiofrequency ablation is highly effective for the treatment of Wolff-Parkinson-White syndrome and may result in the cure of the patient in over 90% of cases. Digoxin is avoided in patients with Wolff-Parkinson-White syndrome since it may shorten the refractory period of the bypass tract, resulting in more rapid conduction in atrial fibrillation. Sole therapy using agents which block the A-V node should usually be avoided in Wolff-Parkinson-White syndrome, since the rates in atrial fibrillation should be avoided. Intravenous verapamil should be avoided for this reason and because of its acute hypotensive effects.

The treatment of atrial fibrillation may consist of several components. The absence of coordinated contraction of the atria may lead to stasis of blood, promoting thrombus formation, which may be the source of embolism including stroke. Anticoagulation with warfarin and aspirin may be employed. In most patients the extremely rapid rate of atrial depolarization will result in high ventricular rate. Thus, agents such as digoxin, beta-receptor antagonists, or calcium channel antagonists such as diltiazem or verapamil may be used to modulate the ventricular rate.

Antiarrhythmic drugs of Class IA, IC, or III may be used to maintain sinus rhythm. Electrical cardioversion may be needed in some patients to re-establish sinus rhythm. Catheter ablation for atrial fibrillation is having increasing success in treating patients with atrial fibrillation. In selected patients with difficult to control ventricular rates, a catheter based technique for the ablation of the A-V node to destroy conduction completely may be employed with implantation of a permanent pacemaker.

C. Treatment of Ventricular Arrhythmias

Patients with ventricular arrhythmias within 48 hours of an acute myocardial infarction are not felt to be at substantial risk of long term recurrence of these arrhythmias. However, patients with sustained ventricular tachycardia or fibrillation which does not occur



acutely during a myocardial infarction are at extremely high risk for recurrence, approaching 20 to 50% per year. Patients with these arrhythmias are usually treated with implantation of a special device called an implantable cardioverter defibrillator (ICD). This type of device is implanted subcutaneously and connected via a special lead which is inserted via the cephalic or subclavian vein and advanced to the right ventricle. The device automatically monitors the heart rate using this lead and when a programmed is achieved, the device will deliver a synchronized electrical shock to the lead in the right ventricle (and possibly right atrium or superior vena cava) which will result in conversion of the ventricular tachycardia or ventricular fibrillation. For some reentrant ventricular tachycardias, the implantable defibrillator may pace in the heart at rates faster than the ventricular tachycardia, resulting in termination of the arrhythmia without the need for an electrical shock. ICD therapy is the most commonly used therapy. For the acute treatment of ventricular arrhythmias, intravenous lidocaine and amiodarone and less commonly procainamide may be administered. Catheter ablation techniques for ventricular tachycardia may be used but are more complex than for supraventricular tachycardias.

D. ECG Recording for the Diagnosis of Arrhythmias

Patients may receive a 24 hour continuous ECG recording using a device that records the ambulatory ECG (Holter monitor). Such a device may be used to quantitate frequency symptomatic or asymptomatic arrhythmias. Patients with less frequent but prolonged (> 1 minute) episodes of arrhythmias without syncope may use an event monitor which is carried with the patient and connected only in the event of an arrhythmia. Patients with episodes of syncope or very brief episodes of arrhythmias may use a "loop" monitor which is connected to the patient for several weeks to several months. This device records the ECG continuously in a closed loop and is activated by pushing a button on the recorder. The recorder saves the preceding several minutes and may be transmitted via a telephone hookup



Last Year's (2010) Syllabus

Autonomic Drugs: Sympathomimetic Drugs I

Reading assignment: Katzung (10th ed), Ch. 9

LEARNING OBJECTIVES:

- A. Learn (1) the biosynthesis, storage, release, and termination of action of NE and (2) drugs that inhibit these processes.
- B. Understand the differences between direct-acting and indirect acting sympathomimetic drugs.
- C. Learn the major enzymes that metabolize catecholamines.
- D. Become familiar with the major structure-activity relationships among sympathomimetic drugs.
- E. Continue to learn the tissue distribution of adrenergic receptor subtypes and their responses following agonist administration.

TOPICS

- A. Direct-acting agonists at adrenergic receptors
- B. Indirect-acting sympathomimetic drugs
- C. Metabolism of sympathomimetic amines
- D. Structure-activity relationships
- E. Effects of sympathomimetic drugs



Last Year's (2010) Syllabus

VENTRICULAR PHYSIOLOGY

OBJECTIVES

- A. Understanding the PV Loop
 - 1. Definition
 - 2. Axes
 - 3. Events of the cardiac cycle within the loop
 - 4. Diastolic pressure-volume relationship
 - 5. End-systolic pressure-volume relationship (ESPVR)
 - 6. ESPVR and contractility
 - 7. PV Loop and afterload
 - 8. Interaction of LV performance and the arterial system

** Note: Refer to the definitions list at the end of this lecture for any words or abbreviations that you are unfamiliar with.

I. INTRODUCTION

- A. The heart is functionally divided into a right side and a left side. Each side may be further subdivided into a ventricle and an atrium. The primary role of each atrium is to act as a reservoir and "booster pump" for venous blood entering the ventricles. Recently, with the discovery of atrial natriuretic hormone, other homeostatic roles of the atrium have been proposed. The primary physiologic function of each ventricle is to maintain circulation of blood to the organs of the body. The left heart receives oxygenated blood from the pulmonary circulation, and contraction of the muscles of the left ventricle provide energy to propel that blood through the systemic arterial network. The right ventricle receives blood from the systemic venous system and propels it through the lungs and onward to the left ventricle. The reason that blood flows through the system is because of the pressure gradients set up by the ventricles between the various parts of the circulatory system.
- B. In order to understand how the heart performs its task, one must have an appreciation of the force-generating properties of cardiac muscle, the factors which regulate the transformation of muscle force into intraventricular pressure, the functioning of the cardiac valves, and something about the load against which the ventricles contract, i.e., the properties of the systemic and pulmonic vascular systems. You have learned about the properties of cardiac muscle and vascular systems in previous lectures. This session will focus on a description of the pump function of the ventricles with particular attention to a description of those properties as represented on the pressure-volume diagram.



II. RELATIONSHIP BETWEEN MUSCLE AND VENTRICULAR PROPERTIES

- A. The ventricles are chambers whose walls are composed predominantly of cardiac muscle. Therefore, when considering the properties of the ventricle as a mechanical pump, one should keep in mind the underlying force-generating properties of cardiac muscle and the structural features of the ventricle which determine how muscle force translates into pressure inside the ventricle. In particular, it should be recalled that:
 - 1. The force generated by a muscle is directly influenced by the initial (or "diastolic") length of the muscle -- increased diastolic length results in greater force production.
 - 2. When the volume of the heart is changed, so too is the length of the muscles in the wall of the heart.
 - 3. There is a correlation between force generated by the muscle fibers in the ventricular wall and intraventricular pressure; for example, through a relation such as Laplace's Law -- $P = f/r$ where f = wall force and r = chamber radius.
- B. There are at least four factors that contribute to determining the relationship between muscle properties (length and force) and ventricular properties (volume and pressure):
 - 1. Muscle Mass

It is intuitively obvious that the more muscle that comprises the chamber wall the stronger the ventricle will be. As one example of this, compare the functioning of the right and left ventricles of the same heart. The left ventricle generates about 4 to 5 times the pressure of the right ventricle when the wall stress (stress = force/unit area of muscle) is the same. There are several factors which contribute to this difference, but the predominant one is that left ventricular weight (the amount of muscle) is roughly 3 to 4 times that of the right.
 - 2. Ventricular Geometry

Compare a chamber with a circular cross-section to one with an elliptical cross-section. The mathematical equations relating wall stress and chamber pressure will be different. Thus for the same muscle mass and wall stress, the pressure inside these two chambers would be different.



3. Architecture of the wall

This refers to the how the fibers are put together to form the ventricular wall. Histologic studies have shown that the fiber bundles wrap around the ventricular chamber in a standard way. If one cuts out a small piece of the ventricular wall and examines the fibers, one finds that the angle at which the fibers run relative to the axis of the chamber varies with the depth of the layer within the wall.

4. Activation Sequence

The muscles of the chamber do not contract simultaneously. The muscles are activated by the specialized Purkinje network which conducts electrical impulses an order of magnitude faster than ventricular muscle. In the normal human heart, it takes about 80 ms for all the muscle to become activated and start contracting. This can be greatly prolonged if activation is initiated from outside the normal pathways or when the Purkinje network is diseased. When the activation time is increased, there is greater dispersion in the onset of mechanical contraction of the muscles and the strength of the chamber is reduced an amount proportional to the increase in the dispersion time.

III. ATRIOVENTRICULAR VALVES

- A. Each ventricle has an inlet valve and outlet valve. For the LV, these are the mitral and aortic valves, respectively; for the RV, these are the tricuspid and pulmonic valves, respectively. Each valve allows flow to pass through its orifice in only one direction. Therefore, there is a directionality to the valves, as shown Fig. 1.

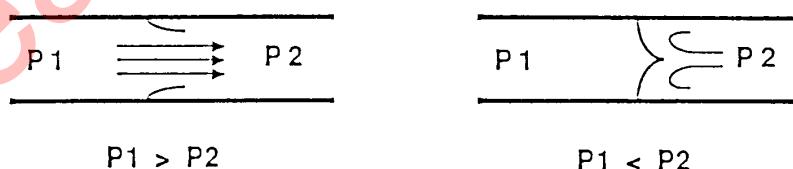


Fig 1. The valves open and close in response to pressure gradients, ensuring one-way flow of blood across the valve orifice.

- B. When the pressure P1 is greater than P2, as in the left side of the figure, flow tends towards the right and fluid pushes on the convex surfaces of the leaflets, opening the valve. In contrast if P2 is greater than P1, as in the right side of the figure, flow tends towards the left and fluid is caught in the concave portion of the leaflets,



expanding then (much like wind filling a sail), causing the leaflets to abut and close the valve. Thus, the main (though not exclusive) determinant of whether the valve is open or closed is the pressure gradient across it.

- C. The heart valves are responsible for enabling the heart to propel blood in only one direction.

IV. THE CARDIAC CYCLE

- A. The cardiac cycle (the period of time required for one heart beat) is divided into two parts: systole and diastole. Systole (from Greek, meaning "contracting") is the period of time during which the muscle transforms from its rested state to the instant of maximal mechanical activation; this period of time includes the electrical events responsible for initiating the contraction. Diastole (from Greek, meaning "dilation") is the period of time during which the muscle relaxes from the end-systolic (maximally activated) state back towards its resting state. Systole is considered to start at the onset of electrical activation of the myocardium (onset of the ECG); systole ends and diastole begins as the activation process of the myofilaments passes through a maximum. These "physiologic" definitions of onsets of systole and diastole differ from the "clinical" definitions which use the first and second heart sounds to define these events.
- B. In the discussion to follow, we will review the cardiac cycle as viewed from the LV. The events in the RV are similar, though occurring at slightly different times and at different levels of pressure than in the LV.
- C. The mechanical events occurring during the cardiac cycle consist of changes in pressure in the ventricular chamber which cause blood to move in and out of the ventricle. Thus, we can characterize the cardiac cycle by tracking changes in pressures and volumes in the ventricle as shown in the Fig. 2 where ventricular volume (LVV), ventricular pressure (LVP) and aortic pressure (AoP) are plotted as a function of time.



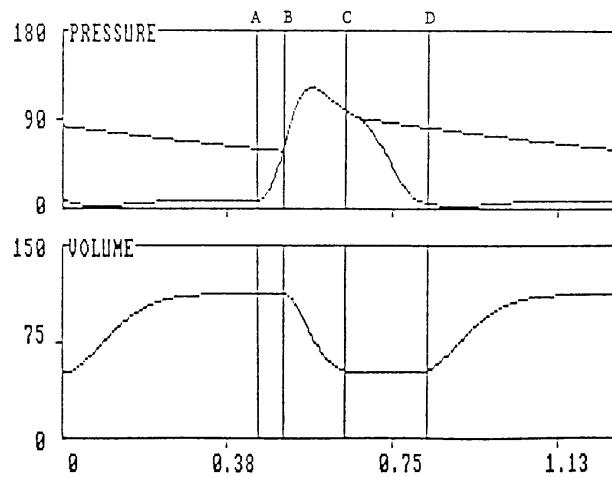
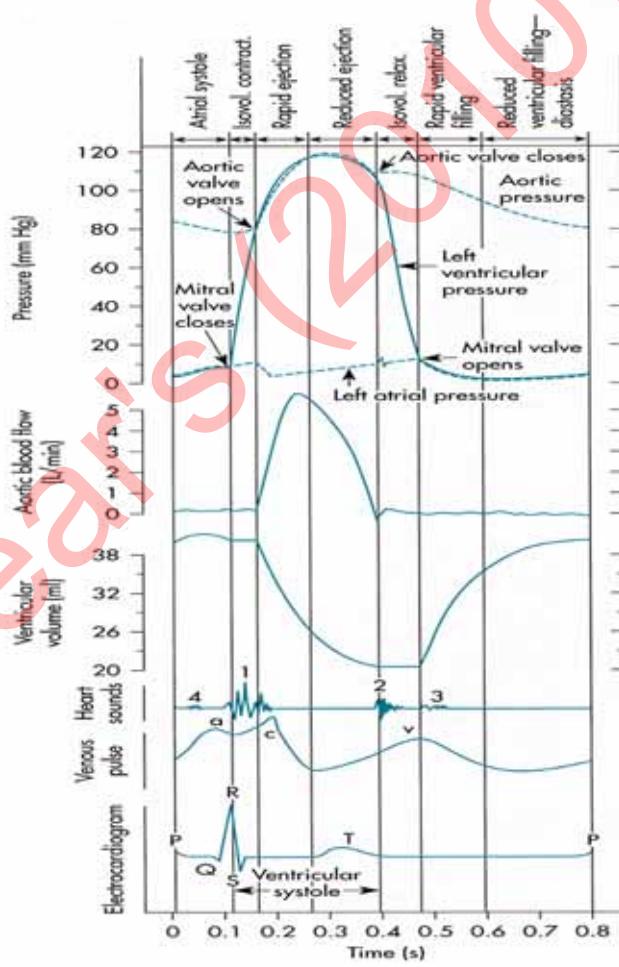


Fig 2. Plots of Aortic pressure, LV pressure and LV volume during a cardiac cycle. A denotes the end of diastole and the onset of systole; B, the onset of ejection; C, the end of ejection; and D, the onset of filling.



- D. Shortly prior to time "A" LVP and LVV are constant and AoP is gradually declining. During this time the heart is in its relaxed (diastolic) state; AoP falls as the blood ejected into the arterial system on the previous beat gradually moves from the large arteries to the capillary bed. At time "A" contraction begins, and pressure rises inside the chamber. Early after contraction begins, LVP rises to be greater than left atrial pressure (LAP, not shown in the graph) and the mitral valve closes. Since LVP is less than AoP, the aortic valve is closed as well. Since both valves are closed, no blood can enter or leave the ventricle during this time, and therefore the ventricle is contracting "isovolumically" (at a constant volume). This period is called "isovolumic contraction". Eventually (at time "B"), LVP slightly exceeds AoP and the aortic valve opens. During the time when the aortic valve is open there is very little difference between LVP and AoP, provided that AoP is measured just on the distal side of the aortic valve. During this time, blood is ejected from the ventricle into the aorta, as indicated on the LVV tracing as a reduction in ventricular volume. The exact shape of the aortic pressure wave and LVV wave during this "ejection" phase is determined by the complex interaction between the ongoing contraction process of the cardiac muscles and the properties of the arterial system, and is beyond the scope of this lecture. As the contraction process of the cardiac muscle reaches its maximal effort, ejection slows down and ultimately, as the muscles begin to relax, LVP falls below AoP (time "C") and the aortic valve closes. At this point ejection has ended and the ventricle is at its lowest volume. The relaxation process continues as indicated by the continued decline of LVP, but LVV is constant at its low level. This is because, once again, both mitral and aortic valves are closed; this phase is called "isovolumic relaxation." Eventually, LVP falls below the pressure existing in the left atrium and the mitral valve opens (at time "D"). At this point, blood flows from the LA into the LV as indicated by the rise of LVV; also note the slight rise in LVP as filling proceeds. This phase is called "filling". In general terms, systole includes isovolumic contraction and ejection; diastole includes isovolumic relaxation and filling.
- E. Whereas the four phases of the cardiac cycle are clearly illustrated on the plots of LVV, LVP and AoP as a function of time, it turns out that there are many advantages to displaying LVP as a function of LVV on a "pressure-volume diagram" (these advantages will be clear to you by the end of the lecture). This is accomplished simply by plotting the simultaneously measured LVV and LVP on appropriately scaled axes; the pressure-volume diagram corresponding to the curves of Fig. 2 is shown in Fig. 3, with volume on the x-axis and pressure on the y-axis. As shown, the plot of pressure vs. volume for one cardiac cycle forms a closed



loop. This loop is called the "pressure volume loop" (abbreviated PV loop).

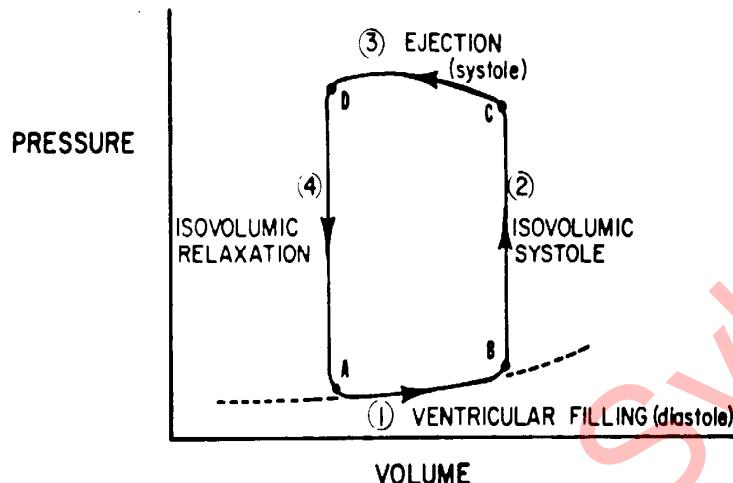


Figure 3. Representative pressure-volume loop of the left ventricle during a single cardiac cycle.

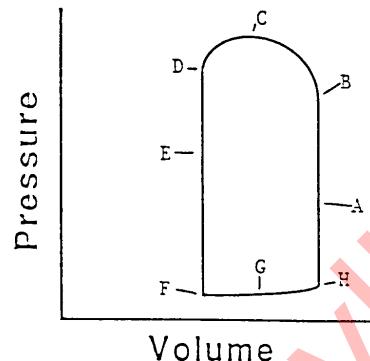
As time proceeds, the PV points go around the loop in a counter clockwise direction. The fact that this loop is closed indicates that the pressure-volume point at the end of the cycle returns to that existing at the beginning of the cycle. The point of maximal volume and minimal pressure (i.e., the bottom right corner of the loop) corresponds to time "A" on Figure 2, the onset of systole. During the first part of the cycle, pressure rises but volume stays the same (isovolumic contraction). Ultimately LVP rises above AoP, the aortic valve opens, ejection begins and volume starts to go down. (Obviously, with this representation, AoP is not explicitly plotted; however as will be reviewed below, several features of AoP are readily obtained from the PV loop.) After the ventricle reaches its maximum activated state (upper left corner of PV loop), LVP falls below AoP, the aortic valve closes and isovolumic relaxation commences. Finally, filling begins with mitral valve opening (bottom left corner).

The four phases of the cardiac cycle and the openings and closings of the aortic and mitral valves are reviewed in Figure 4.



Fig 4. Phases of the cardiac cycle and valve openings and closings as shown on the "pressure-volume loop"

- a. isovolumic contraction
- b. opening of aortic valve
- c. ejection
- d. closing of aortic valve
- e. isovolumic relaxation
- f. opening of mitral valve
- g. filling
- h. closing of mitral valve



G. Physiologic measurements retrievable from the pressure-volume loop

1. As reviewed above, the ventricular pressure-volume loop displays the instantaneous relationship between intraventricular pressure and volume throughout the cardiac cycle. It turns out that with this representation it is easy to ascertain values of several parameters and variables of physiologic importance.
2. Consider first the volume axis (Fig. 5). It is appreciated that we can readily pick out the maximum volume of the cardiac cycle. This volume is called the "end-diastolic volume" (EDV) because this is the ventricular volume at the end of a cardiac cycle. Also, the minimum volume the heart attains is also retrieved; this volume is known as the "end-systolic volume" (ESV) and is the ventricular volume at the end of the ejection phase. The difference between EDV and ESV represents the amount of blood ejected during the cardiac cycle and is called the "stroke volume" (SV).
3. Now consider the pressure axis (Fig. 6). Near the top of the loop we can identify the point at which the ventricle begins to eject (that is, the point at which volume starts to decrease) is the point at which ventricular pressure just exceeds aortic pressure; this pressure therefore reflects the pressure existing in the aorta at the onset of ejection and is called the "diastolic blood pressure" (DBP). During the ejection phase, aortic and ventricular pressures are essentially equal; therefore, the point of greatest pressure on the loop also represents the greatest pressure in the aorta, and this is called the "systolic blood pressure" (SBP). One additional pressure, the "end-systolic pressure" (Pes) is identified as the pressure of the left upper corner of the loop; the significance of this pressure will be discussed in detail



below. Moving to the bottom of the loop, we can reason that the pressure of the left lower corner (the point at which the mitral valve opens and filling begins) is roughly equal to the pressure existing in the left atrium (LAP) at that instant in time (note that atrial pressure is not a constant, but varies with atrial contraction and instantaneous atrial volume). The pressure of the point at the bottom right corner of the loop is the pressure in the ventricle at the end of the cardiac cycle and is called the "end-diastolic pressure" (EDP).

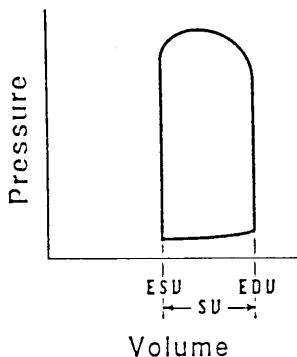


Fig 5. Volumes retrievable from PV loop: EDV, ESV and the difference, SV. See text for abbreviations.

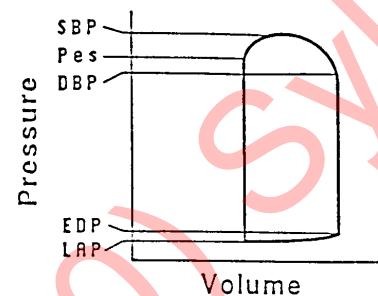


Fig 6. Pressures retrievable from PV loop: LAP, EDP, DBP, Pes, and SBP. See text for abbreviations.

V. PRESSURE-VOLUME RELATIONSHIPS

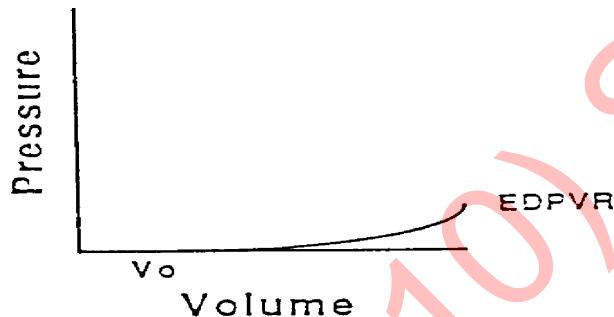
By this point you probably have a mental image of how, with each cardiac cycle, the muscles in the ventricular wall contract and relax causing the chamber to stiffen (reaching a maximal "stiffness" at the end of systole) and then to become less stiff during the relaxation phase (reaching its minimal "stiffness" at end-diastole). Thus, the mechanical properties of the ventricle are time-varying, they vary in a cyclic manner, and the period of the cardiac cycle is the interval between beats. In the following discussion we will explore one way to represent the time-varying mechanical properties of the heart using the pressure-volume diagram. We will start with a consideration of ventricular properties at the extreme states of "stiffness" -- end systole and end diastole -- and then explore the mechanical properties throughout the cardiac cycle.

A. End-diastolic pressure-volume relationship

1. Let us first examine the properties of the ventricle at enddiastole. Imagine the ventricle frozen in time in a state of complete relaxation. We can think of the properties of this ventricle with weak, relaxed muscles, as being similar to those of a floppy balloon. What would happen to the pressure inside a floppy balloon if we were to vary its volume? Let's start with no volume inside the balloon;



naturally there would be no pressure. As we start blowing air into the balloon there is initially little resistance to our efforts as the balloon wall expands to a certain point. Up to that point, the volume increases but pressure does not change. We will refer to this volume as "Vo" or the maximal volume at which pressure is still zero mm Hg. As the volume increases we meet with increasing resistance to our efforts to expand the balloon, indicating that the pressure inside the balloon is becoming higher and higher. The ventricle, frozen in its diastolic state, is much like this balloon. A typical relationship between pressure and volume in the ventricle at enddiastole is shown in Fig. 7.



The PV relationship with the ventricle "frozen" in a state of complete relaxation.

Fig 7

- As volume is increased initially, there is no increase in pressure until a certain point, designated "Vo". After this point, pressure increases with further increases in volume. Quantitative analysis of such curves measured from animal as well as from patient hearts has shown that pressure and volume are related by a nonlinear function such as:

$$EDP = k \{ ea(V-Vo) - 1 \} \quad [1]$$

where EDP is the end-diastolic pressure, V is the volume inside the ventricle, Vo is as defined above, and k and a are constants which specify the curvature of the line and are determined by the mechanical properties of the muscle as well as the structural features of the ventricle. This curve is called the "end-diastolic pressure-volume relationship" (EDPVR). Under normal conditions, the heart would never exist in such a frozen state. However, with each contraction, the heart does pass through this state; knowledge of the EDPVR allows one to specify, for the end of diastole, EDP if EDV is known, or visa versa. Furthermore, since the EDPVR provides the pressure-volume relation with the heart



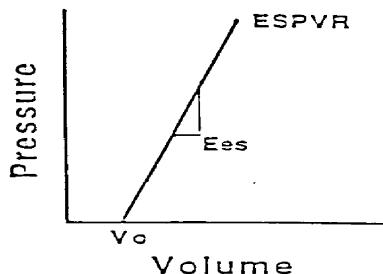
in its most relaxed state, the EDPVR provides a boundary on which the PV loop must fall at the end of the cardiac cycle.

3. Under certain circumstances, the EDPVR may change. Physiologically, the EDPVR changes as the heart grows during childhood. Most other changes in the EDPVR accompany pathologic situations; examples include the changes which occur with hypertrophy, the healing of an infarct, and the evolution of a dilated cardiomyopathy, to name a few.
4. There is a term which is frequently used in discussions of the end-diastolic ventricular properties: "compliance". Technically, "compliance" is the change in volume for a given change in pressure or, expressed in mathematical terms, it is the reciprocal of the derivative of the EDPVR ($[dP/dV]^{-1}$). Since the EDPVR is nonlinear, the compliance varies with volume; compliance is greatest at low volume and lowest at high volumes. In the clinical arena, however, "compliance" is used in two different ways. First, it is used to express the idea that the diastolic properties are, in a general way, stiffer or more relaxed than normal; that is, that the EDPVR is either elevated or depressed compared to normal. Second, it is used to express the idea that the heart is working at a point on the EDPVR where its slope is either high or low (this usage is technically more correct). Undoubtedly you will hear this word used in the clinical setting, usually in a casual manner: "The patient's heart is noncompliant." Such a statement relays no specific information about what is going on with the diastolic properties of the heart. Statements specifying changes in the EDPVR or changes in the working volume range relay much more information.

B. End-systolic pressure-volume relationship

1. Let us move now to the opposite extreme in the cardiac cycle: end-systole. At this instant of the cardiac cycle, the muscles are in their maximally activated state during the cycle and it is easy to imagine the heart as a much stiffer chamber. As for end diastole, we can construct a pressure-volume relationship at end systole if we imagine the heart frozen in this state of maximal activation. An example is shown in Fig. 8.





Pressure-Volume relation with the ventricle "frozen" in a state of maximal activation.

Fig 8

2. As for the EDPVR, the end-systolic pressure volume relationship (ESPVR) intersects the volume axis at a slightly positive value (Vo), indicating that a finite amount of volume must fill the ventricle before it can generate any pressure. For our purposes, we can assume that the Vo of the ESPVR and the Vo of the EDPVR are the same (this is not exactly true, but little error is made in assuming this and it simplifies further discussions). In contrast to the nonlinear EDPVR, the ESPVR has been shown to be linear over a wide range of conditions, and can therefore be expressed by a simple equation:

$$Pes = Ees(V-Vo) \quad [2]$$

where Pes is the end-systolic pressure, Vo is as defined above, V is the volume of interest and Ees is the slope of the linear relation. There is no reason to expect that this relationship should be linear, it is simply an experimental observation. "Ees" stands for "end systolic elastance." "Elastance" means essentially the same thing as "stiffness", and is defined as the change in pressure for a given change in volume within a chamber; the higher the elastance, the stiffer the wall of the chamber.

3. As discussed above for the EDPVR, the heart would never exist in a "frozen" state of maximal activation. However, it does pass through this state during each cardiac cycle. The ESPVR provides a line which the PV loop will hit at the end-systole, thus providing a boundary for the upper left hand corner of the PV loop.
 4. We will return to a discussion of the properties of the ESPVR below after a discussion of the properties of the ventricle throughout the cardiac cycle.
- C. Time varying elastance
1. In the above discussion we have described the pressure-volume relationships at two instances in the cardiac cycle:



end diastole and end systole. The idea of considering the pressure-volume relation with the heart frozen in a given state can be generalized to any point during the cardiac cycle. That is, there exists a pressure-volume relationship at each instant of the cycle. Such relations have been investigated in the physiology lab. These experiments show, basically, that there is a relatively smooth transition from the EDPVR to the ESPVR and back. For the most parts of the cycle these relations can be considered to be linear and all intersect at a common point, namely V_0 . This is expressed in Fig. 9.

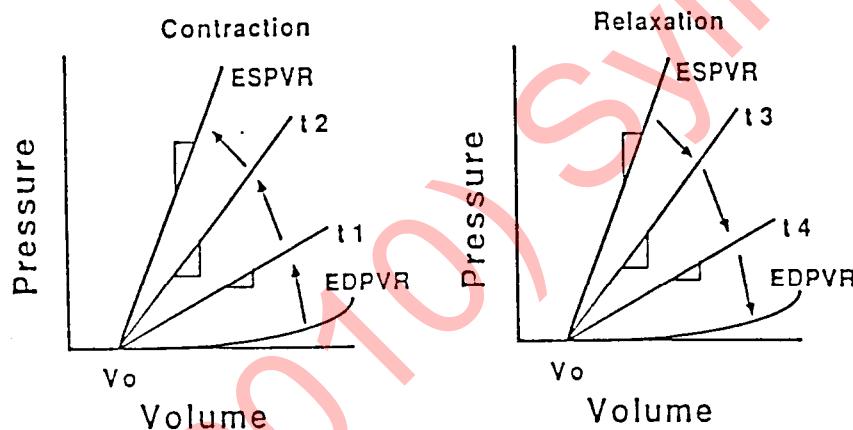


Fig 9. The slope of instantaneous P-V relationship increases during contraction from that of the EDPVR to that of the ESPVR, and back again during diastole.

2. In the left panel the transition from the EDPVR towards the ESPVR during the contraction phase is illustrated, and the relaxation phase is depicted in the right panel. Since the instantaneous pressure-volume relations (PVR) are reasonably linear and intersect at a common point, it is possible to characterize the time course of change in ventricular properties by plotting the time course of change in the slope of the instantaneous PVR. Above, we referred to the slope of the ESPVR as an "elastance". Similarly, we can refer to the slopes of the instantaneous PVRs as "elastances". A rough approximation of the instantaneous elastance throughout a cardiac cycle is shown in Fig. 10.



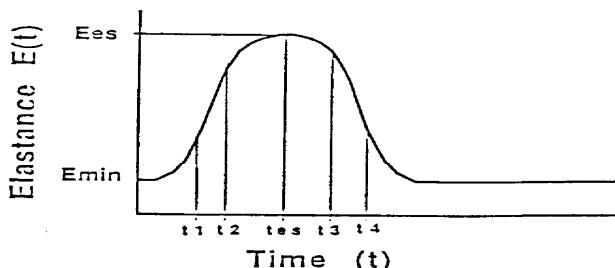


Fig 10. Instantaneous LV elastance.

3. Note that the maximal value, E_{es} , is the slope of the ESPVR. The minimum slope, E_{min} , is the slope of the EDPVR in the low volume range. We refer to the function depicted in Fig. 10 as the "time varying elastance" and it is referred to as " $E(t)$ ". With this function it is possible to relate the instantaneous pressure (P) and volume (V) throughout the cardiac cycle:

$$P(V,t) = E(t) [V(t) - V_0] \quad [3]$$

where V_0 and $E(t)$ are as defined above and $V(t)$ is the time varying volume. This relationship breaks down near end-diastole and early systole when there are significant nonlinearities in the pressure-volume relations at higher volumes. The implication of this equation is that if one knows the $E(t)$ function and if one knows the time course of volume changes during the cycle, one can predict the time course of pressure changes throughout the cycle.

4. In our original discussions of PV loops we put no constraints on the positioning of the loops on the pressure-volume plane. As we have seen, the properties of the ventricle provide specific boundaries within which the PV loop sits; specifically, these are the end-systolic and end-diastolic pressure-volume relations. Examples of PV loops bounded by the ESPVR and EDPVR are shown in Fig. 11.

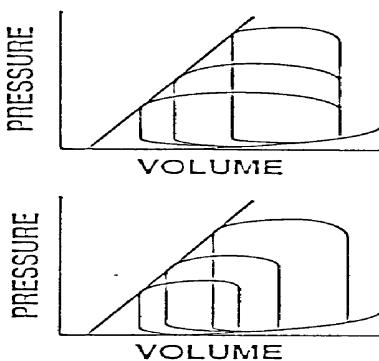


Fig 11. Examples of how ESPVR and EDPVR provide boundaries for PV loops.



5. In the top figure (Fig. 11), there are three PV loops which have the same EDV but have different aortic pressures; in obtaining these loops the properties of the arterial system were changed (specifically, the total peripheral resistance was modified) without modifying anything about the way the ventricle works. The upper left hand corner of each loop falls on the ESPVR, while the bottom right part of the loop falls on the EDPVR.
6. In the bottom panel, three different loops are shown which have different EDVs and different aortic pressures. Here, the loops were obtained by modifying only the EDV without modifying anything about the heart or the arterial system (the reason that aortic pressure changes despite there being no modification in arterial properties in this case will become clear below). The upper left hand corner of each loop falls on the ESPVR, while the bottom right part of the loop falls on the EDPVR.

** Note: these two diagrams "reappear" as Figures 16 and 17, which are accompanied by a further discussion of these concepts. **

D. Preload

1. The "preload" provides an additional constraint for positioning the PV loop on the PV plane. "Preload" is the "load" on the ventricle at the end of diastole, just before contraction begins. The term was originally coined in studies of isolated strips of cardiac muscle where a weight was hung from the muscle to prestretch it to the specified load before (pre-) contraction. For the ventricle, there are several possible measures of "preload": 1) EDP, 2) EDV and 3) wall stress at end-diastole. EDV is useful since it indicates the volume from which the contraction starts. EDP is simple to measure and, if the EDPVR is known serves to localize the PV loop on the PV diagram as well. Enddiastolic wall stress is the measure which most closely corresponds to the definition of preload developed for the muscle. However, this is not a directly measurable quantity, but rather can be derived from measurement of EDP and assumptions about the structure of the ventricle.
2. The constraints which determine the remaining features of the PV loop depend on properties of both the ventricle and the arterial system; this will be explored further below.
3. In the next section we will examine how the ESPVR is modified by humoral and pharmacological agents, and how those changes make the ESPVR useful in assessing the intrinsic strength of the heart.



VI. CONTRACTILITY

- A. "Contractility" is an ill-defined concept used when referring to the intrinsic strength of the ventricle or cardiac muscle. By "intrinsic strength" we mean those features of the cardiac contraction process that are intrinsic to the ventricle and are independent of conditions imposed by either the preload or afterload (i.e., the atrial or arterial system properties). For example consider, once again, the PV loops in Fig. 11. We see that in the top panel that the actual amount of pressure generated by the ventricle and the stroke volume are different in the three cases, but we stated that these loops were obtained by modifying the arterial system and not changing anything about the ventricle. Thus, the changes in pressure generation in that figure do not represent changes in "contractility". Similarly, the changes in pressure generation and stroke volume shown in the bottom panel of the figure were brought about simply by changing the EDV of the ventricle and do not represent changes in ventricular "contractility".
- B. Now that we have demonstrated changes in ventricular performance (i.e., pressure generation and SV) which do not represent changes in contractility, let's explore some changes that do. First, how can contractility be changed? Basically, we consider ventricular contractility to be altered when any one or combination of the following events occurs:
1. the amount of calcium released to the myofilaments is changed.
 2. the affinity of the myofilaments for calcium is changed.
 3. there is an alteration in the number of myofilaments available to participate in the contraction process.
- C. You will recall that calcium interacts with troponin to trigger a sequence of events which allows actin and myosin to interact and generate force. The more calcium available for this process, the greater the number of actin-myosin interactions. Similarly, the greater troponin's affinity for calcium the greater the amount of calcium bound and the greater the number of actin-myosin interactions. Here we are linking "contractility" to cellular mechanisms which underlie excitation-contraction coupling and thus, changes in ventricular contractility would be the global expression of changes in contractility of the cells that make up the heart. Stated another way, ventricular contractility reflects "myocardial contractility" (the contractility of individual cardiac cells).



- D. Through the third mechanism, changes in the number of muscle cells, as opposed to the functioning of any given muscle cell, cause changes in the performance of the ventricle as an organ. However, in acknowledging this as a mechanism through which ventricular contractility can be modified we recognize that ventricular contractility and myocardial contractility are not always linked to each other.
- E. Humoral and pharmacological agents can modify ventricular contractility by the first two mechanisms. Epinephrine increases the amount of calcium released to the myofilaments and is also believed to modify myofilament affinity for calcium, both creating an increase in contractility. In contrast, propranolol, an agent which blocks the actions of epinephrine, blocks the effects of circulating epinephrine and norepinephrine and reduces contractility. Nifedipine is a drug that blocks entry of calcium into the cell and therefore reduces contractility. One example of how ventricular contractility can be modified by the third mechanism mentioned above is the reduction in ventricular contractility following a myocardial infarction where there is loss of myocardial tissue, but the unaffected regions of the ventricle function normally.
- F. How can changes in contractility be assessed? While it is true that when contractility is changed there are generally changes in ventricular pressure generation and stroke volume, we have seen above that both of these can occur as a result of changes in EDV or arterial properties alone. Thus, these measures would not be reliable indices of contractility. It turns out that we can look towards changes in the ESPVR to indicate changes in contractility, as shown in Fig. 12. When agents known to increase ventricular contractility (e.g., those that increase calcium release) are administered to the heart there is an increase in Ees, the slope of the ESPVR. Such agents are known as positive "inotropic" agents. ("Inotropic": from Greek meaning influencing the contractility of muscular tissue.) Conversely, agents which are negatively inotropic reduce Ees. It is significant that neither Vo (the volume-axis intercept of the ESPVR) nor the EDPVR are affected significantly by changes in contractility. Thus, because Ees varies with ventricular contractility but is not affected by changes in the arterial system properties nor changes in EDV, Ees is considered to be an index of contractility.



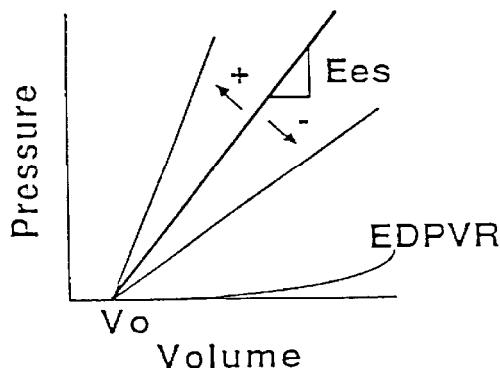


Fig 12. E_{es} varies with inotropic stimulation and is considered an index of contractility.

- G. The major draw back to the use of E_{es} in the clinical setting is that it is not that easy, at present, to measure ventricular volume. Clearly, it is required that volume be measured in the assessment of E_{es} . If E_{es} is not used that much in the clinical setting now, why learn about it?
- H. There are at least two good reasons. First, methods for measuring ventricular volume (both invasive and noninvasive) are currently being perfected and should be available in the next several years (indeed, some are already being validated in clinical research protocols). Second, E_{es} (and the ESPVR in general) allows for a simple yet powerful way of understanding the complex interaction between the ventricle and the arterial system, as will be shown below.
- I. Currently, the most commonly employed index of contractility in the clinical arena is "ejection fraction" (EF). EF is defined as the ratio between EDV and SV:

$$EF = SV/EDV \quad [4]$$

This number ranges from 0 to 1 and represents the fraction of the volume present at the start of the contraction that is ejected during the contraction. The normal value of EF ranges between 0.6 and 0.7. This can be estimated by a number of techniques, including echocardiography and nuclear imaging techniques (MUGA). The main disadvantage of this index is that it is a function of the properties of the arterial system. This can be appreciated by examination of the PV loops in the top panel of Fig. 11, where ventricular contractility is constant yet EF is changing as a result of modified arterial properties.



VII. AFTERLOAD AS REPRESENTED ON THE PRESSURE VOLUME DIAGRAM

We have been discussing in detail how ventricular properties are represented on the PV diagram and how these are modified by inotropic agents. We have seen examples of PV loops obtained with constant ventricular properties but with arterial properties modified. Therefore, let us now turn to a brief discussion of arterial properties, and specifically how they can be represented on the PV diagram. There is a term used in discussions of arterial properties in regard to its influence of ventricular performance: "afterload". "Afterload" is the mechanical "load" imposed on the ventricle during ejection, usually by the arterial system. Under pathologic conditions when either the mitral valve is incompetent (i.e., leaky) or the aortic valve is stenotic (i.e., constricted) "afterload" is determined by factors other than the properties of the arterial system (we won't go into this further in this lecture). There are numerous measures of afterload, and there has been much debate over which is "the best". Time has proven that there is no one best measure of afterload ; different measures provide different information which may be useful in answering different questions. We will briefly mention four different measures of afterload.

A. Aortic Pressure

1. This provides a measure of the pressure that the ventricle must overcome to eject blood. It is simple to measure, but has several shortcomings. First, aortic pressure is not a constant during ejection. Thus, many people use the mean value when considering this as the measure of afterload. Second, as will become clear below, aortic pressure is determined by properties of both the arterial system and of the ventricle. Thus, it does not provide a measure which relays information exclusively about the arterial system.

B. Wall Stress

1. The stress (force per unit area) in the wall of the ventricle can be estimated from ventricular pressure and knowledge of the structure of the ventricle. It is, as is aortic pressure, time varying. It is not a directly measurable quantity, but is estimated from LVP and measurements of ventricular structural features using mathematical formulas. This definition of afterload most closely matches afterload as it was originally defined for a strip of cardiac muscle lifting a weight. As with aortic pressure, wall stress varies with ventricular properties as well as ventricular preload.



C. Arterial Resistance

1. The total peripheral resistance (TPR) is the ratio between the mean pressure drop across the arterial system [which is equal to the mean aortic pressure (MAP) minus the central venous pressure (CVP)] and mean flow into the arterial system [which is equal to the cardiac output (CO)]. Unlike aortic pressure by itself, this measure is independent of the functioning of the ventricle. Therefore, it is an index which describes arterial properties. According to its mathematical definition, it can only be used to relate mean flows and pressures through the arterial system.

D. Arterial Impedance

1. This is an analysis of the relationship between pulsatile flow and pressure waves in the arterial system. It is based on the theories of Fourier analysis in which flow and pressure waves are decomposed into their harmonic components. It allows one to relate instantaneous pressure and flow. It is more difficult to understand, most difficult to measure, but the most comprehensive description of the properties of the arterial system as they pertain to understanding the influence of afterload on ventricular performance.

Having provided these four definitions of afterload, I would like to direct your attention to the third, i.e., TPR. In the following passage I will demonstrate how TPR can be represented on the PV diagram and derive a closely related index of afterload called "Ea" which stands for "effective arterial elastance".

The ultimate goal of this discussion is to provide a quantitative method of uniting afterload and contractility (i.e., the ESPVR) on the PV diagram so that cardiovascular variables such as stroke volume and arterial pressure can be determined from ventricular and arterial properties.

We start with the definition of TPR:

$$TPR = [MAP - CVP] / CO \quad [5]$$

2. Cardiac output (CO) represents the mean flow during the cardiac cycle and can be expressed as:

$$CO = SV/T \quad [6]$$

where SV is the stroke volume and T is the duration of the cardiac cycle in seconds. T is equal to 60/HR, where HR is heart rate in beats/minute. Substituting Eq. [6] into Eq. [5] we obtain:

$$TPR = [MAP - CVP] T /SV \quad [7]$$



3. At this point, we make two assumptions:
- First, we assume that CVP is negligible compared to MAP. This is reasonable under normal conditions, since the CVP is generally around 0 mm Hg (sometimes it is even negative).
 - Second, we will make the assumption that MAP is approximately equal to the end-systolic pressure in the ventricle (Pes). This assumption has been validated in experiments in animals, though not yet validated for man. Making these assumptions, we can rewrite Eq. [7] as:

$$TPR \sim Pes \cdot T / SV \quad [8]$$

which can be rearranged to:

$$\frac{TPR}{T} \sim \frac{Pes}{SV}$$

4. Note, as shown in Fig. 13, that the quantity Pes/SV can be easily ascertained from the pressure volume loop by taking the negative value of the slope of the line connecting the point on the volume-axis equal to the EDV with the end-systolic pressure-volume point. Let us define the slope of this line as Ea:

$$Ea = Pes / SV \quad [10]$$

This term is designated E for "elastance" because the units of this index are mm Hg/ml (the same as for Ees). The "a" denotes that this term is for the arterial system. Note that this measure is dependent on the TPR and the duration of the cardiac cycle, and thus is dependent on HR.

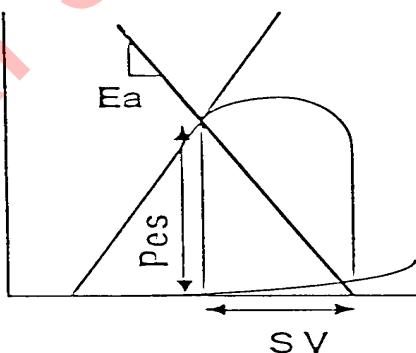


Fig 13. $Ea = Pes / SV$. As indicated in Eq. 9, Ea is proportional to TPR.



5. If the TPR or HR goes up, then Ea goes up, as illustrated in Fig. 14. Reduction in either TPR or HR cause a reduction in Ea. As shown in this Figure, the Ea line is drawn on the pressure-volume diagram (the same set of axes as the ESPVR and the EDPVR); it starts at EDV and has a slope of $-E_a$ and intersects with the ESPVR at one point. In the following section we will use these features of the pressure-volume diagram to demonstrate how it is possible to predict how the ventricle and arterial system interact to determine such things as MAP and SV when contractility, TPR EDV and HR are changed.

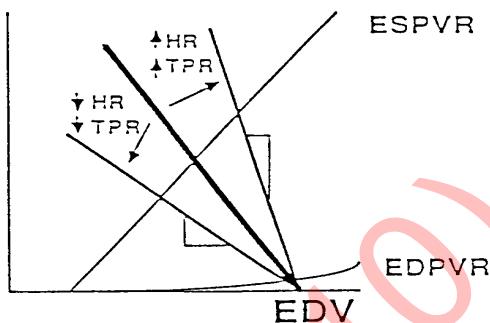


Fig 14. Demonstration of how E_a is influenced on the PV diagram by changes in TPR and in HR.

VIII. USING THE PRESSURE-VOLUME DIAGRAM TO UNDERSTAND THE INTERACTION BETWEEN THE VENTRICLE AND THE ARTERIAL SYSTEM

- A. The primary measurements which characterize the overall functioning of the cardiovascular system are the arterial blood pressure and the cardiac output. We have noted on multiple occasions above that both of these variables are determined by the interaction between the ventricle and the arterial system and the preload. This is an important concept which can be illustrated by considering two extreme, but simple examples. First, consider what would occur if, in a normally functioning cardiovascular system, the arterial system would become drastically vasodilated (TPR greatly reduced); arterial pressure would fall and cardiac output would increase. Second, consider what would happen if, in a normally operating system, the heart were suddenly stopped; both blood pressure and cardiac output would decline. Thus, we can see qualitatively from these two simple examples that arterial pressure and cardiac output are determined by both ventricular properties and arterial properties. It is important, however, to develop a quantitative appreciation of how the heart and vasculature "interact" to determine pressure and flow of blood in the body. We will develop a simple system to provide such an



appreciation using the PV diagram based on the concepts already presented.

- B. In order to do this, we must have a clear idea of the parameters which characterize the state of the cardiovascular system. First, are those parameters necessary to quantify the systolic pump function of the ventricle; these are E_{es} and V_o , the parameters which specify the ESPVR. Second, are the parameters which specify the properties of the arterial system; we will take E_a as our measure of this, which is dependent on TPR and T (or Heart Rate). Finally we must specify a preload; this can be done by simply specifying EDV or, if the EDPVR is known, we can specify EDP. If we specify each of these parameters, then we can estimate a value for MAP and SV (and CO, since $CO = SV \cdot HR$) as depicted in Fig. 15 and explained below.

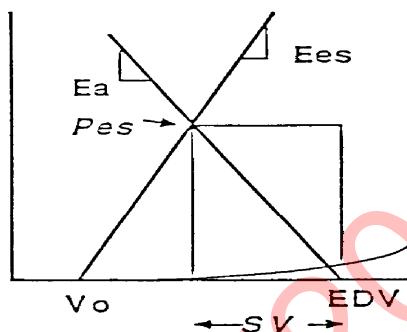


Fig 15. SV and MAP can be estimated from E_a and the ESPVR. See text.

- C. First, draw the ESPVR line. Second, mark the EDV on the volume axis. Draw a line through this EDV point with a slope of $-E_a$. The ESPVR and the E_a line will intersect at one point. This point is the estimate of the end-systolic pressure-volume point. With that knowledge you can draw a box which represents an approximation of the PV loop under the specified conditions, with the bottom of the box determined by the EDPVR. SV and Pes can be measured directly from the diagram. Recall the Pes is roughly equal to MAP. With this method, we cannot estimate any more of the details of the loop, such as the systolic or diastolic blood pressure, or the precise shape of the top of the PV loop.
- D. Use of this technique is illustrated in Figs. 16 through 19. The PV loops in these figures are facsimiles of experimentally determined loops in which all the cardiovascular parameters are known. In each case, the ESPVR and E_a for the specified conditions are drawn on the pressure-volume diagram superimposed on the actual PV loops.



- E. In Fig. 16 we see what happens if TPR is altered, but EDV is the same. As TPR is increased, the magnitude of the slope of the Ea line increases and intersects the ESPVR at an increasingly higher pressure and higher ventricular volume. Thus, increasing TPR increases MAP but decreases SV (and CO) when ventricular properties (Ees and Vo) are constant. It should be noted that the Ea line and ESPVR intersect at a slightly higher volume than the real end-ejection volume in all three cases, thus providing a slight underestimate of stroke volume.

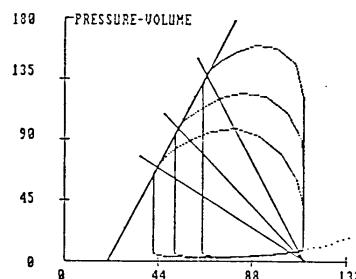


Fig 16. Demonstration of how SV and MAP can be estimated from the ESPVR and Ea. Shown are actual PV loops with the superimposed ESPVR and Ea lines. As resistance is increased, the slope of the Ea line increases and intersect the ESPVR at higher volumes and higher pressures. The method provides a means of quantitative estimation of both stroke volume and MAP (Pes).

- F. The influence of preload (EDV) is shown in the three loops of Fig. 17. Here, the ESPVR is constant and arterial properties are constant. The, slope of the Ea line is not altered when preload is increased, it is simply shifted in a parallel fashion. With each increase in preload volume, Pes and SV increase, and clearly it is possible to make a quantitative prediction of precisely how much.

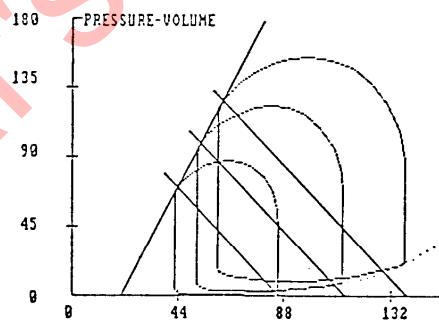


Fig 17. The influence of preload on stroke volume and mean arterial pressure can be estimated as shown. With increased EDV, the Ea line is repositioned on the PV diagram to intersect the volume axis at higher value but are parallel to each other (i.e., slope remains the same).



- G. The influence of contractility is shown in Fig. 18. In this case nothing is changed in the arterial system and the EDV is constant; Ees is the only thing to change. When Ees (contractility) is increased, the Ea line intersect the ESPVR at a higher pressure and lower volume. Therefore, despite increased MAP, SV increased (this is in contrast to the decrease in SV obtained with an increase in MAP when TPR is increased).

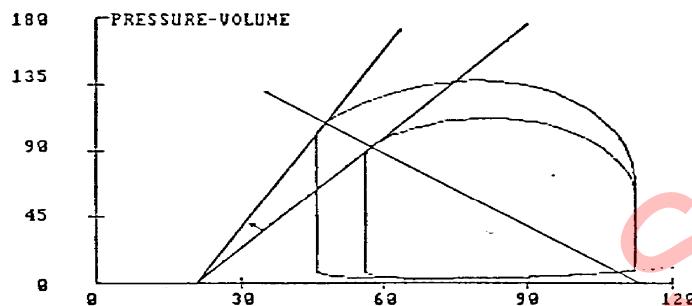


Fig 18. Demonstration of how SV and MAP can be estimated when Ees is increased. See text for details.

- H. This technique of using Es and Ea to define a particular PV loop (as is done in Figure 18) is useful in predicting Pes and SV when the parameters of the system are known. It is also useful in making qualitative predictions (e.g., does SV increase or decrease?) when only rough estimates of the parameters are available. Nevertheless, it provides a simple system for understanding the determinants of cardiac output and arterial pressure. We have reviewed the use of this approach when one parameter at a time is varying. Naturally, you can vary as many of the parameters as you wish. In fact it is frequently the case that multiple parameters will vary at once. For example, during exercise, the autonomic system mediates alterations in contractility, TPR, HR and possibly in EDV. As another example, consider the possible effects of a calcium channel blocker on the system as a whole: contractility can be reduced, TPR can be decreased and HR may be elevated by baroreceptor reflex mechanisms. Thus, when attempting to apply the techniques described above, it is necessary to have an appreciation for the functioning of each of the components of the cardiovascular system (contractility, afterload, preload and HR).



IX. SUMMARY

- A. Muscle properties underlie the mechanical properties of the ventricle. The main factors which determine the relationship between muscle and ventricular properties are i) muscle mass; ii) chamber geometry; iii) architecture of the ventricular wall; and iv) activation sequence.
- B. The heart valves allow flow in only one direction. They open and close predominantly in response to pressure gradients existing across the valve. The valves are arranged in the inflow and outflow tracts to provide for one-way flow of blood through the ventricle.
- C. The cardiac cycle is divided into systole and diastole. Systole is comprised of isovolumic contraction and ejection phases. Diastole consists of isovolumic relaxation and filling phases. The cardiac cycle can be represented on time plots of LVP and LVV or on the pressure-volume diagram (PV loops). You should know the phases of the cardiac cycle and the times when the valves open and close on the time plots and on the PV loop.
- D. The EDPVR is nonlinear. The ESPVR is linear. Vo is the largest volume at which ventricular pressure is 0 mm Hg. Ees is the slope of the ESPVR and varies directly with contractile state. Ees is therefore considered to be an index of "contractility". The PV loop is bounded by the ESPVR and the EDPVR no matter what the loading conditions are.
- E. Know the concepts of "contractility", "preload", "afterload", "compliance" and various indices of each of these.
- F. Afterload resistance can be represented on the PV diagram using the Ea concept. Ea is defined as Pes/SV and is approximately equal to TPR/T. You should know how to use the Ea concept on the PV diagram to estimate SV and Pes once ESPVR, EDV, TPR and HR are specified.

X. GLOSSARY OF TERMS AND ABBREVIATIONS

Afterload: The mechanical "load" on the ventricle during ejection. Under normal physiological conditions, this is determined by the arterial system. Indices of after load include, aortic pressure, ejection wall stress, total peripheral resistance (TPR) and arterial impedance.

AoP aortic pressure



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Compliance: A term used in describing diastolic properties ("stiffness") of the ventricle. Technically, it is defined as the reciprocal of the slope of the EDPVR ($[dP/dV]_I$). Colloquially, it is frequently used in describing the elevation of the EDPVR.

Contractility: An ill-defined concept, referring the intrinsic "strength" of the ventricle or cardiac muscle. This notion is classically considered to be independent of the phenomenon whereby changes in loading conditions (preload or afterload) result in changes in pressure (or force) generation.

CVP: Central Venous Pressure. The pressure in the large veins entering the thoracic cavity (inferior and superior vena cavae) which serves as the filling pressure to the right ventricle.

Diastole: In Greek, means "dilate." The phase of the cardiac cycle during which contractile properties return to their resting state.

DBP: Diastolic Blood Pressure. The pressure existing in the aorta just prior to the onset of ejection.

Ea: Effective Arterial Elastance. It is defined as the ratio between Pes and SV and is approximately equal to TPR/T. It provides a means of representing afterload resistance on the pressure-volume diagram.

EDP: End-Diastolic Pressure. The pressure existing in the ventricle at the end of diastole (i.e., just before the onset of contraction).

EDPVR: End-diastolic Pressure-Volume Relationship. The relationship between pressure and volume in the ventricle with the heart frozen in the state existing at the instant of complete relaxation (end-diastole). There are a number of mathematical equations which describe this with reasonable accuracy, including : $EDP = k \{ \exp[a(EDV-Vo)] - 1 \}$.

EDV: End-Diastolic Volume. The volume existing in the ventricle at the end of diastole (i.e., just before the onset of contraction).

Ees: End-Systolic Elastance. The slope of the ESPVR; has units of mm Hg/ml, and is considered to be an index of "contractility".

EF: Ejection fraction. The ratio between SV and EDV. It is the most commonly used index of contractility, mostly because it is relatively easy to measure in the clinical setting. Its major limitation is that it is influenced by afterload conditions.

Elastance: The change in pressure for a given change in volume within a chamber and is an indication of the "stiffness" of the chamber. It has units of mm Hg/ml. The higher the elastance the stiffer the wall of the chamber.



ESPVR: End-Systolic Pressure-Volume Relationship. The relationship between pressure and volume in the ventricle with the heart frozen in the state existing at the instant of maximal activation (end-systole) during the cardiac cycle. This relationship is considered to be linear, and independent of the loading conditions of the ventricle: Pes - Ees [ESV-Vo].

ESV: End-Systolic Volume. The volume existing in the ventricle at the end of systole.

HR: Heart Rate. The number of ventricular contractions per minute.

LA: Left Atrium.

LAP: Left Atrial Pressure. The pressure in the left atrium. LAP serves as the filling pressure for the left ventricle.

LV: Left Ventricle.

LVP: Left Ventricular Pressure.

LVV: Left Ventricular Volume.

MAP: Mean arterial pressure, mm Hg millimeters of Mercury - the measuring system of pressure is based on this unit.

Pes: End-Systolic Pressure. The pressure existing in the ventricle at the end of systole. This pressure is determined by the ESPVR and the volume at end systole (ESV).

Preload: The "load" imposed on the ventricle at the end of diastole. Measures of preload include EDV, EDP and enddiastolic wall stress.

RA: Right Atrium.

RV: Right Ventricle.

SBP: Systolic Blood Pressure. The maximal aortic pressure during the cardiac cycle.

Systole: The first phase of the cardiac cycle which includes the period of time during which the electrical events responsible for initiating contraction and the mechanical events responsible for contraction occur. It ends when the muscles are in the greatest state of activation during the contraction.

SV Stroke Volume. The amount of blood expelled during each cardiac cycle. SV is equal to the difference between EDV and ESV.

T: The duration of the cardiac cycle (usually measured in seconds or milliseconds). $T=60/\text{HR}$.



Tes: Time to End Systole - the duration of the cardiac cycle from end diastole to end systole.

TPR: Total Peripheral Resistance.

Vo : Volume at zero pressure - the volume-axis intercept of the ESPVR. It is the volume at which peak systolic pressure is zero mm Hg MAP mean arterial pressure

mm Hg millimeters of Mercury - the measuring system of pressure is based on this unit.

XI. USEFUL EQUATIONS

$$CO = SV \cdot HR$$

$$(MAP - CVP) = CO \cdot TPR \text{ or rearranged,}$$

$$TPR = (MAP - CVP) / CO$$

under normal physiologic conditions, $CVP = 0 \text{ mm Hg}$ (range -2 to 5)

$$MAP \sim (SBP + 2 DBP) / 3$$

$$MAP \sim Pes$$

$$Ea \sim Pes/SV$$

$$Ea \sim TPR/T$$

$$T (\text{seconds}) = 60/HR$$

$$Pes = Ees (ESV - Vo)$$

$$SV = EDV - ESV$$

$$SV = (EDV - Vo) / (1 + Ea/Ees)$$

$$EF = SV/EDV$$

$$EF = [EDV - Vo] / [EDV (1+Ea/Ees)]$$



Last Year's (2010) Syllabus

Autonomic Drugs: Sympathomimetic Drugs II

Reading assignment: Katzung (10th ed), Ch. 9

LEARNING OBJECTIVES:

Learn the pharmacology of sympathomimetic drugs. Understand how they produce both beneficial and undesirable effects, particularly in the cardiovascular system.

TOPICS

- A. Cardiovascular effects
- B. Adverse effects
- C. Clinical uses

Last Year's (2010) Syllabus



Last Year's (2010) Syllabus

STARLING CURVE AND VENOUS RETURN

OBJECTIVES

- A. Understanding interaction between filling pressures and cardiac performance.
- B. Understanding the relationship between diastolic volume, pressure and compliance.
- C. The role of shifts in the Starling curve to define altered contractility:
 - 1. Effects of the autonomic nervous system.
 - 2. Effects of positive/negative inotropic agents.
- D. The veins are the major reservoir for blood.
- E. Venous return depends upon:
 - 1. Pressure generated by the left ventricle.
 - 2. One-way valves in the peripheral veins.
 - 3. Respiratory variations in intrathoracic pressure.
- F. Constriction of veins by sympathetic stimulation increases preload and may be an important factor in the control of cardiac output.

I. STARLING'S LAW

- A. In steady-state situations, it is easy to imagine that the heart acts in a machine-like fashion, ejecting exactly the same quantity of blood in systole as enters in diastole. Different steady states can be compared and the work of the heart as a pump or its O₂ consumption can be measured. It was recognized very early that the heart could adapt to changes in filling (venous return) by changing its performance as a pump. This was first shown in the isolated frog heart by Otto Frank at the turn of the century (Fig. 1) in Germany. In the experiment pictured, the heart was filled to different diastolic pressures and then allowed to contract isovolumically (i.e. no ejection was permitted) and pressure was monitored. As diastolic pressure rose, so did systolic pressure.



Figure 1

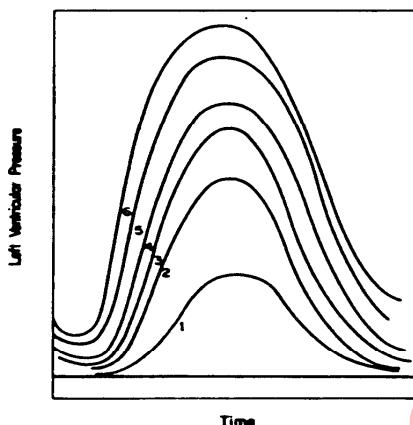


Fig. 8-10. Response of the frog ventricle to increased filling. The initial tension (intraventricular pressure at the onset of each contraction) increases as the filling volume is increased (denoted by the successively higher numbers in the figure). As initial tension is raised, the peak pressure developed during systole is also augmented. (Redrawn from Frank, O.: Z. Biol. 32:370, 1895.)

- B. Approximately 25 years later Dr. Starling in England elaborated upon these studies in mammals and showed that changing right atrial filling led to elevation in stroke volume (ventricular end-diastolic volume minus end-systolic volume) and increased aortic pressures. In other words cardiac output or cardiac work (volume x pressure) was a function of filling pressure. Such a function could be plotted as shown in Fig. 2. This function is a "Starling Curve." It has represented an extremely convenient way to analyze cardiac performance as a function of volume or pre-load. (Fig. 2)

Figure 2

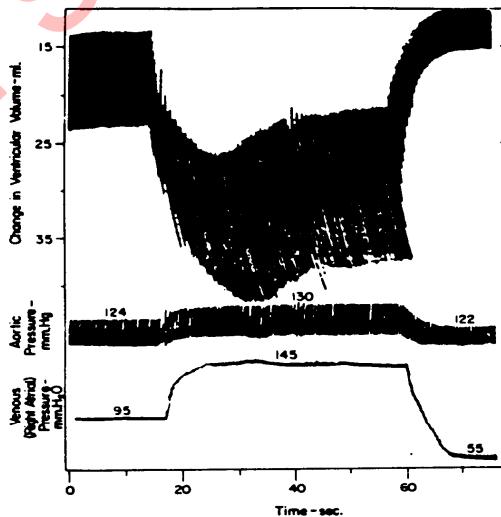


Fig. 8-12. Changes in ventricular volume in a heart-lung preparation when the venous reservoir was suddenly raised (right atrial pressure increased from 95 to 145 mm. H₂O) and subsequently lowered (right atrial pressure decreased from 145 to 55 mm. H₂O). Note that an increase in ventricular volume is registered as a downward shift in the tracing. (Redrawn from Patterson, S. W., Piper, H., and Starling, E. H. J. Physiol. [London] 48:465, 1914.)



- C. Approximately 30 years ago, Dr. Sarnoff at the NIH reexamined the Starling Curve using newer technology which allowed correlation of left-sided performance with left atrial pressure. He expanded our understanding by demonstrating that a given curve corresponds to a given level of contractility (inotropism). Interventions which increased contractility, such as the administration of epinephrine or Ca++ would allow the experimental heart preparation to increase its work for a given filling pressure. Conversely, negative inotropic influences such as sympathetic blockade would reduce cardiac work below control levels for a given filling pressure. Thus, for each heart there was a "family" of Starling curves. (Fig 3)

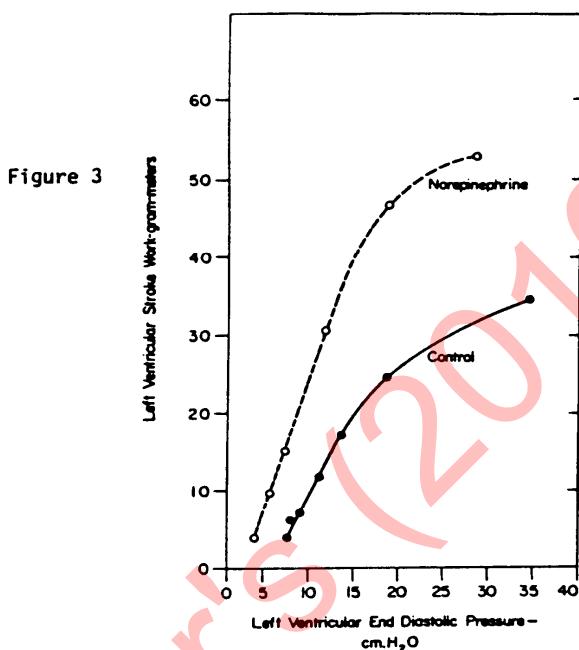


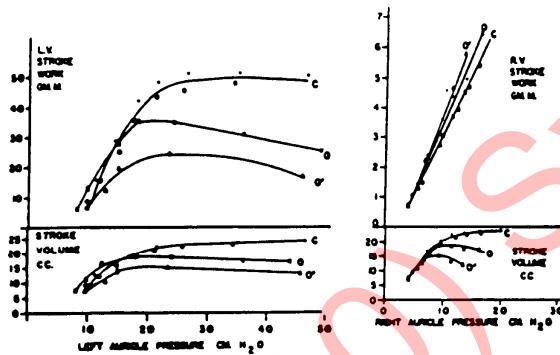
Fig. 8-14. A constant infusion of norepinephrine in the dog causes the ventricular function curve to shift to the left, signifying an enhancement of ventricular contractility. (Redrawn from Sarnoff, S. J., Brockman, S. K., Gilmore, J. P., Linden, R. J., and Mitchell, J. H.: Circ Res. 8:1108, 1960)

- D. Although this may seem obvious, it has raised some interesting questions and provided some new explanations for physiological observations. For example, during exercise with its attendant increase in cardiac output, was cardiac work in the normal heart increased due to increase in filling pressure? Or was filling pressure maintained constant by shifting cardiac function to a more positively inotropic curve due to sympathetic stimulation of the heart by locally released norepinephrine? (As methods of hemodynamic monitoring of conscious exercising dogs and humans became available, it was shown that in fact an increase in inotropism and not an increase in filling pressure was the normal mechanism.)



- E. In the case of heart failure, Starling demonstrated that as filling pressure rose to extremely high levels, cardiac performance initially increased, reached a plateau and then eventually declined ("The descending limb of the Starling Curve"). Was this the hemodynamic mechanism of heart failure or was a sustained low cardiac output due to depression of the normal curve to a lower inotropic state without being on a "descending limb"? Work by Ross and others has helped to demonstrate that Sarnoff's solution to this question (a depressed flat curve) was the correct one.

Figure 4



C = Control
O = Obstruction of left coronary artery
O' = Second obstruction of left coronary artery

1. Note that:
 - a. Filling pressures LV > RV
 - b. There is no "descending limb" under normal (C) circumstances even at extreme supraphysiologic LV filling (left atrial) pressures.
 - c. Only with major ischemic injury does a descending LV limb develop.
 - d. RV stroke work rise with LV injury despite decreased RV stroke volume reflects an increase in RV systolic pressure, probably secondary to high left atrial pressure.

- F. Subsequently, Drs. Sonnenblick, Braunwald, Parmley and others reinvestigated the question of myocardial performance and contractility. Although the different Starling-Sarnoff curves defined different degrees of contractility, the work of the heart was measured exclusively as external work: systolic pressure x stroke volume. However, since the time of A.V. Hill's studies of skeletal muscle physiology, it was known that isometric tension and its rate of development could also create metabolic demands. With measurement of work during ejection alone, Sarnoff had been measuring only isotonic work, whereas the heart was doing isometric and isotonic work.



- G. The importance of these differences will reappear in the discussion of angina. However, with reference to the Starling curves, the point is that since the work of Sarnoff, cardiac performance was seen as a function of filling pressure. Since reexamination of the heart as a muscle, it is clear that the change in myofibril length by preload is the variable which correlates best with subsequent stroke work. Since fiber length and filling pressure do not vary linearly, measurement of one cannot entirely substitute for the other.
- H. What is the physiological importance of this difference (i.e. selecting end-diastolic pressure or end-diastolic volume)? These two variables are related by the end-diastolic pressure-volume relationship (EDPVR). Compliance is the change in volume per unit change in diastolic pressure:
1. $C = \Delta \text{Volume}$
 2. $\Delta \text{Pressure}$
- I. A weather balloon is compliant; a party balloon much less so (i.e. it is stiffer). Thus a given ventricle, filled to a given end-diastolic pressure and volume would produce some specified stroke work with each beat. If, by some pathologic process, the ventricle would become stiffer during diastole (i.e. less compliant) with no other change in its performance characteristics, then when it was filled to the same pressure at end-diastole, it would contain a smaller volume, that is, there would be less stretch of the myofibrils and we could predict less (external) work (PxV) per beat than in the control state.
- J. Measurement of Starling curves for the right heart and left heart differ (see Figs. 4, 5 & 6). By now you should be able to explain the differences. Since both ventricles pump the same volume output, the stroke work differences are due to lower arterial pressure in the pulmonary artery than in the aorta. Filling pressure will differ also. After all, in the human the thickness of the ventricular wall will be appropriate to the work (esp. the pressure work) of the ventricle. Since the left ventricular peak systolic pressure (120 mm Hg) is 5-6x higher than right ventricular peak systolic pressure (20 mm Hg), the left ventricular wall (10-12 mm) is 5-6x thicker than the right ventricular wall (1-2 mm). Similarly, the thicker wall will be less compliant, so that filling pressures for the left ventricle (5-12 mm Hg) are 5-10 x higher than filling pressures for the right ventricle (1-2 mm hg) in the normally functioning heart.



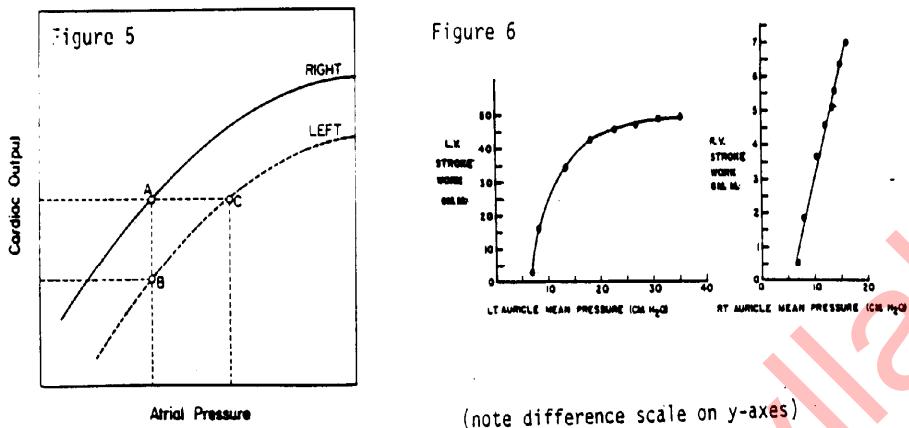


Fig. 5: The increased compliance of the thinner-walled right ventricle stretches the sarcomeres more for a given filling pressure. Similarly, for a given output of volume, the (lower arterial) pressures on the right side require an RVED < LVED.

- K. Although volume measurement would permit better correlation with fiber length, it is commoner to measure pressures in clinical situations. Reasons include the fact that it is easier to measure pressure (fluid-filled catheters are left in the atria or pulmonary artery) than volume; measurements are usually made over relatively short periods of time (minutes-days) and as a rule no important changes in compliance or heart size occur during such short times and compliance is difficult to measure precisely.
- L. For the right side of the heart clinical measurements usually utilize right atrial pressures, since these are in equilibrium with right ventricular end-diastolic pressures.
- M. For the left ventricle, pulmonary artery diastolic (sometimes pulmonary capillary, or "wedge") pressures are used. These approximate pulmonary venous pressures which are, in turn, in equilibrium with mean left atrial, and therefore, left ventricular pressures.
- N. For any stable compliance (or stiffness) a reduction in filling pressure would reflect a decrease in filling volume. A very low cardiac output might be repaired by volume infusion. A very high filling pressure might signal hypervolemia and the need for addition of an inotropic drug (e.g. Ca++) and/or a reduction in intravasacular volume. Repeated measurements of cardiac output by indicator-dilution techniques may be made throughout such a series of pressure measurements and medical interventions. Peripheral resistance can then be calculated (Peripheral Resistance = Mean Arterial Pressure/Cardiac Output) and it, too, can be modified to maintain output at optimum levels.
- O. Some examples of different situations may help to clarify the changes in the Starling curves:



Clinical Correlates:

1. 25 y.o. seated medical student reading a boring slide while waiting for physiology class to end.
2. 25 y.o. medical student running from physiology lecture to Dean of Student Affairs Office to pick up loan check.
3. 38 y.o. male doing his daily required bicycle exercises after having completely recovered from cardiac transplantation surgery (at which time he received a denervated donor heart).
4. 25 y.o. medical student has a bleeding peptic ulcer.
5. 25 y.o. medical student undergoes emergency surgery at which time 10 liters of blood replacement are given (excess replacement).
6. 25 y.o. medical student develops cardiomyopathy with fatigue, pulmonary congestion, distended neck veins, edema.

Hemodynamics:

	<u>EDP</u>	<u>CO</u>	<u>Resistance</u>	<u>Starling Curve</u>
1. Normal, resting	nl.	nl.	nl.	nl.
2. Normal, exercise	nl.	↑	↓	(+) inotropic
3. Denervated heart (exercise)	↑*	↑	↓	nl. (→ +inotropic)
4. Hemorrhage	↑*	↓*	↑	(+) inotropic
5. Hypervolemia	↑*	↑nl	↑nl	(-) inotropic
6. Heart failure	↑	↓	↓	(-) inotropic*

* Means that this variable is the “initial” cause of the altered physiology.



Last Year's (2010) Syllabus

CARDIAC OUTPUT

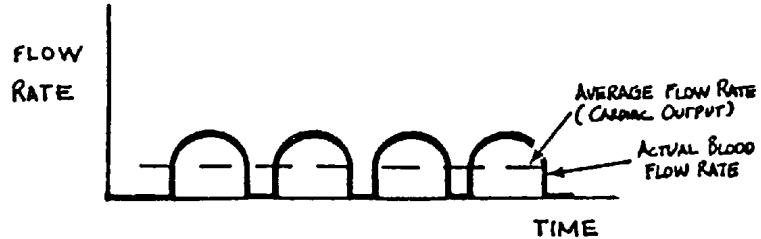
OBJECTIVES AND SUMMARY

- A. To understand the bases of measurement of intracardiac pressures, their significance and their normal range.
- B. To understand the rationale of measurement of cardiac output by:
 - 1. Fick Method
 - 2. Indicator dilution Method
- 1. What is cardiac output?
- 2. How is it measured clinically?
- 3. What physical phenomena form the bases for these methods?
- 4. How do you use these phenomena to compute cardiac output?
- 5. How do you execute these measurements in man?
- 6. What are the potential sources for error?

I. CARDIAC OUTPUT

- A. One can consider the volume of blood the heart pumps per unit time two ways. You could measure blood's instantaneous flow rate from the left (or right) ventricle into the aorta (or pulmonary artery); under normal circumstances this value starts at zero (no flow) during diastole, increases during systole, then drops back to zero again when the aortic valve closes (Fig. 1). This detailed characterization describes how the ventricle functions during a single beat, but from the point of view of the heart as a blood pump to serve the body's nutritional and waste removal needs, the average volume of blood the heart propels over many beats is the more important parameter. (Fig.1)

FIG. 1

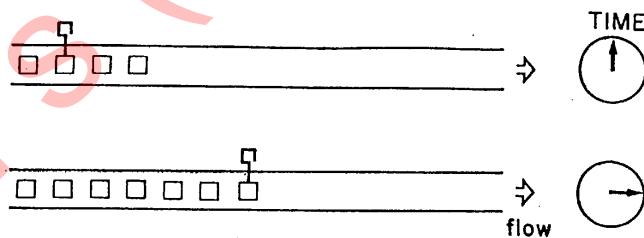


This average flow rate is called the cardiac output. The net volume of blood propelled from the heart in one beat is denoted the stroke volume. (Typical values in normal resting adults: SV = 70 ml, CO = 6 L/min.). Even though the actual flow is pulsatile with instantaneous flow rate changing rapidly with time, constant demand on the heart to pump blood leads to a constant average flow rate, the cardiac output, which remains stable. When the cardiac output remains constant it equals the stroke volume produced by each beat times the heart rate, the number of beats per minute:

$$\text{CO} = \text{SV} \times \text{HR}$$
$$\text{ml/min} / \text{ml/beat} \quad \text{beats/min}$$

We wish to measure this average flow rate, the cardiac output.

- B. The cardiac output's stability, despite the underlying flow's rapid pulsatile nature provides the basis for the two methods most commonly used clinically to measure cardiac output: Fick and Indicator-Dilution. Both methods involve tagging blood fluid particles then observing how these particles move over time. If blood flowed in a simple tube and in discrete mass elements, one could flag one or more elements then watch the flag move to compute the flow rate. Oxygen attached to the blood in the lungs generally serves as the Fick method's flag and an injected indicator, such as (in the past) cardiogreen dye or (more commonly) iced saline solution, serves for the Indicator-Dilution method. (Fig. 2)



II. FICK METHOD

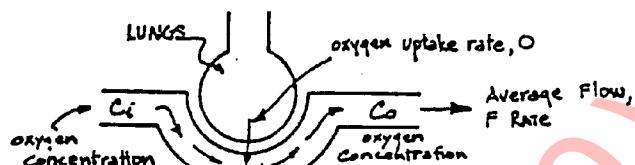
- A. The Fick method follows directly from a statement of conservation of mass, assuming the subject remains in a constant physiological state. To obtain accurately measured cardiac output, the oxygen concentration in the blood entering and leaving the lungs as well as the cardiac output itself must remain constant during the period of measurement. Under these conditions the mass flow rate of oxygen away from the lungs equals the rate at which it is being carried in by - venous blood plus the rate of absorption from the air in the alveoli (Fig. 3). The rate at which blood carries oxygen into (or out of) the lungs equals the concentration of oxygen in blood entering (or leaving) the lungs times the blood's flow rate.



Assuming the patient's activity remains constant, and therefore that the concentrations of oxygen for the blood entering and leaving the lungs remain constant, his breathing remains constant and the cardiac output remains constant, it is possible to translate this statement into the equation:

$$F \times C_i + O = F \times C_o \text{ or } F = O/(C_o - C_i)$$

Key:
 C_i = O_2 concentration of pulmonary artery blood
 O = O_2 uptake/min
 C_o = O_2 concentration of pulmonary venous blood
 F = Flow rate (F must be constant during measurement.)
(Fick output is better in low cardiac output states.)



$$F \times C_i + O = F \times C_o$$

$$F = O / (C_o - C_i)$$

Key: C_i = O_2 concentration of pulmonary artery blood (entering the lungs)

O = O_2 uptake/min

C_o = O_2 concentration of pulmonary venous blood (leaving the lungs)

F = Flow rate (F must be constant during measurement.)

(Note: Fick output is better in low cardiac output states.)

- B. In addition to requiring that the patient be in physiological steady state (especially constant respiratory activity and cardiac output), the indicator substance (generally oxygen) must be thoroughly mixed with the blood to truly represent the average concentration at each sampling point. This is not a trivial consideration. Only passing through the heart assures adequate mixing; therefore, the Fick method requires obtaining blood samples in the heart or an artery beyond its mixing chambers. Typically, one takes blood samples to measure for oxygen saturation from any systemic artery (all arterial blood has the same oxygen concentration as the aorta) and from the pulmonary artery (equivalent to mixed venous blood). Furthermore, since the actual flow is highly pulsatile, the sample should be taken slowly, over 5-10 seconds, to insure measuring the average oxygen concentration (averaged over time, i.e., a few beats) for the sampling site.

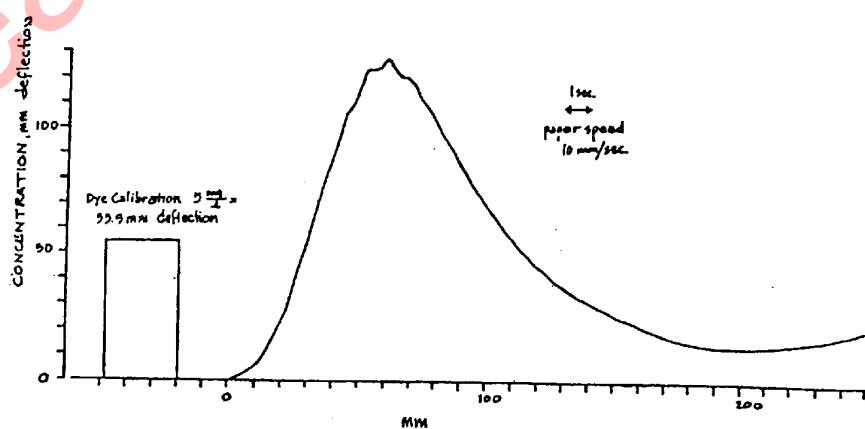


- C. Finally, one computes the patient's oxygen consumption, O , by collecting his expired air for a known time interval. Measuring this collected expired air's oxygen content then subtracting it from room air's oxygen divided by the sampling time interval produces the average oxygen consumption rate, O (In practice O is usually taken from tables which give normal O_2 consumption based on height, weight and gender). Having found C_i , C_o , and O , one can use the Fick formula to compute cardiac output, F .

III. THE INDICATOR-DILUTION METHOD

- A. If we inject a marker such as cardiogreen dye, radioactive tracer or cold saline solution, which the blood carries, then watch how the marker passes a downstream point, some blood will move quickly in large arteries and veins while other moves slowly through longer, smaller parts of the vasculature. Different blood particles, and the markers moving with them, require different times to move between two points within the vasculature. This effect spreads out the initial injected indicator marker as it moves through the vascular system with the blood. Eventually the indicator which moves through the vasculature faster than average will reach the sensor which in turn will detect increasing concentrations of indicator*. As time progresses the bulk of the indicator will pass, the concentration curve will peak, then return to zero as the slowest moving indicator-carrying blood passes the sensor. (Fig. 4) The curve's exact form depends on the cardiac output, the distribution of transit times between the indicator injection site and sensing site and the vasculature's geometry between these two points. Fortunately, differences in the curve's exact shape due to differences in the vascular beds do not affect cardiac output calculations.

FIG. 4



We now compute cardiac output from this measured curve.

I	=	f c(t)	x	F(t)	x	dt
amount		indicator(mg.)		ml blood		min
indicator		ml blood	'			
(i.e. mg.)						

So,

$$F = \frac{I}{\int c(t) dt}$$

This is equation for computing cardiac output using the Indicator-Dilution method. (Check the units.)

- * If the indicator is a dye you would detect changing opacity of the blood with a photocell system; if it were radioactive tracer you would use a Geiger counter; if it were heat, you would use a thermistor (thermometer).
- B. As with the Fick method, this equation's accuracy critically depends on the cardiac output remaining constant from the time of indicator injection until the curve has been measured. Since the definite integral equals the area under the curve, this equation says: the cardiac output equals the amount of indicator injected divided by the area under the concentration vs. time curve.
- C. The major limitation inherent in this method arises from the circulation being a closed system. Before the indicator concentration curve returns to zero (i.e. all the indicator has passed the sensor), the indicator concentration again rises due to recirculation. The most satisfactory method to account for recirculation is to remove it from the observed indicator washout curve. This correction follows from the observation that once the indicator concentration curve starts dropping, it drops according to the inverse exponential function of time (Ae^{-kt} ; with A and k being constants) until recirculation begins. A concentration which falls according to an inverse exponential vs. time follows a straight line on semilog graph paper. (Figs. 5, 6, 7) On the basis of these observations it is possible to replot the indicator concentration curve on semilog paper, then simply extrapolate the initial straight line drop in concentration before recirculation begins to appear, to negligible concentrations and assume you would obtain the resulting curve without recirculation. With these assumptions, you can then read the extrapolated values off the semilog plot and replot them on the actual dye curve, then find the area under this corrected curve and proceed with the original formula which did not allow for recirculation. (Fig. 4,5,6,7)



- D. In the vast majority of clinical situations, temperature is now used as the marker in the Indicator-Dilution technique. Theoretically, thermodilution eliminates the problem of recirculation through heat's propensity to dissipate completely during a single passage through the circulation (when small quantities of saline solution at 4.0 C. are used).

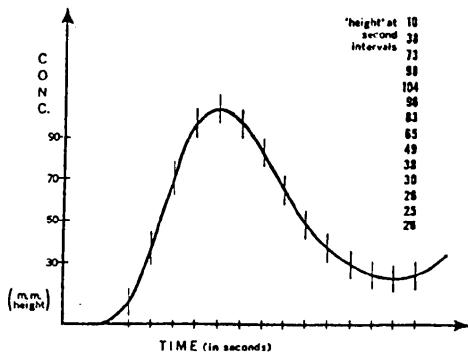


Figure 5

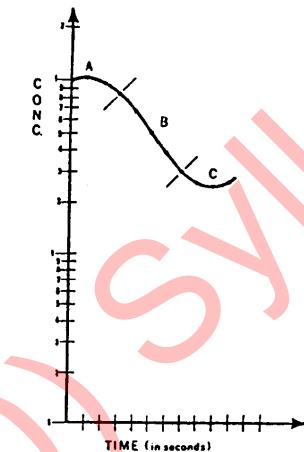


Figure 6

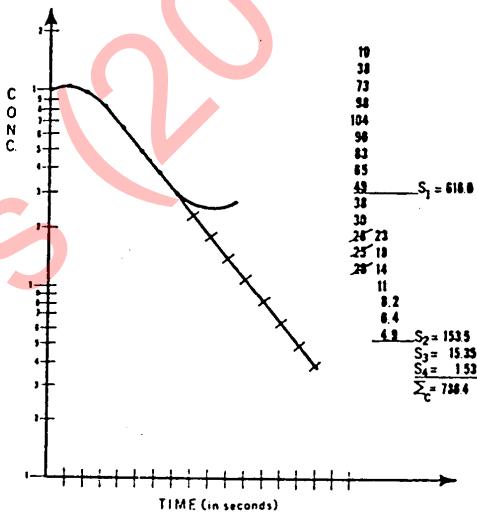


Figure 7

- E. From a practical point of view, one injects the dye or other indicator into the pulmonary artery or right heart (through which all the blood must flow) through a catheter, then samples from another catheter downstream in the central circulation which yields the concentration-time curve which is recorded on paper (or in a computer) for subsequent analysis.



IV. WHAT ARE SOME PRACTICAL ADVANTAGES?

- A. Repeated cardiac outputs may be done at short intervals, if the dye is rapidly cleared from the circulation (this is especially true when a thermistor (thermometer) is used and the indicator is cooled saline solution).
- B. Minimal patient effort is required. Once the catheters and sensors are in place no further cooperation is needed (in contrast to the Fick procedure in which the patient must breathe into a closed system for several minutes).
- C. Although sensing in the aorta or pulmonary artery seems necessary, at first glance, this is not the case since as the marker passes out of the aorta into its branches, the wave-front of advancing marker concentration will be more or less the same as it was in the aorta and since it is only concentration versus time we are interested in, sampling can take place in any one of the peripheral arteries (i.e. we do not have to see all the marker we injected, we need to see only the profile of its concentration).
- D. Disadvantages
 - 1. As cardiac output falls, the flow rate is (by definition) slower and the area under the curve is larger, with a longer time of inscription. This means that recirculation may occur before the curve is completely described, exaggerating the area under the curve and thus artificially diminishing the already low cardiac output. A corollary of this is that Indicator-dilution outputs are generally more accurate with high outputs and vice versa. (n.b. Fick output, on the other hand, are more accurate with low outputs and less so with high outputs having small arteriovenous O₂ differences. Why?)
- E. Misconceptions
 - 1. When the cardiac output is high, one would expect a higher peak concentration of the curve (conc. vs. time) and therefore a greater area and therefore a lower cardiac output. Paradox? No. Although the peak may be slightly higher with a high cardiac output, the slope of decay of the indicator concentration is much more rapid and the area under the curve less.



2. If only a fractional sample of arterial blood goes through the sensor then we are only looking at a fraction of the indicator injected, yet we are dividing this into the whole quantity of indicator. Isn't this producing an error? Since the concentration of different substances does not change during the brief time that the blood is in the arterial tree and since we are measuring concentration, this does not introduce an error.
3. The responses to these confusions may be clearer if we examine some examples of the indicator-dilution system at work: (figs. 8, 9, and 10)

Fig. 8

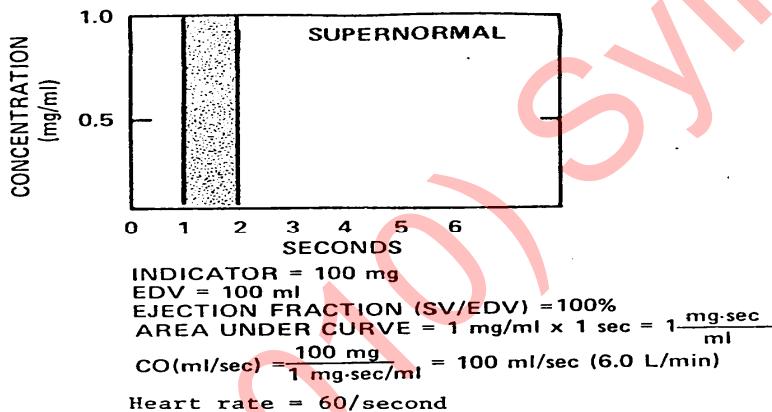
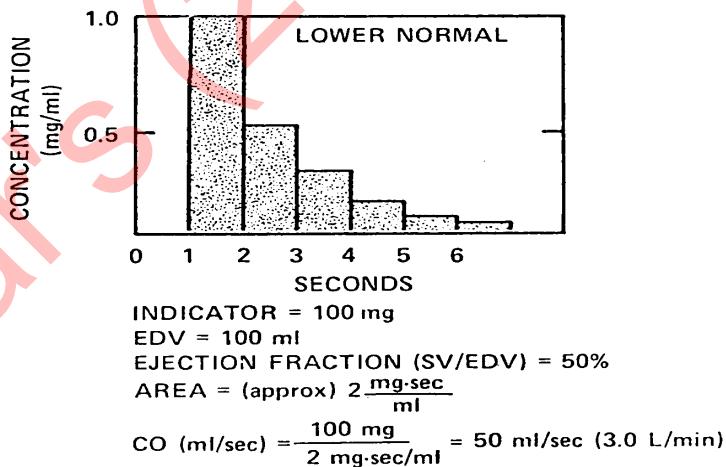


Fig. 9

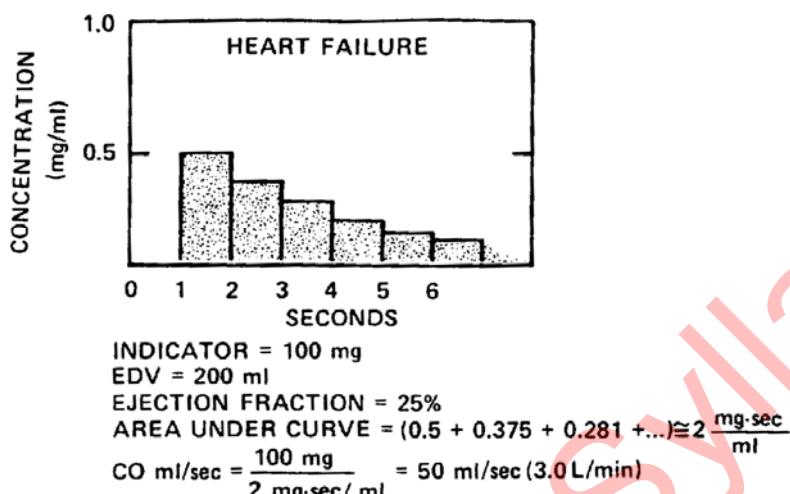


V. QUESTIONS

- A. Consider what would happen to the area under the curve if the heart rate doubled? (from 60 to 120/minute)



Fig. 10



- B. Despite a drop in E.F. to 25% (well below lower limits of normal), cardiac output is reasonably maintained. By what compensatory mechanism is this accomplished? What is the cost of this compensation?
- C. Having looked at several indicator dilution curves, can you explain:
1. Why there is a logarithmic decay?
 2. What the relationship is between the slope and the ejection fraction?

VI. SUMMARY

- A. Both the Fick and Indicator-Dilution methods for determining cardiac output, the average volume flow rate of blood pumped from the heart, follow from identifying specific particles of blood and monitoring their movement. In the Fick method, oxygen breathed normally from a room serves as the most natural and common indicator. Both Fick and Indicator-dilution methods produce similar values for cardiac output and both critically depend on satisfying the assumption of steady state: for the Fick method, constant respiratory activity, and for both methods, constant cardiac output.



- B. The Fick method is more accurate at low cardiac outputs and the Indicator-Dilution method more accurate at high outputs. When the cardiac output is low the difference between arterial and venous oxygen concentrations tend to be high; therefore, a given absolute measurement error induces a small percentage error in the difference $\text{Co} - \text{Ci}$. High cardiac outputs go with lower $\text{Co} - \text{Ci}$, so the same absolute measurement error in oxygen content will induce a much larger percentage error. On the other hand, in the Indicator-Dilution method recirculation introduces relatively greater errors when cardiac output is low than when it is high because it appears earlier in washout.

VII. REFERENCES

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2. D.A. Bloomfield: Dye Curves: The Theory and Practice of Indicator Dilution. University Park Press, Baltimore, 1974. Chapter 2: Foundations of Indicator Dilution Theory; Chapter 3: A Method for Performing an Indicator-Dilution Curve to Measure Cardiac Output.
3. K.L. Zierler: Circulation Times and The Theory of Indicator-Dilution Methods for Determining Blood Flow and Volume. In Handbook of Physiology, v. I, pp 585-615, Am. Phys. Soc., Washington, D.C. 1962.



VIII. EXAMPLES (TAKEN FROM REAL PATIENTS)

Fick Method

Data:

Expired Air Collection Time: 7 minutes
Total Ventilation (corrected to STP): 50.4 L
Oxygen Concentrations:

Room Air: 0.211 L O₂

L air

Expired Air: 0.179 L O₂

L air

Arterial Blood: 0.192 L O₂

L blood

Venous Blood: 0.095 L O₂

L blood

Solution:

1. Oxygen consumption rate:

$$O = \frac{50.4 \text{ L air}}{7 \text{ min}} \cdot (0.211 \text{ L O}_2 - 0.179 \text{ L O}_2) \text{ L air}$$
$$O = 0.230 \text{ L O}_2 \text{ min}$$

2. From direct measurement:

$$CO = \frac{0.192 \text{ L O}_2}{\text{L blood}} ; Ci = \frac{0.095 \text{ L O}_2}{\text{L blood}}$$

3. So the cardiac output is:

$$F = \frac{O}{Co-Ci} = \frac{0.230 \text{ L O}_2}{\text{min}} \cdot \frac{\text{L blood}}{(0.192 - 0.095) \text{ L O}_2}$$
$$(0.097)$$

$$F = 2.37 \text{ L/min (low for a normal adult)}$$



Indicator - Dilution

Data:

Dye Indicator: Cardiogreen dye

Dye concentration: 2.5 mg /ml

Size of injection: 2.27 ml

Figure 4 shows the dye curve

Solution:

1. To estimate the area work in mm deflection of the recorder, then convert to mg/L using the calibration factor 5 mg/L = 55.5 mm deflection and the known paper speed of 10 mm/sec.

2. Replot the washout curve on semilog paper then extrapolate the exponential decay to negligible concentration, and plot the resulting extrapolation on the original washout curve (Fig. 7)

3. Find the area under the resulting curve and convert to the actual units:

$$c(t) dt = \text{Area} = 10690 \text{ mm}^2 \cdot \frac{5 \text{ mg dye/L}}{\text{mg} \cdot \text{sec}} \cdot \frac{55.5 \text{ mm}}{\text{sec}} = 96.3 \text{ mg L}$$

4. Compute the total quantity of dye injected, I:

$$I = 2.5 \text{ mg/ml} \cdot 2.27 \text{ ml} = 5.68 \text{ mg.}$$

5. Compute the cardiac output using the indicator-dilution formula:

$$F = \frac{I}{c(t) dt} = \frac{5.68 \text{ mg} \cdot \text{L}}{96.3 \text{ mg} \cdot \text{sec}} \cdot \frac{60 \text{ sec}}{\text{min}} = 3.54 \text{ L/min}$$

IX. PROBLEMS

Find the cardiac output in each case.

1. Fick Method

Expired air collection time: 5 min

Total ventilation (corrected to STP): 29.9 L

Oxygen concentrations:

Room Air: 0.211 L O₂
 L air

Expired Air: 0.179 L O₂
 L air

Arterial Blood: 0.192 L O₂
 L blood



Venous Blood: 0.125 L O₂
 L blood

(Answer: F = 2.87 L/min)

2. Indicator-dilution

Indicator: Cardiogreen dye

Dye Concentration: 2.5 mg/ml

Size of injection: 2.44 ml.

Calibration: 5mg/L per 55.5 mm deflection

Figs. 4-7 show the dye curve. (Area=786 mm-sec)

(Answer: F = 5.17 L/min)



Last Year's (2010) Syllabus

CARDIAC CATHETERIZATION

The development of simple, safe methods of access to the cardiac chambers and many portions of the venous and arterial beds has been one of the most important advances in cardiology and medicine over the past 50 years, permitting many diagnostic and therapeutic maneuvers. It is the purpose of this presentation to review current methods of diagnostic cardiac catheterization with particular reference to studies of the right heart, pulmonary circulation and the left heart. The hemodynamics of the pulmonary and systemic circulation, cardiac output measurements, valvular stenosis and pericardial disease are presented elsewhere.

I. HISTORICAL DEVELOPMENT

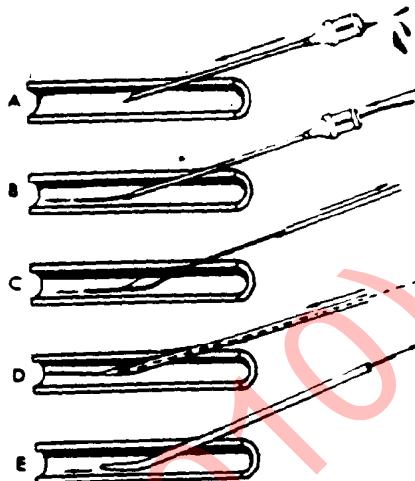
In 1844 cardiac catheterization of the right and left ventricles of the horse was performed using the jugular vein and carotid artery. Pressures were recorded on a smoked drum via a long air filled rubber tube with a balloon at each end. Exercise studies were even performed using a treadmill! In 1870 Adolph Fick described the method of determining cardiac output by a knowledge of the oxygen content of mixed venous blood, the arterial blood and the oxygen consumption. However it was not until 1925 that the 25 year old Werner Forssmann inserted a ureteral catheter in his own antecubital vein and guided it by fluoroscopy into his right atrium. He then walked upstairs to the Radiology Department where a chest film confirmed the position of the catheter. Forssmann was a surgeon and did not realize the potential diagnostic value of his procedure. He thought that it might be a method of central administration of drugs where peripheral venous access was difficult. In 1930 Klein first measured the cardiac output in 11 studies in man. It was not until 1941 when Richards and Cournand began a series of cardiac catheterizations at Bellevue Hospital in New York City that right heart catheterization became accepted as an important method of studying the circulation. Subsequent developments are listed next:

- 1947 - Pulmonary artery and pulmonary wedge pressure measurements; Dexter
- 1947 - Diagnosis of congenital heart disease-valvular stenoses and shunt flows; Bing - Dexter
- 1950 - Retrograde catheterization of the left ventricle; Zimmerman
- 1953 - Seldinger technique of percutaneous arterial catheterization
- 1959 - Transseptal left atrial catheterization; Ross and Cope
- 1959 - Selective coronary arteriography; Sones
- 1970 - Balloon tipped flow guided catheter; Swan & Ganz



II. RIGHT HEART CATHETERIZATION

Access to the right heart and pulmonary artery can be achieved most commonly via a peripheral vein - either by a cutdown exposing and isolating the vein or by percutaneous puncture of the femoral, external or internal jugular or the subclavian vein. The fluid filled catheter is then advanced under fluoroscopic control to the right atrium, right ventricle and pulmonary artery for pressure measurements, blood sampling or injections of dye or cold saline to measure cardiac output.



The Seldinger technique. The needle is inserted at an angle of about 45 degrees. The needle stylet is withdrawn, and the needle is slowly pulled out until blood return signifies that you are within the lumen of the vessel (A). A flexible-tipped guidewire is then inserted through the needle into the vessel (B), and the needle is withdrawn (C). A catheter (or sheath with dilator) is then inserted into the vessel over the guidewire (D). The guidewire is removed, leaving the catheter (or sheath) in the vessel lumen (E).

Fig. 1 Multiple lumen catheter for right heart catheterization.

- A. Right atrial or central venous catheterization:
1. This is usually a bedside maneuver and localization of the catheter in the right atrium can be performed by a chest film, pressure contour or advancing to the RV and then pulling back until an atrial pressure contour is observed on the monitor.
 2. Cardiac output can be estimated by the AV difference if arterial blood samples are obtained at the same time as a right atrial sample is obtained. The normal A-V difference is 3-5 ml/100 ml. In high output states A-V will be <3 and in low output states >5. Errors may occur if the catheter tip is in the SVC, IVC or coronary sinus which are not representative of true mixed venous blood.



3. Right atrial mean pressure using the midchest in the supine position as a reference point will provide a rough estimate of the intravascular fluid volume if cardiac function is normal, a low pressure 0-2 mm indicating hypovolemia and a high pressure >12 mm indicating hypervolemia. The effect of an IV fluid challenge can be estimated by a rise or no change in RA pressure.
- B. Pulmonary: artery catheterization:
1. With the advent of the Swan-Ganz catheter -a balloon tipped flow guided catheter that can be inserted percutaneously at the bedside-pulmonary artery catheterization has been greatly simplified and is the most common method of right heart catheterization employed in intensive care units. (Fig 2)
 2. The position of the catheter in the pulmonary artery can be identified without fluoroscopy by the appearance of the characteristic PA pressure contour. Inflation of the balloon will obstruct flow in the catheterized branch of the pulmonary artery and the retrograde pressure of the left atrium can be measured (pulmonary wedge or capillary pressure). (Fig 3). A second proximal lumen will permit blood sampling or injection of dye or cold saline in the pulmonary artery.

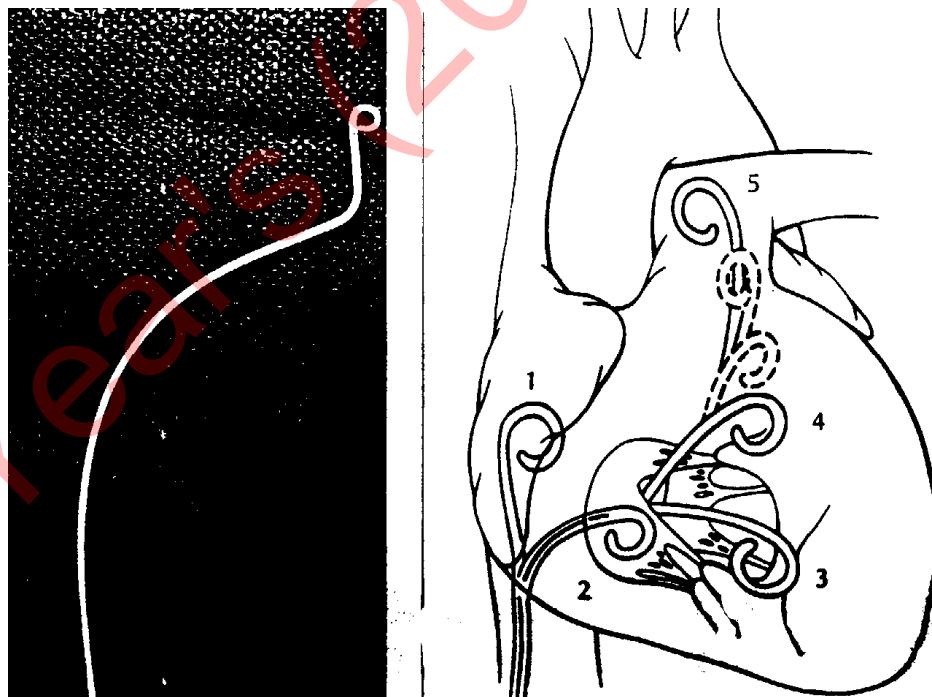


Fig. 2 Entry of a right-heart catheter from the IVC into the RA, RV and PA.



- C. Pulmonary artery pressure:
1. The Ohm equation for flow ($Q=\Delta Pr/R$) may be rearranged for the pulmonary circulation as follows: PA (mean)= $Qp \times Rp + PCW$, where $\Delta Pr=PA(\text{mean})-PCW$, Qp is pulmonary flow, Rp is pulmonary vascular resistance and PCW is mean pulmonary capillary “wedge” pressure (roughly equivalent to LA pressure).
 2. The mean pulmonary artery pressure may be increased due to:
 - a. Increased pulmonary blood flow as in a left to right shunt,
 - b. Increased pulmonary arteriolar resistance as in hypoxic pulmonary disease or,
 - c. An increase in left atrial pressure.
 3. For these reasons the pulmonary artery pressure is not a reliable guide to left atrial pressure except when the systolic PA pressure is < 50 mm. In this situation the PA diastolic pressure usually is similar to the PA wedge and left atrial pressure. Of course if the PA mean pressure is normal an elevated left atrial pressure can be excluded.
- D. Pulmonary artery wedge or capillary pressure (PCW):
1. When the pulmonary artery balloon is inflated (Swan-Ganz catheter) or an ordinary cardiac catheter is advanced so that it "wedges" in a small pulmonary artery the retrograde pressure reflects left atrial pressure minus about 2 mmHg. In some instances of obliterative pulmonary hypertension or pulmonary venous occlusive disease a true wedge pressure may not be obtained. An elevated wedge pressure > 12 mmHg indicates a raised left atrial pressure as in mitral stenosis or LV failure. In the calculation of pulmonary vascular resistance the pulmonary flow must be calculated (Fick principle or dye curve) and the mean PA and mean PA wedge pressure must be determined.
- E. Pulmonary artery blood sampling:
1. Pulmonary artery blood samples are a more reliable measure of true mixed venous blood than right atrial samples since mixing is more complete and streaming of blood of variable oxygen contents via the SVC, IVC and coronary sinus is eliminated. For calculation of most left to right shunts i.e. atrial or ventricular septal defects or a patent ductus arteriosus both pulmonary and systemic blood flows must be calculated by the Fick principle. Systemic (peripheral) blood flow is then established by averaging the



mixed venous oxygen content of the IVC and SVC as the mixed venous sample and using peripheral arterial blood O₂ content and minute O₂ consumption to calculate the systemic blood flow by the Fick equation.

2. Pulmonary flow is estimated by entering the O₂ contents of the pulmonary artery and a peripheral artery into the Fick equation (the minute O₂ uptake in the steady state is the same for lungs as for the systemic peripheral circulation; i.e., O₂ uptake=O₂ metabolized.) For example in an atrial septal defect peripheral blood flow may be 4 liters/minute and pulmonary blood flow 12 liters/minute indicating a left to right shunt of 8 liter/min (In which case the systemic A-V O₂ difference might be [190 cc O₂/L – 130 cc O₂/L] 60 ml O₂/L while the pulmonary A-V O₂ difference would be [190 cc O₂/L – 170 cc O₂/L] 20 ml O₂/L.) of oxygenated blood being diverted from the LA across the atrial septal defect (ASD) into the right heart.

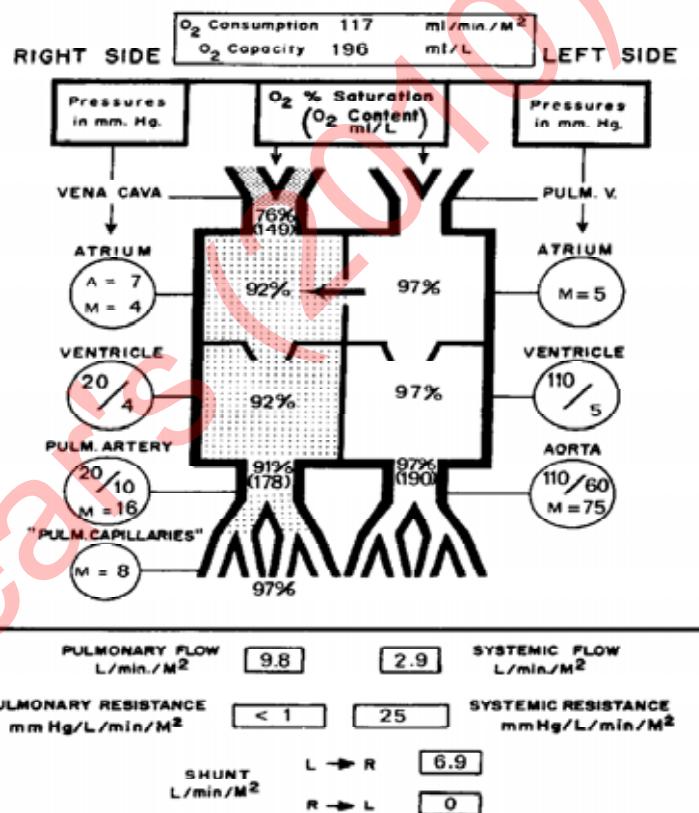


Fig. 3 Diagrammatic representation of Atrial Septal Defect hemodynamics.
(From Nadas, A & Fyler DC. Pediatric Cardiology , WB Saunders, 1972)



3. Serial sampling of oxygen contents of the proximal vena cavae, right atrium, right ventricle and pulmonary artery will localize the shunt, including atrial and ventricular septal defects and a patent ductus arteriosus. (There will be an abrupt increase in O₂ content of blood when the chamber (or vessel) into which the L-R shunt is located is entered by the catheter.) Injection of radio-opaque contrast substance into these chambers will also localize the shunt.

III. ARTERIAL AND LEFT HEART CATHETERIZATION

A. Arterial catheterization

1. The femoral artery is the usual site of catheter insertion. In cases of occlusive disease of the iliac or femoral vessels the brachial (or radial) artery may be used.

B. Left ventricular catheterization

1. Catheterization of the left ventricle is usually performed via the femoral artery and occasionally via the brachial artery using a percutaneous puncture via a modified Seldinger method (femoral artery) or direct exposure (brachial artery). The catheter is advanced retrograde into the ascending aorta and passed across the aortic valve into the left ventricle. Fluoroscopic control is essential. Ventricular pressures can be recorded using either fluid filled catheters or in special studies a catheter tipped pressure manometer (Mylar catheter) may be employed. The latter method gives more precise pressure measurements but is not usually employed in diagnostic studies. Central aortic pressures are recorded by pulling the catheter back across the aortic valve while recording the pressure. This method is employed in the diagnosis of aortic stenosis.



Fig. 4. Pressure gradient in patient with aortic stenosis. Note the left ventricular pressure of approximately 180 mm HG, and the aortic pressure on pull-back of approximately 100 mm Hg.



2. Contrast medium can be injected into the LV or aorta to evaluate chamber size, LV function and to detect aortic or mitral regurgitation. A simultaneous recording of LV and PA wedge pressure will permit the estimation of the pressure gradient across the mitral valve in mitral stenosis.

IV. DANGERS AND COMPLICATIONS

- A. A major risk of arterial and left heart catheterization is local arterial damage - thrombosis or hemorrhage. Operator skill is important. Ventricular arrhythmias, detachment of mural thrombi from the aorta or LV resulting in systemic embolism, inadvertent entry into coronary arteries with obstruction and vasovagal reactions may occur but fatalities are rare i.e. < 0.1%.

Typical Normal Values:

RA mean	1-7 mm Hg
RV systolic/end-diastolic	25-<7mm Hg
PA s/d/mean	25/7/15 mm Hg
PCW mean	5-12 mm Hg
LV systolic/end-diastolic	120/8-12 mm Hg
Aorta s/d/mean	120/80/90
CO	5-7 L/min
Cardiac Index	>2.5 L/min/M ² (Body surface area)
Rs	10-20 (Wood) units
Rp	1-2 (Wood) units

V. OTHER CARDIAC PROCEDURES INVOLVING VENOUS OR ARTERIAL ACCESS TO THE HEART AND CIRCULATION

The methods of venous and arterial access to the heart and special circulatory beds have resulted in a large number of diagnostic and therapeutic methods which are partially listed below:

- A. Diagnostic:
 1. Angiographic studies of the heart, coronary arterial bed and other circulations
 2. Electrophysiologic studies - His bundle electrograms - induced arrhythmias



3. Coronary sinus studies of the coronary circulation
 4. Angioscopy (fiberoptic visualization of vessels)
 5. Intravascular Ultrasound imaging
- B. Therapeutic:
1. Balloon angioplasty/valvuloplasty, stenting of obstructed vessels
 2. Embolization of abnormal vascular structures (e.g. cerebral aneurysm)
 3. Drug delivery (thrombolytics, selective chemotherapy)
 4. Temporary and permanent pacemakers
 5. Right atrial ablation of the conduction system to treat cardiac arrhythmias
 6. Defibrillation via the right atrium
 7. Retrieval of broken guide wires and catheters
 8. Laser ablation of lesions
- VI. REFERENCES**
1. Invasive bedside monitoring. McGrath, R. in Progress in Cardiovascular Diseases 29:129-144, 1986.
 2. A prospective study of complications of pulmonary artery catheterizations in 500 consecutive patients. Chest 84:245, 1984.
 3. Is pulmonary artery catheterization necessary for the diagnosis of pulmonary edema? Am Rev Resp Dis 129:1006, 1984.
 4. The cult of the Swan Ganz catheter. Overuse and abuse of pulmonary flow catheters. Ann Int Med 103:445, 1985.



Autonomic Drugs: Adrenoceptor Blockers

Reading assignment: Katzung (10th ed), Ch. 10

LEARNING OBJECTIVES:

- A. Learn the pharmacology of drugs that are antagonists at alpha adrenergic receptors. Understand how they produce both beneficial and undesirable effects, particularly in the cardiovascular system.
- B. Do the same for drugs that are antagonists at beta adrenergic receptors.

TOPICS

- A. Alpha adrenergic receptor antagonists
- B. Beta adrenergic receptor antagonists



Last Year's (2010) Syllabus

PHYSICS OF THE CIRCULATION

Basics: Pressure, Flow, & Resistance

The objective of the Physics of the Circulation lectures is to understand:

- A. The relationships among pressure, flow, and velocity.
- B. Vascular resistance and how it varies in different parts of the circulation.
- C. How conservation of energy causes a trade-off between pressure and velocity.
- D. Vessel wall compliance and stress.
- E. Non-linear aspects of the circulation, including turbulent flow, blood viscosity, and trans-capillary flow.

I. PHYSICS OF BLOOD FLOW

The primary function of the cardiovascular system is to circulate blood throughout the body in order to deliver nutrients and remove waste products. The goal of these lectures is to apply several basic laws of physics toward understanding how blood flows and how the properties of the circulation - pressure, flow, velocity, vessel size, resistance, etc. - all inter-relate.

The first step in understanding the physics of the circulation is to apply our intuition about the physics of solids to the physics of a fluid, in this case blood. Normally when we think of force, velocity, or potential and kinetic energy, we think in terms of a discrete, solid object. A fluid is more dynamic - it can change its shape and different parts can move at different velocities. Yet the same basic laws apply, it is simply a matter of expanding our intuition and terminology to describe the physics of fluid flow.

We will refer to pressure (P) on a fluid as analogous to force (F) on an object. A fluid has an overall flow (Q) as well as the velocities (v) of its components. While an object has a mass (m) and coefficient of friction (k_f), a fluid will be described by its density (ρ) and viscosity η . It is important to see that the laws have not changed, just the environment in which we apply them.

- A. Pressure is Force
 - 1. As fluids are not discrete objects, it is more convenient to consider the force (F) per surface area (A), which is pressure (P).

$$P = F/A$$

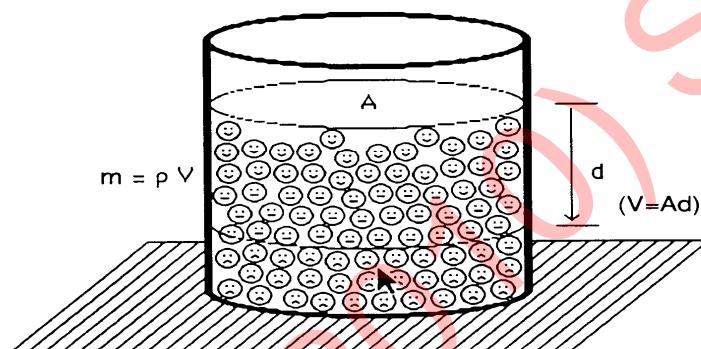


2. Consider the situation (fortunate or unfortunate) of 86 medical students piled into a sizable hot tub (like water in a beaker), as shown in the figure below. Imagine that you are down near the bottom; say a depth (d) from the surface. You would not have much difficulty reporting that there is a force acting on you due to the gravitational force on the mass above you. If we represent this mass by its density (ρ) and volume (V), we can say:

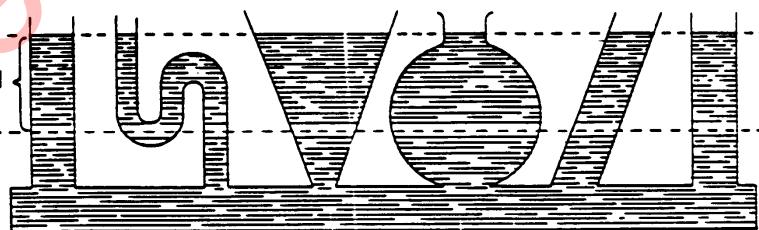
$$F = mg = (\rho V) g \quad (m = \rho V)$$

Normalizing for the surface area at depth (d), which will be the cross-sectional area of the tub (A), we can derive the pressure (P):

$$P = F/A = \rho g (V/A) = \rho g d$$



3. While we use the geometry of the tub in the above example to illustrate the relationship of pressure to force, the pressure is actually independent of the geometry of the container. The figure below shows a variety of different geometries, and yet the height of each column is the same and the pressure at depth d is also identical. Pressure depends solely on the distance from the surface (d), as can be seen from the formula. The independence from specific geometry makes pressure an ideal variable to describe force on fluids.



B. Flow vs. Velocity - Conservation of Mass

1. Just as force can cause the motion of an object, pressure can generate the flow of a fluid. Flow (Q) is defined as the amount, or volume (V), of fluid passing a point per unit time (t):



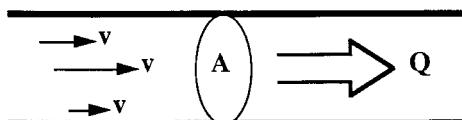
$$Q = \Delta V / \Delta t \text{ (units - m}^3/\text{sec)}$$

2. Velocity (v), on the other hand, is the speed with which individual elements of the fluid pass that point:

$$v = \Delta x / \Delta t \text{ (units - m/sec)}$$

3. Flow (Q) through a cylindrical tube is equal to the average velocity (v) of the fluid multiplied by the cross-sectional area (A) of the tube:

$$Q = Av$$



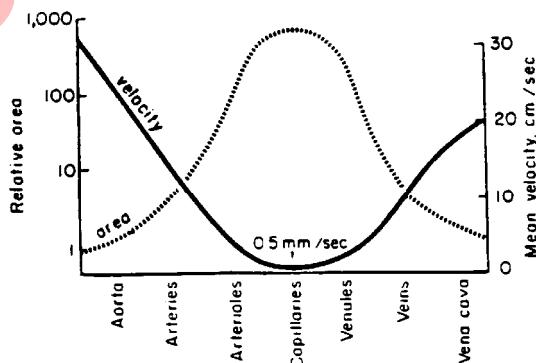
4. For a closed-loop system, like the circulation, fluid cannot enter nor leave, so there is conservation of mass or a conservation of volume (assuming density is constant). Thus, the amount of blood that leaves the heart through the aorta must equal the amount of blood that flows through the capillary bed, which must equal the amount of blood that returns to the heart via the venae cavae (ignoring coronary and bronchial circulation). Otherwise there would be a build-up or loss of blood somewhere in the circulation.

$$QAO = Qcap = QVC = \text{constant}$$

With flow (Q) being constant throughout the vasculature, there then exists a tradeoff between cross-sectional area (A) and fluid velocity (v), as shown in the figure below. For example, the aorta has a high velocity and small area, whereas the capillary bed has a low velocity and large area. This tradeoff comes directly from the above conservation of mass equation.

$$QAO = AA_O VAO = Qcap = Acap Vcap$$

$$AAo/Acap = Vcap/VAo$$



C. Resistance to Flow - Ohm's Law

1. An important characteristic of the circulation is the resistance to blood flow through the vasculature. Resistance can best be thought of as friction. When an object slides across a table, it loses energy due to friction. Similarly, blood loses energy as it flows through vessels due to resistance. For an object sliding across a table, it is clear that the more friction the greater the force necessary to insure that the object makes it all the way across. Similarly, the more resistance to flow through the vasculature, the greater the pressure needed to drive blood from one end to the other. Thus, pressure (P) is directly related to resistance (R), in order to maintain a constant flow (Q):

$$P \propto R \quad (Q \text{ constant})$$

2. Pressure (P) is also directly related to flow (Q), in that an increased pressure generates a higher flow, if resistance (R) is constant:

$$P \propto Q \quad (R \text{ constant})$$

The full equation is simply Ohm's law for fluids:

$$P = Q R \quad [V = I R]$$

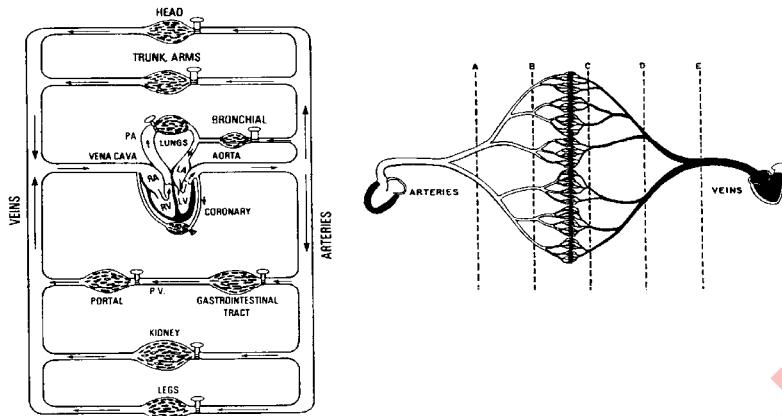
3. Defining Ohm's law for fluids introduces a new dimension to understanding the physics of the circulation. The circulation can actually be thought of as a circuit, with blood flow (Q) equivalent to electron flow or current (I), and pressure (P) equivalent to voltage (V). Notice that resistance (R) is used in both formulas - the resistance to blood flow through a vessel is analogous to the resistance to electron flow through an electrical resistor. Thus the vascular tree can be thought of as a large number of resistors, some in parallel and some in series. This means that we can apply our knowledge of how resistors sum (in series vs. in parallel) to analyze the resistances of the different parts of the vasculature system.

- a. In Series: $R_{\text{Total}} = R_1 + R_2 + R_3 + R_{\text{etc.}}$
- b. In Parallel: $\frac{1}{R_{\text{Total}}} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} + \frac{1}{R_{\text{etc.}}}$
4. An important contrast between resistors in series and in parallel is that adding resistors in series always makes the total resistance larger whereas adding resistors in parallel always makes the total resistance smaller. Adding S resistors all of the same resistance (R) yields:

$$R_{\text{Total}} = S R \text{ (in series) vs. } R_{\text{Total}} = R/S \text{ (in parallel)}$$

5. The figures below show how the blood vessels and vascular beds are organized both in series and in parallel.

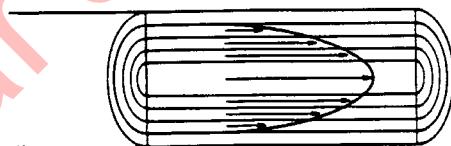




D. Vessel Resistance - Poiseuille's Law

While earlier we defined a formula for resistance based on pressure and flow, it is actually independent of these variables. Resistance is dependent on, and can be calculated from the physical properties of the fluid (i.e., blood) and the tube (i.e., vessel) through which it flows.

1. First, we must take a closer look at how fluid is actually impeded in a vessel. If there were no frictional forces (i.e., no resistance) then fluid flowing close to the vessel wall would travel as fast as the fluid traveling in the center of the vessel. In reality, fluid near the vessel wall is slowed dramatically as it has to move along a stationary surface (in the limit, the fluid at the wall has zero velocity). This slow moving outer layer of fluid then slows down the next layer closer to the center, setting up a "laminar" (i.e., "layered") flow.



The resulting velocity profile is parabolic or quadratic, as shown above, which means that velocity increases as a function of x^2 , where x is the distance from the vessel wall. Integrating the velocity profile allows us to derive the average velocity of the fluid. For this laminar flow, the average velocity (v_{ave}) is equal to half the velocity at the center (v_{max}), where $x=r$, the vessel radius. The overall result is that the average velocity (v_{ave}) is proportional to the vessel radius (r) squared.

$$v \propto x^2 \rightarrow v_{max} \propto r^2 [v = v_{max} \text{ at } x = r]$$

$$v_{ave} = v_{max}/2$$

$$v_{ave} \propto r^2$$



2. The other factors that affect velocity are the pressure (P) and viscosity η of the fluid, and the length (L) of the vessel. Pressure, as we have shown, is directly related to flow, which is directly related to velocity. Thus:

$$v \propto P$$

3. Viscosity is a measure of the frictional or viscous drag of a fluid. The more viscous the fluid, the slower the velocity, so they are inversely related:

$$v \propto 1/\eta$$

4. Finally, for a given pressure, the longer the vessel length (L) the less the velocity generated (think of how fast you can blow water out of a straw compared to a garden hose). So again they are inversely related:

$$v \propto 1/L$$

5. Putting it all together:

$$v_{ave} \propto P r^2 / \eta L$$

6. For a cylindrical tube is, the exact relationship needs a factor of 1/8:

$$v_{ave} = P r^2 / 8\eta L$$

7. To find the flow (Q), we simply multiply by the cross-sectional area (A) of our cylindrical vessel of radius r:

$$Q = A v_{ave} = (\pi r^2)(P r^2 / 8\eta L) \quad [A = \pi r^2 - \text{circle}]$$

$$\text{or } Q = (\pi/8) P r^4 / \eta L$$

This is Poiseuille's (roughly pronounced pwa-say's) law for laminar flow through a cylindrical tube. Note the fourth order dependence of flow (Q) on radius (r) - halving the radius reduces flow by a factor of 16!

8. Using Ohm's law, we can find the resistance (R) from the flow (Q) and the pressure (P):

$$R = P/Q \quad [\text{Circuits: } R = V/I]$$

9. So the final formula for resistance is:

$$R = (8/\pi)\eta L/r^4$$

E. Distribution of Vascular Resistance - An Exercise

1. As an exercise, we can use Poiseuille's law to compare the resistances of the different components of the vascular tree. See if you can follow the calculation below, using the table below, to derive the relative resistance of the arterioles vs. the capillaries.



Table 6 – Geometry of Mesenteric Vascular Bed of the Dog

<u>Kind of Vessel</u>	<u>Diameter</u> <u>(Mm)</u>	<u>No.</u>	<u>Total</u> <u>Cross-</u> <u>section</u> <u>al Area</u> <u>(Cm²)</u>	<u>Length</u> <u>(Cm)</u>	<u>Total</u> <u>Volume</u> <u>(Cm³)</u>
Aorta	10	1	0.8	40	30
Large arteries	3	40	3.0	20	60
Main artery branches	1	600	5.0	10	50
Terminal branches	0.6	1,800	5.0	1	25
Arterioles	0.02	40,000,000	125	0.2	25
Capillaries	0.008	1,200,000,000	600	0.1	60
Venules	0.03	80,000,000	570	0.2	110
Terminal veins	1.5	1,800	30	1	30
Main venous branches	2.4	600	27	10	270
Large veins	6.0	40	11	20	220
Vena cava	12.5	1	1.2	40	50
					930

2. To compare the resistance of the arteriolar bed to that of the capillary bed, we must start with the resistances of a single arteriole and capillary:

$$R_{art} = (8/\pi)\eta L_{art}/r_{art}^4$$

$$R_{cap} = (8/\pi)\eta L_{cap}/r_{cap}^4$$

Taking the ratio between the two allows several factors to cancel out (we will assume that viscosity remains constant - a topic to be discussed later.):

$$R_{art}/R_{cap} = (L_{art}/L_{cap})(r_{cap}/r_{art})^4$$

$$R_{art}/R_{cap} = (/)(/)^4 =$$

If you plug in the numbers from the table, you should get that the resistance of a single arteriole is significantly less than that of a single capillary. This would be



expected given the l/r^4 effect of Poiseuille's law. However, the total resistance of a vascular bed is the combination of the resistances of all the individual vessels, which are organized in parallel. Thus, the total resistance is equal to the resistance of a single vessel divided by the number of vessels.

$$R_{\text{art}}(\text{total}) = R_{\text{art}}/\#\text{arts}$$

$$R_{\text{cap}}(\text{total}) = R_{\text{cap}}/\#\text{caps}$$

$$R_{\text{art}}(\text{total})/R_{\text{cap}}(\text{total}) = (R_{\text{art}}/R_{\text{cap}})(\#\text{caps}/\#\text{arts})$$

$$R_{\text{art}}(\text{total})/R_{\text{cap}}(\text{total}) = (/)(/) \sim 1.5$$

3. Given the larger cross-sectional area of the capillary bed and thus the much greater number of capillary vessels, the total resistance works out to be greater in the arteriolar bed by approximately 50%. Below is a comparison of the relative resistances of all the vascular beds. based on the above dimension table.

Table 9 - Relative Resistance to Flow in the Vascular Bed:

<u>Calculated from Table 6</u>			
<u>Poiseuille's Law</u>			
Aorta	4%	Venules	4%
Large arteries	5%	Terminal veins	0.3%
Mean arterial branches	10%	Main venous branches	0.7%
Terminal branches	6%	Large veins	0.5%
Arterioles	41%	Vena cava	1.5%
Capillaries	27%		
Total: arterial + capillary = 93%		Total venous = 7%	



PHYSICS OF THE CIRCULATION

Dynamics: Energy, Gravity, Compliance, & Stress

I. CONSERVATION OF ENERGY - BERNOULLI'S EQUATION

- A. In the previous section we presented the conservation of mass and the resulting tradeoff between cross-sectional area and fluid velocity. In this section we will discuss the conservation of energy, where there is a balance between the potential energy and the kinetic energy of a fluid. This balance produces a tradeoff between pressure, a measure of potential energy, and velocity, a measure of kinetic energy. This will add to our understanding of the relationships among pressure, flow, velocity, and vessel geometry.
- B. Pressure represents a form of potential energy. Work must be done on a volume of fluid (V) to bring it to a pressure (P). Going back to our hot tub example, it takes "pressure work" to squeeze in under that pile in the tub. This work or potential energy (PE) is simply:

$$PE = P \cdot V$$

Note that the units of pressure \times volume are the same as force \times distance, which is how we describe work or potential energy for solids.

- C. The kinetic energy (KE) of a fluid, as for a solid, is based on mass and velocity:

$$KE = 1/2 mv^2 = 1/2 (\rho V) v^2$$

- D. Combining potential and kinetic energies, the total energy (E) is:

$$E = PE + KE = PV + 1/2 (\rho V) v^2$$

- E. From the conservation of energy, the total energy (E) must remain constant as blood flows through the vascular tree. This, however, ignores any loss of energy due to frictional forces, which only applies over short distances where resistance is negligible. Just as we approximate the potential energy of a ball when we drop it from a height as equal to its kinetic energy when it hits the ground, we are applying conservation of energy to blood flow in order to gain a qualitative understanding of the relationship between pressure and velocity.

$$\text{So: } E = PV + 1/2 (\rho V) v^2 = \text{constant}$$

- F. This can be simplified by dividing by V :

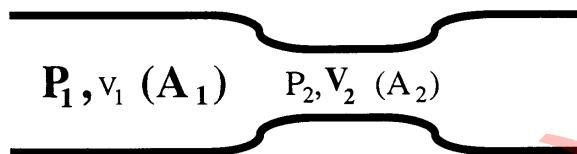
$$E/V = P + 1/2 \rho v^2 = \text{constant}$$



This is known as Bernoulli's equation, and it describes how the energy of a fluid can be distributed between pressure and velocity. Equating the energies at two different points in the circulation yields:

$$P_1 + \frac{1}{2} \rho v_{12}^2 = P_2 + \frac{1}{2} \rho v_{22}^2$$

- G. Thus, there is a direct tradeoff between pressure and velocity. As fluid velocity increases pressure drops, and vice-versa. If we use the example of fluid flowing through a narrow region of a blood vessel we know from intuition and from the conservation of mass that the velocity is higher ($v_2 > v_1$) in the region of smaller cross-sectional area ($A_2 < A_1$).



- H. From Bernoulli's equation, we can calculate the pressure (P_2) in the narrow region:

$$P_2 = P_1 + \frac{1}{2} \rho (v_{12}^2 - v_{22}^2)$$

$$\text{since } v_2 > v_1: \quad P_2 < P_1$$

1. Derivations of Bernoulli's equation are used clinically to calculate the velocity and pressure gradient in a vessel or across a valve, as well as to estimate the valve area in a stenotic valve.

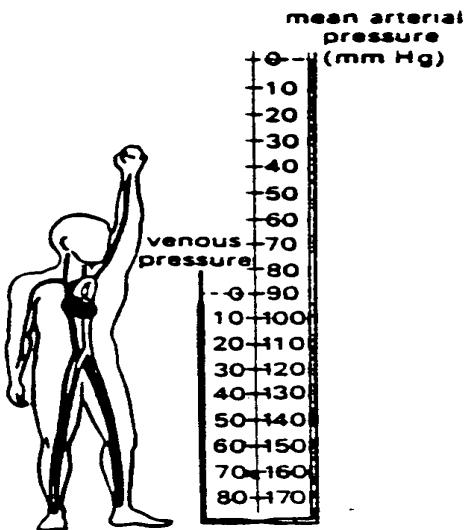
II. GRAVITATIONAL EFFECTS

- A. Gravity has several effects on the circulation, which are often misunderstood. It is important to understand what these effects are and why they occur. First of all, gravity affects the hydrostatic pressure of any fluid, as we discussed at the very beginning:

$$P_{\text{grav}} = \rho g d$$

This causes the pressure to increase with depth, i.e., blood pressure increases towards the feet and decreases towards the head, as shown in the figure below. Note that the right atrium is used as the reference or zero point for the circulation, which is roughly the level where a blood pressure cuff is placed.





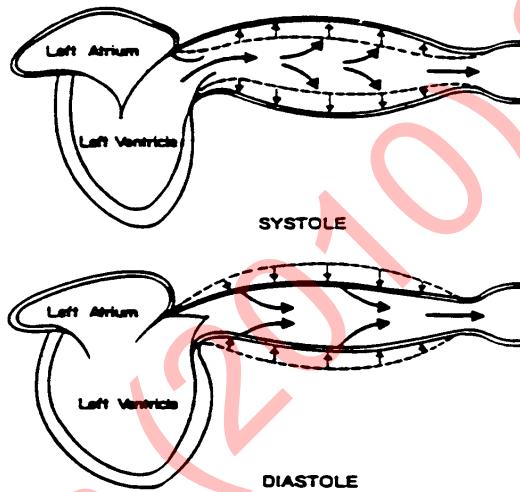
- B. The misunderstood aspect is the effect of gravity on blood flow. While gravity does affect the hydrostatic blood pressure, that is not what determines blood flow. It is often assumed that pressure drives blood flow, such as from the high pressure arteries to the low pressure veins. If it were that simple then why, looking at the figure above, does blood flow from the aorta to the arteries in the feet, where the pressure is greater? In fact, it is the total energy of a fluid that determines the direction of flow. Gravity actually has no effect on the total energy of the fluid. Any increase in hydrostatic pressure from gravity is balanced by a decrease in gravitational potential energy and vice versa. Blood flows from the arteries to the veins because the total potential and kinetic energy is greater in the arteries than in the veins.
- C. Then why does our hand turn pale if we hold it up or why do we faint? Blood vessels are compliant, not rigid tubes, and can distend and collapse to changes in pressure. The farther above the heart the lower the hydrostatic pressure, and thus the more collapsed (less distended) the vessels are. The smaller the vessel the greater the resistance (from Poiseuille's law), and thus less blood flow. Therefore, gravity does not effect the direction of blood flow, but it does decrease the hydrostatic pressure above the heart - decreasing vessel size, increasing resistance, decreasing flow - potentially resulting in ischemia.

III. VESSEL COMPLIANCE

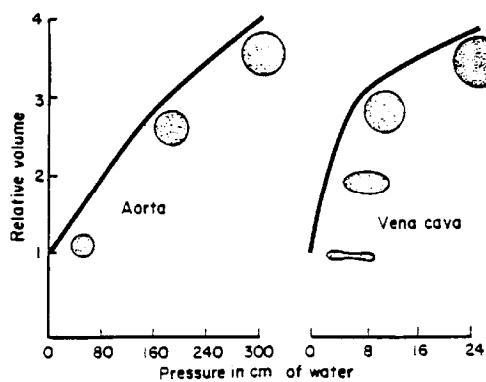
- A. Previously we talked about resistance as an important property of the circulation. Another important physical property is compliance, which is the ability of a vessel to change its size relative to the pressure of the fluid inside it. This serves differing functions in the arteries and the veins.



- B. On the arterial side, the heart pumps out a bolus of blood into the proximal or "elastic" arteries, which can distend and accommodate the ejected blood. The arteries store up energy as they distend and then return that energy when they elastically recoil, as shown in the figure below. If the arteries were stiff instead of compliant, the heart would have to generate a much higher pressure to eject an equal volume of blood, as though banging into a brick wall instead of hitting a wall made of rubber. Thus, individuals with less compliant arteries, as occurs with aging, have a higher pulse pressure (the difference between systolic and diastolic pressures) compared to individuals with very compliant arteries who have lower pulse pressure. The overall effect of arterial compliance is to reduce the work of the heart and provide a smooth, steady flow.

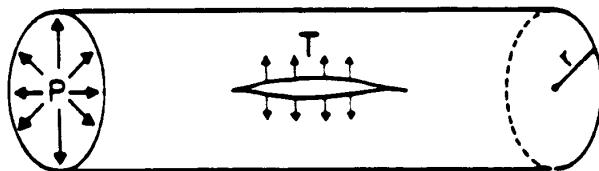


- C. The veins are also compliant, but they operate in a much lower pressure range, as shown below. Small changes in pressure on the venous side result in significant changes in vessel size and therefore substantial changes in venous blood volume. Thus, the compliance of the veins allows them to serve as the storage site for the vast majority of the blood volume.



IV. WALL TENSION AND STRESS - LAPLACE'S LAW

- A. The force causing compliant vessels to stretch and distend is usually described as wall tension or wall stress. Wall tension can be thought of as the force (per unit length) trying to pull the vessel apart at the seams as shown in the figure below.



- B. We can derive the formula for wall tension, or Laplace's law (one of many), by noting that the force from the pressure (P) inside the vessel must be balanced by the force from the tension (T) within the vessel wall. Referring to the figure below, equating these forces for a thin-walled vessel of radius r gives:

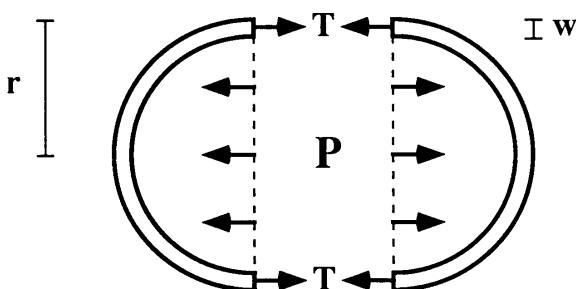
$$2T = P(2r)$$

Note that the effective distance over which the pressure acts is $2r$ not πr , as this accounts for the component of the pressure force opposite to the tension. This simplifies to:

$$T = Pr$$

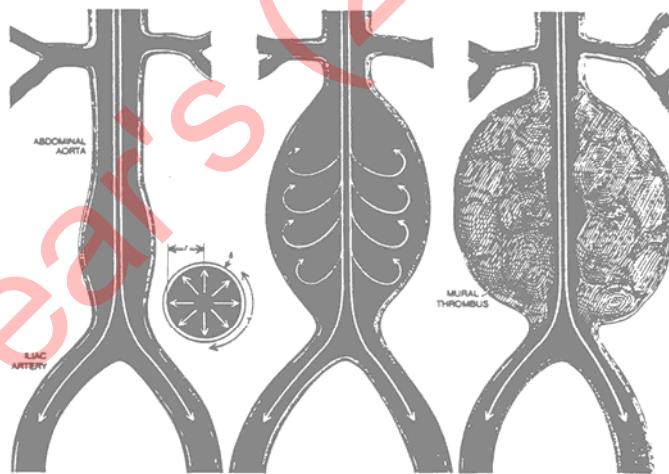
- C. Thus, wall tension is proportional not only to pressure but also to vessel size. As the radius increases, the tension increases. That is because force is pressure \times area, so increasing the radius increases the area which increases the force and the tension.
- D. Arteries are not thin-walled - they have thick walls in order to distribute the tension. Therefore, wall stress (σ) is the preferred measure for the internal force exerted on a vessel wall, as it takes into account the wall thickness (w). The thicker the wall, the less the stress:

$$\sigma = T/w = Pr/w$$



V. AORTIC ANEURYSMS - A CLINICAL EXAMPLE

- A. With this lengthy discussion of pressure vs. velocity, compliance, and wall stress, the clinical syndrome of an aortic aneurysm is an ideal example to pull together all of these ideas.
- B. If one imagines a slight weakening of the wall of the aorta in a small region, one can picture that the wall would distend slightly more than the regions around it. From conservation of mass, the velocity (v) would be slower in the distended region as it has a larger cross-sectional area (A). Then, from Bernoulli's equation, the lower velocity (v) would mean a higher pressure (P) in that region. Going back to our equation for wall stress (σ'), both the pressure (P) and the radius (r) are increased in the affected region. In addition, the stretched wall would have a smaller thickness (w). Thus, all three components of the formula have changed to increase wall stress. This will only make it more likely that the region will weaken and distend further, continuing in a positive feedback cycle.
- C. The figure below shows this progression in an abdominal aortic aneurysm, the most common site of occurrence. The natural history of this condition is continued dilatation over years with increased risk of rupture, especially when the diameter becomes greater than 5 centimeters. Note that the formation of a mural thrombus may help to compensate by reducing the effective vessel diameter and increasing the effective wall thickness.



PHYSICS OF THE CIRCULATION

Non-Linearities: Turbulence, Viscosity & Starling's Hypothesis

I. TURBULENCE AND REYNOLDS NUMBER

- A. In our discussion of the linear relationship of pressure to flow (Ohm's law), and the derivation of the 1/4 dependence of resistance (Poiseuille's law), we assumed a layered or laminar flow. This laminar flow is due to the frictional or viscous drag of the fluid, which makes the fluid move more slowly closer to the vessel wall. Counterbalancing this viscous force is an inertial force propelling the fluid forward. The higher the inertial force the less favorable it is for the viscous drag to produce a smooth, laminar flow.
- B. This balance between inertial and viscous forces can be quantified with the Reynolds number (Re), which is a dimensionless ratio of inertial to viscous forces. The inertial force is proportional to the density (ρ) and the velocity (v) squared:

$$\text{Inertial force} = \rho v^2$$

The viscous force is proportional to the viscosity (η), the velocity (v), and the inverse of the tube diameter (D):

$$\text{Viscous force} = \eta v/D$$

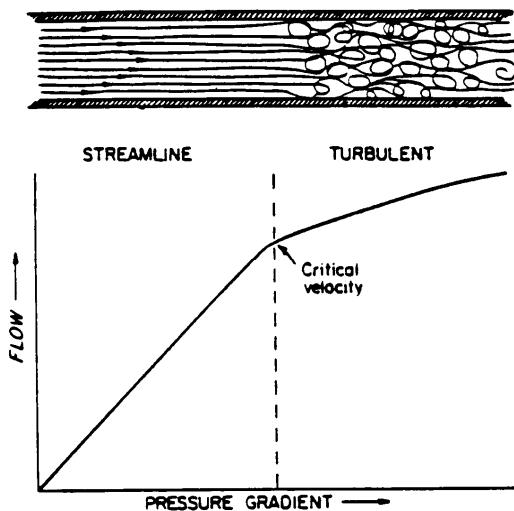
The Reynolds number is the ratio:

$$Re = (\rho v^2) / (\eta v/D) = (\rho / \eta) Dv$$

From this equation it is clear that as the density, tube size, and velocity increase, and as the viscosity decreases, inertia is favored. Similarly, viscous drag is favored as the viscosity increases and the other components decrease.

- C. For a smooth, laminar flow the Reynolds number should be below about 2000. When the Reynolds number exceeds 2000, turbulence begins to set in. Turbulence is characterized by random, disorganized flow in which energy is lost in other forms (heat, sound, etc.). The relationship of pressure to flow is no longer linear, as shown in the figure below. Higher pressures are needed to generate increased flows, as pressure is now closer to being a function of the flow squared due to the energy losses. Doubling the flow would require quadrupling the pressure in turbulent flow.
 1. Laminar Flow: $P \propto Q$
 2. Turbulent Flow $P \propto Q^2$

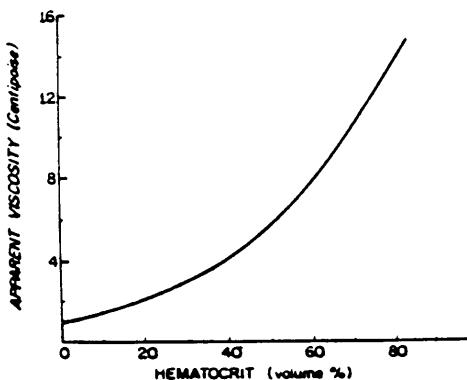




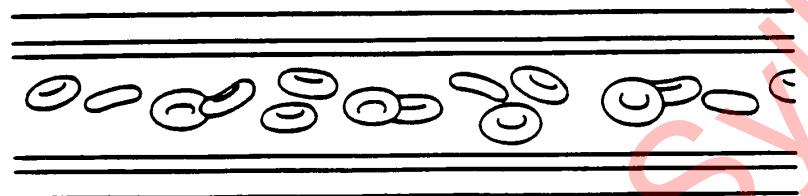
- D. Under normal physiologic conditions, turbulent flow usually occurs only in the proximal aorta and pulmonary artery. In pathologic situations, turbulence can occur where the velocities are high, such as in narrowed blood vessels, stenotic valves, or septal defects. Severe anemia, due to the reduced viscosity¹ can also produce turbulence. These situations often produce audible murmurs or bruits which can be found on physical examination.

II. VISCOSITY OF BLOOD

- A. Blood viscosity plays an important role in the circulation, with its most profound effect on vascular resistance. Blood is not a simple fluid and viscosity does not remain constant throughout the circulatory system. As blood passes through the smaller vessels of the vascular tree, the viscosity actually falls. Blood has two main components, namely plasma and red blood cells. The viscosity of plasma alone is quite low, but as the percentage of red blood cells (hematocrit) increases, the viscosity increases up to ten-fold, as shown below.

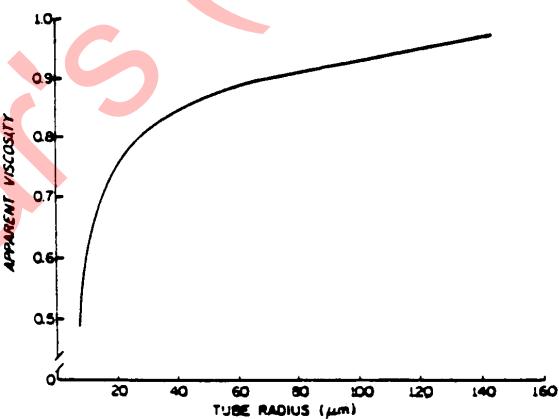


- B. In the large vessels, much larger than the diameter of a red blood cell (approximately 8 microns), the blood acts homogeneously. However, as the vessel diameter drops below approximately 100 microns, the two components tend to behave differently. The red blood cells shun the vessel walls (as pictured below) and tend to concentrate in the fast-moving center, referred to as "axial streaming". This means that the lower viscosity plasma predominates at the interface with the vessel wall, lowering the effective viscosity, while the red blood cells stream on through.



In addition, the red blood cells are moving through at a higher velocity compared to the plasma, so they tend to be more spread apart. If one took a snapshot there would appear to be fewer red blood cells per unit plasma than in whole blood, i.e. the effective hematocrit is reduced. The overall effect of vessel size on viscosity is shown in the figure below.

This property of reduced effective viscosity with decreased vessel size helps to counterbalance the dramatic ($1/r^4$) rise in resistance that occurs from Poiseuille's law.



III. STARLING'S HYPOTHESIS OF TRANSCAPILLARY EXCHANGE

- A. For our discussion of conservation of mass we have assumed a closed-loop circulatory system. Actually, at the capillary level, there is a continual process of filtration and reabsorption. The thin-walled capillaries allow hydrostatic pressure to push water and small molecular components of the plasma across the capillary wall into the interstitium. Counterbalancing this is the oncotic pressure of the plasma, which draws in fluid from the interstitium by osmosis due to the higher protein concentration of the plasma.
- B. The hydrostatic pressure (P) driving fluid out of the capillary is the difference between capillary hydrostatic pressure (P_c) and interstitial hydrostatic pressure (P_i):

$$P = P_c - P_i$$

- C. The oncotic pressure (Π) drawing fluid back into the capillary is the difference between capillary oncotic pressure (Π_{lc}) and interstitial oncotic pressure (Π_{li}) [Note that fluid moves toward the higher oncotic pressure]:

$$\Pi = \Pi_{lc} - \Pi_{li}$$

Thus, the overall driving force out of the capillary (ΔP) is:

$$\Delta P = P - \Pi = (P_c - P_i) - (\Pi_{lc} - \Pi_{li})$$

- D. From Ohm's law, we know that the flow (Q_s) must be the ratio of the driving pressure (ΔP) to the resistance of the capillary wall (R_c):

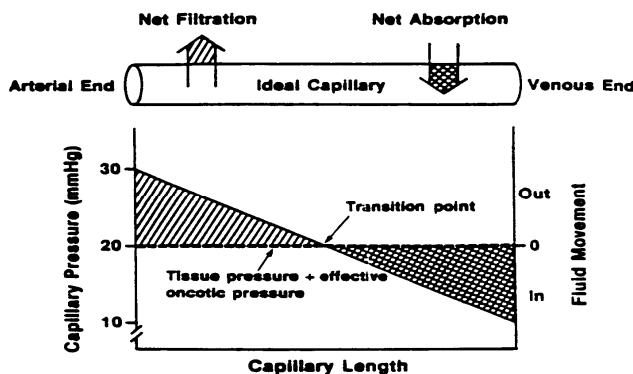
$$Q_s = \Delta P / R_c$$

- E. Letting $1/R_c$ equal K , we get Starling's Hypothesis:

$$Q_s = K \Delta P = K [(P_c - P_i) - (\Pi_{lc} - \Pi_{li})]$$

- F. As shown in the figure below, the main parameter that changes in this equation is the capillary hydrostatic pressure (P_c), the other parameters (P_i, Π_{lc}, Π_{li}) remain relatively constant. The overall effect is that at the arterial end P_c is high, making ΔP positive, and filtration occurs (i.e., fluid moves out into the interstitium). However, P_c decreases as one goes from the arterial to the venous end of the capillary so that ΔP becomes negative at the venous end and reabsorption occurs. On average, 85% of the filtered plasma is reabsorbed, with the remaining 15% taken up by the lymphatics.





- G. An important clinical situation arises when venous pressure becomes sufficiently high such that ΔP is positive for most of the length of the capillary. Then filtration significantly exceeds reabsorption and fluid accumulates in the interstitium, which is termed edema. In left heart failure, for example, pulmonary venous pressure rises and often results in pulmonary edema.

IV. LIST OF SYMBOLS

<u>Symbol</u>	<u>Quantity</u>	<u>Definition</u>	<u>Units (cgs)</u>
F	force	mass x acc	g-cm/sec ²
P, Π	pressure	force/area	g/cm-sec ²
Q	flow	volume/time	cm ³ /sec
V	velocity	length/time	cm/sec
K	resistance	pressure/flow	g/cm ⁴ -sec
PE	potential energy	force x dist	g-cm ² /sec ²
KE	kinetic energy	mass x vel ²	g-cm ² /sec ²
T	tension	force/length	g/sec ²
σ	wall stress	force/area	g/cm-sec ²
ρ	density	mass/volume	g/cm ³
η	viscosity	poise	g/cm-sec
Re	Reynold's #	inertial/viscous	unitless



Last Year's (2010) Syllabus

Case Discussions: Autonomic Drugs

Reading assignment: Katzung (10th ed) Ch. 6 – 10 (review)

LEARNING OBJECTIVES:

Review autonomic pharmacology in preparation for case discussions.

TOPICS

- A. Case discussions



Last Year's (2010) Syllabus

SMOOTH MUSCLE AND CARDIOVASCULAR FUNCTION

OBJECTIVES:

- A. Cellular organization of smooth muscle that sets it apart from striated muscle
- B. How smooth muscle is specialized for efficient force generation
- C. Unusual features of Excitation contraction coupling
- D. Control of contraction by sympathetic innervation and by other agents

I. CELL BIOLOGY OF SMOOTH MUSCLE

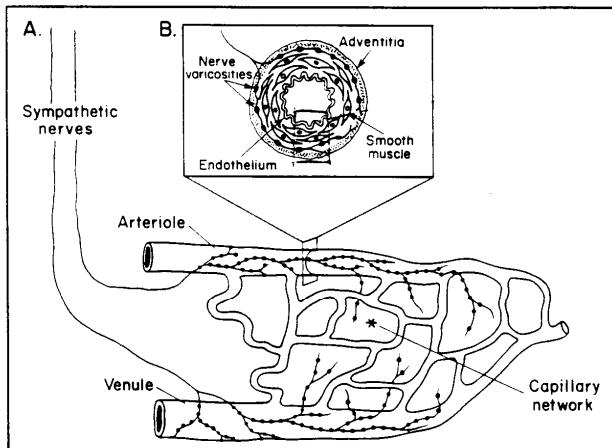
- A. Comparisons between smooth and striated muscles:
 - 1. Smooth muscle is named for its lack of sarcomeres, in contrast to striated muscles (skeletal or cardiac muscle). It is found in almost all of the hollow organs of the body, including blood vessels and gastrointestinal, urinary and reproductive tracts. It has been argued that "smooth muscle is far more important to health care professionals than striated muscle" (R.A. Murphy in Berne and Levy's textbook). There is some truth to this, since inappropriate (pathological) behavior of smooth muscle is involved in many illnesses, for example hypertension, atherosclerosis, coronary artery disease, asthma, gastrointestinal disorders. Nevertheless, smooth muscle often receives less attention than its counterparts, in part because less is known about how it works.
 - 2. Is smooth muscle more primitive than striated muscle? Yes and no. Skeletal muscles are highly specialized in their structure and function for rapid activation and rapid shortening. Smooth muscles are much less developed in this particular way -- quite the contrary, they seem to have evolved in a different way, to generate large amounts of force, often under steady conditions, with relatively little expenditure of metabolic energy. Smooth muscle performs this kind of function by means of its own specialized mechanisms and does its job very well.
- B. Cellular structure and organization:
 - 1. Smooth muscles may usefully be categorized as multi-unit or unitary. This classification (Bozler) is based on how activity is controlled. Multi-unit smooth muscle is organized into



motor units, groups of muscle cells innervated by a nerve axon. As in skeletal muscle, but unlike heart, contraction of the smooth muscle is thus orchestrated in detail by the CNS. This functional organization is found in the eye (ciliary, iris muscle) and in association with skin hairs (pilomotor). Thus' multi-unit smooth muscle appears to be used for tasks where a large degree of voluntary motor control is required.

2. Unitary smooth muscle is distinguished by the fact that the individual cells function together as a community, even in the absence of commands from the CNS. Unitary smooth muscle is exemplified by the gut or the uterus. As in heart, unitary smooth muscle is capable of spontaneous activity, and hormones and neurotransmitters play a modulatory rather than a commanding role.
3. Unitary smooth muscle is composed of discrete cells, usually thin (often as little as 2-5 mm in diameter) and spindle-shaped (ranging from 20 μm up to 100 μm in length). Adjacent cells are often connected electrically by gap junctions like those in the heart. The gap junctions allow the movements of ions and small molecules and mediate the flow of ionic current and the spread of action potentials from one cell to the next. The degree of coupling between cells varies from one organ to another. Cells are also mechanically connected to each other at specialized junctions analogous to desmosomes in heart muscle (see Fig. 3).
4. Vascular smooth muscle is sometimes classified as unitary, but often the properties are somewhat intermediate between the multi-unit and unitary extremes. Some regions are heavily innervated and come under strong control of the sympathetic nervous system (arterioles, as opposed to capillaries in the microcirculation -- see Fig. 1). The cells can also show a degree of electrical connectivity.





Sympathetic innervation of blood vessels. (A) Sympathetic nerve terminals containing varicosities anastomose freely in the adventitia of arteries and veins. The smallest vessels in the microcirculation are not heavily innervated. (B) The varicosities are located in the outer portions of the vascular wall.

Figure 1

5. The smooth muscle in blood vessels may be only one or two cell layers thick in arterioles. The smooth muscle cells are oriented transversely to the long axis of the arteriole when the vessel is relaxed but change to a spiral orientation upon contraction. In large vessels like the aorta, the smooth muscle is many cells thick and lies in the media, a layer between the intima and the adventitia (Fig. 2). The outermost cells of the media come into contact with sympathetic nerve axons with bead-like varicosities (Fig. 1 and 2). The varicosities are loaded with vesicles containing norepinephrine and ATP. The cells in the innermost layers of the media are not directly contacted by varicosities, but may receive stimuli from circulating factors, or from depolarizing current flow from the outer layers, mediated via gap junctions.

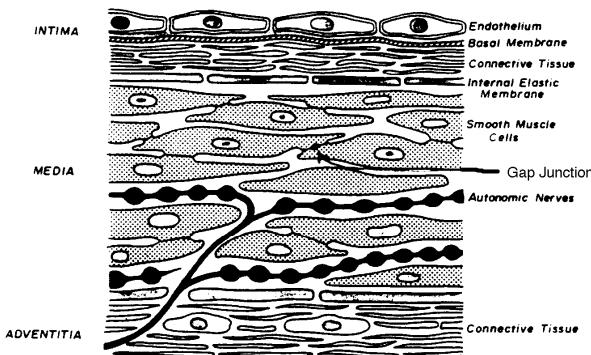


Fig. 2 Structure of the wall of a large artery showing the various layers (intima, internal elastic membrane, media, and adventitia). Depending on the type of vessel, only endothelium (capillaries), mainly smooth muscle (arterioles), or large quantities of elastic connective tissue (large arteries and veins) may be present. In arteries the autonomic nerves usually do not penetrate deep into the media; in veins the media usually is innervated throughout.



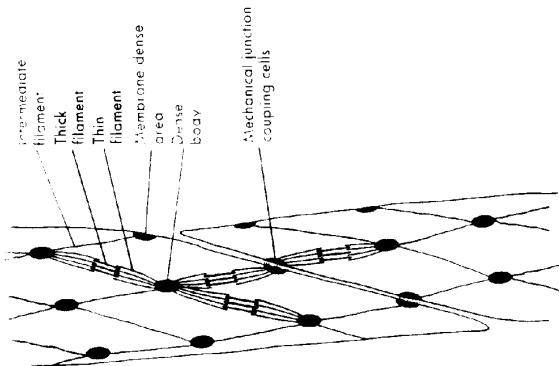


Fig. 3 Apparent organization of the cytoskeleton (color) and myofilaments in smooth muscles. Small contractile elements functionally equivalent to a sarcomere presumably underlie the similarities in mechanics between smooth and skeletal muscles. Linkages consisting of specialized junctions or interstitial fibrillar material functionally couple the contractile apparatus of adjacent cells.

C. Contractile proteins

1. The contractile machinery in smooth muscle is remarkably suited for its function in systems like blood vessels. Smooth muscle can generate large amounts of tension (force per unit cross-sectional area). During maximal activation, the tension can reach 6 kg/cm^2 , twice that found in skeletal muscle, even though smooth muscle has less contractile protein and much less myosin. The large tension in smooth muscle is produced at unusually low metabolic cost. Knowledge about the structure of the contractile machinery is incomplete, but gives some insights into how the remarkable performance is achieved.
2. Force is generated in smooth muscle along multiple axes, running oblique to the fiber axis (Fig. 3). Long actin filaments are attached to the surface membrane at membrane dense areas. The criss-crossing actin filaments are linked at structures called dense bodies.
3. This cross-striated organization allows efficient, if slow, contractions. This is because slanted force generators tend to act in parallel, like people pulling on a common rope in a tug-of-war (see idealized example in Fig. 4). The parallel force generators add up to a total force with a large component along the long axis of the cell. This is unlike the situation in skeletal muscle, where the force generators are arranged in series. In that case, each force generator bears the same force, and it is their shortening that adds up. For a given amount of contractile protein per unit volume, the parallel arrangement gives more force, slower maximal velocity, and decreased energy consumption. This is well-suited for the function of smooth muscle.



Mechanism: Force generators in smooth muscle are oblique to the fiber axis



Consequence: Slanted force generators tend to act in parallel rather than in series

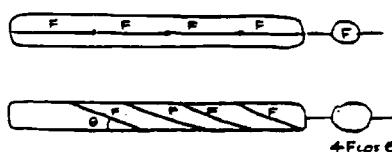
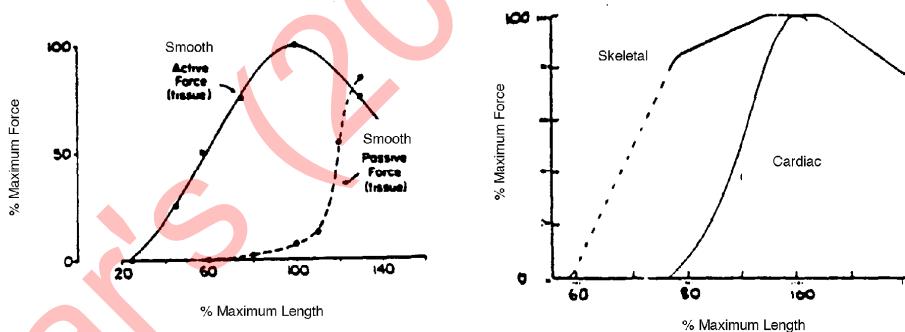


Fig. 4. An idealized comparison between two muscle cells, each with four units capable of generating a force F . When the units are arranged in series, the total force is simply F . When the units are slanted, and pull in parallel, the same total force is $4F \cos \theta$ where θ is the angle with the axis of the fiber. This would be close to $2F$ as long as the angle is small.

- Smooth muscle can produce force over a very wide range of muscle lengths, and shorten down to as little as 20% of the length where force is maximal. Skeletal and cardiac muscle work over a much narrower range of fiber lengths (Fig. 5).

Fig. 5 Smooth muscle can produce force over a very wide range of muscle lengths.



Mechanism Long actin filaments without interruptions with Z-lines.
 (?) Arrangement of myosin molecules in "side-polar filaments"

- As an explanation of the dynamic range of smooth muscle shortening, it has been suggested that the myosin in smooth muscle forms "side polar filaments" in contrast to the bipolar thick filaments found in skeletal or cardiac muscle. Side polar organization would allow myosin heads to move along the very long actin filaments in smooth muscle, without the limitation of unfavorable myosin-actin interactions that arise in the case of bipolar thick filaments. This hypothesis has not been firmly established or refuted. See Figure 6 for a hypothesized schematic.



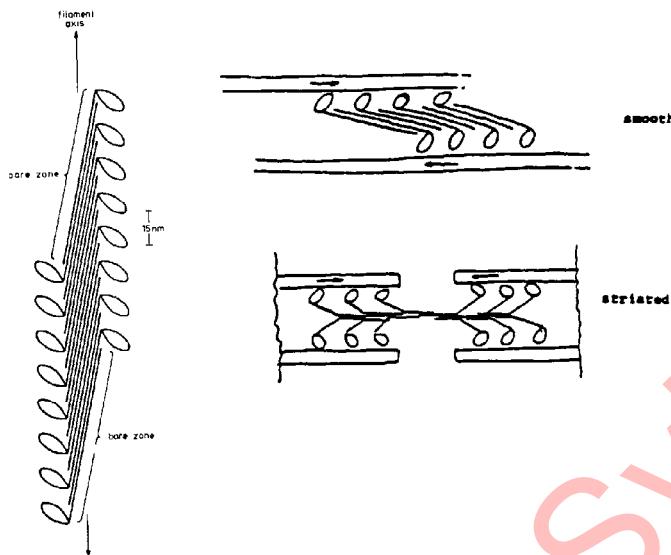


Figure 6

II. PHYSIOLOGY OF EXCITATION-CONTRACTION COUPLING

A. Ca-sensitive activation mechanisms:

1. Ca^{2+} ions carry the key message that controls contraction in smooth muscle, as in striated muscles. Contractile activity varies very steeply with rises in $[\text{Ca}^{2+}]_i$. However, there are some fundamental differences in the mechanism of activation by Ca^{2+} ions.
2. You will recall that Ca^{2+} activates skeletal or cardiac muscle by binding to the Ca^{2+} -binding molecule troponin in a highly cooperative fashion. The Ca^{2+} -bound troponin in turn triggers conformational changes in tropomyosin, which normally blocks the active sites on the underlying actin filament. The unblocked actin sites are thus freed up to interact with myosin crossbridges and to promote contractile activity and ATP hydrolysis.
3. The predominant Ca-dependent mechanism in smooth muscle is very different. Ca^{2+} activates contraction rather than disinhibiting it. Activation of contraction follows delivery of Ca^{2+} to the myoplasm by mechanisms described in Fig. 7. Ca^{2+} binds in a steeply cooperative manner to calmodulin, and the Ca^{2+} -calmodulin complex binds to and activates a protein kinase called myosin light chain kinase (MLCK). MLCK phosphorylates the light chains of myosin and thereby enables the myosin heads to interact with actin. The process is reversed (inactivation of contraction) by a fall in free Ca^{2+} , dissociation of the Ca^{2+} from calmodulin, and ensuing dissociation of calmodulin from MLCK.



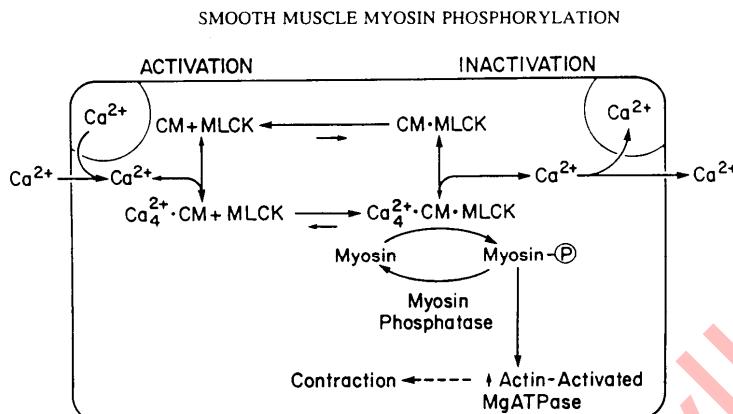


Figure 7 A general scheme for the biochemical regulation of myosin phosphorylation in smooth muscle cells. CM = calmodulin; MLCK = myosin light chain kinase; myosin- \textcircled{P} = phosphorylated myosin.

4. There is general agreement that MLC phosphorylation is the primary mechanism of activation in smooth muscle, and there is no troponin. The possibility remains that Ca^{2+} plays a dual regulatory role through interactions with regulatory systems residing on the thin filament and acting through tropomyosin. The candidates for the Ca^{2+} -sensitive protein on the thin filament include proteins called leiomotin or caldesmon.
- B. Dynamic changes during contractile activation
1. In single smooth muscle cells, simultaneous measurements of contractile force and free cytoplasmic Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$) give some idea of the sensitivity and dynamics of the process of Ca^{2+} -activation (Fig. 8). $[\text{Ca}^{2+}]_i$ rises quickly following a stimulus, but force does not change detectably for several tenths of a second. This is incredibly slow compared to the onset of contraction in skeletal muscle (less than 5 milliseconds) or even cardiac muscle (roughly 20 milliseconds). The long delay can be attributed to (1) the steps leading up to and including phosphorylation of myosin light chains, and (2) the slow ATPase activity of smooth muscle myosin, even after it is strongly activated.



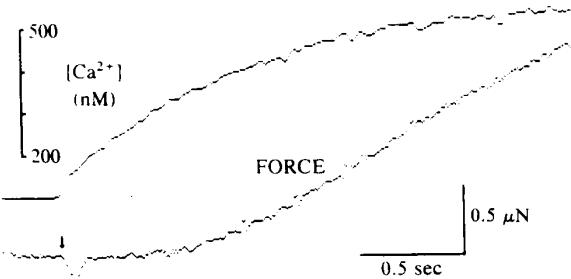


Figure 8 Calcium and force records from a single fura-2-loaded smooth-muscle cell showing delay between increase in cytosolic [Ca²⁺] and onset of force development. Arrow, time of 0.1-msec electrical stimulus to cell. The first apparent drop in force is an electrical artifact caused by our event marker and represents neither mechanical perturbation nor force change. Delay was calculated as the time interval from initiation of stimulus to the point at which force increased above its baseline value.

2. Even if it is slow, the contraction of smooth muscle is extremely Ca²⁺-sensitive. If measurements of steady contractile force and steady Ca²⁺ are plotted against each other (Fig. 9), it appears that force develops very steeply with elevations of [Ca²⁺] above basal levels of 50-100 nM. About 500-1000 nM [Ca²⁺] is sufficient to give maximal contractile force. The steepness of the [Ca²⁺] -force relationship can probably be accounted for by the steeply cooperative binding of four Ca²⁺ ions to a single calmodulin molecule.

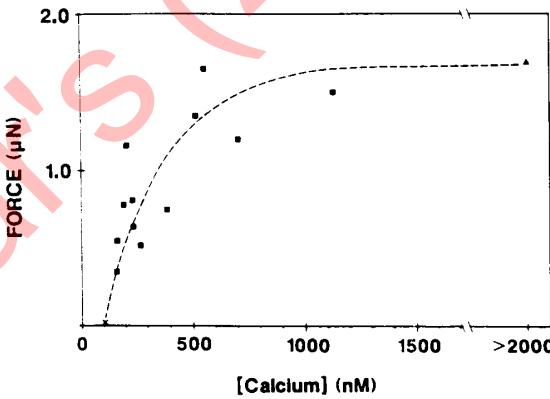


Figure 9 The relationship between force and calcium. Cell records were chosen where force and [Ca²⁺] both peaked or remained stable for several seconds at the same time. ■, Individual measurements (12 observations in 8 cells); X, average resting Ca²⁺ in these cells before stimulation (103 nM ± 11 SEM; n = 11); Δ, average force (1.69 μN ± 0.48 SEM) of three cells in which Ca²⁺ exceeded 2000 nM.

- C. Efficient production of sustained force
1. During sustained stimulation, [Ca²⁺]i rises to a peak and then decays to a much lower plateau level. Despite the falling off of [Ca²⁺]i, contractile force can remain elevated



indefinitely. Although a force is maintained if the muscle is held at fixed length, the muscle's capability to shorten falls off, very much in parallel with the decay in $[Ca^{2+}]_i$, and also in parallel with measured changes in myosin light chain phosphorylation. Somehow, the muscle is able to give sustained forces, despite the reversal of the normal steps of activation. The mechanism is not known, but the current hypothesis is that myosin crossbridges can form a "latch" state. In this special conformation, myosin stays linked to actin and generates force, but does not undergo the normal cycle of detachment and ATP hydrolysis that accompanies shortening. (Expressed in terms of a force-velocity curve (active stress vs. shortening velocity), the latch state corresponds to a decreased VO with no change in F_o). Ca^{2+} -control is changed but not lost. The "latch" state can be maintained with a slight elevation of $[Ca^{2+}]_i$ above basal levels, but is abolished quickly once $[Ca^{2+}]_i$ finally returns to its original value.

2. In many respects then, the physiological behavior of smooth muscle seems well adapted to the task of maintaining vessel diameter and blood pressure constant over long periods of time. The somewhat slow but highly responsive activation system purrs along by comparison to skeletal or cardiac muscle. Whatever the molecular mechanism, the "latch" state provides sustained force in a very energy efficient manner. Experiments which illustrate the ability of smooth muscle to produce sustained force are shown in Figures 10 and 11.

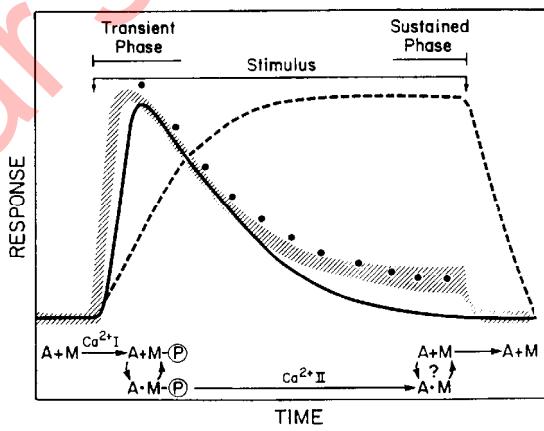


Figure 10 Schematic representative of the processes involved in smooth muscle contraction. The stimulation of resting smooth muscle results in a rapid increase in Ca^{2+}_{cell} (shaded profile), which may be transient. The first regulatory site ($Ca^{2+}I$) for initiating the cyclic interaction of myosin (M) with actin (A) is the $Ca^{2+} \cdot$ calmodulin activation of myosin light chain kinase, which results in P-light chain phosphorylation (— and $M-\overset{\oplus}{P}$). Attached cross bridges ($A+M \circledast$ or $A+M$) may be rapidly cycling when phosphorylated, resulting in force development (---) and high maximal shortening velocities (●), or non- or slowly cycling when dephosphorylated. Whether the low, but measurable, shortening velocities during the sustained phase of contraction reflect the cycling of non-phosphorylated cross bridges or the cycling of a small population of phosphorylated cross bridges is unknown. The second regulatory site ($Ca^{2+}II$) for force maintenance in the absence of myosin phosphorylation remains unidentified.



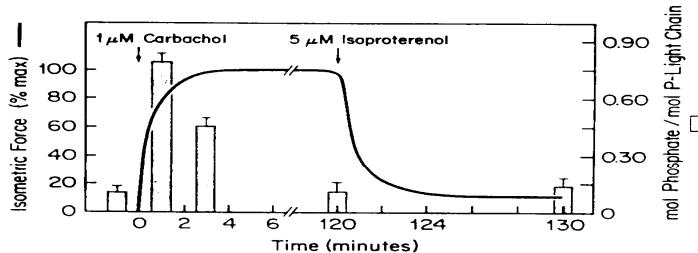


Figure 11 Phosphorylation of myosin P-light chain in bovine trachealis smooth muscle. Muscle strips were contracted by the addition of 1 μ M carbachol; after two hours, 5 μ M isoproterenol was added. The extent of myosin P-light chain phosphorylation was the same at both 120 and 130 minutes as that in control muscles (adapted from (22)).

D. Sympathetic control of blood vessel diameter

Controlling blood vessel tone largely involves the regulation of $[Ca^{2+}]_i$ within smooth muscle cells by transmitters released from prejunctional sympathetic nerve varicosities or circulating hormones or local factors. Let us consider the sequence of events leading from sympathetic nerve excitation to vascular smooth muscle contraction. (Fig 12)

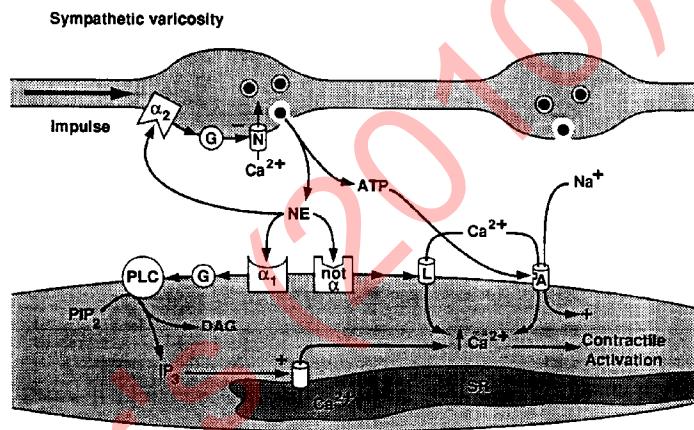


Fig. 12. Sympathetic control of smooth muscle $[Ca^{2+}]_i$

E. Steps leading to normal vascular smooth muscle contraction:

1. sympathetic neuron excitation
 - a. action potential depolarization mediated by Na channels
 - b. Ca^{2+} entry via voltage-gated Ca channels
 - c. Ca^{2+} -triggered exocytosis
 - d. release of norepinephrine (NE) and ATP from vesicles

(negative feedback effect of NE on its own release mediated by α_2 receptors; important in ensuring the spatially uniform delivery of transmitter to the target cells).



2. excitatory junction potential in smooth muscle results from opening of ATP-activated cation channels (analogous to acetylcholine and its receptor channels in skeletal muscle endplates).
3. action potential
 - a. can follow if the depolarization is strong enough to open voltage-gated Ca channels. These are usually supported by Ca²⁺ entry through Ca channels. (Arteries lack conventional Na channels. Some veins have Na channels but these are unusual in their insensitivity to tetrodotoxin). The action potential in blood vessels is brief because of rapid repolarization. The repolarization is driven by outward current through K channels activated by depolarization and/or Ca²⁺
4. rise in intracellular Ca: delivery from multiple sources
 - a. Ca²⁺ entry through voltage-gated or ATP-activated channels.
 - b. Ca²⁺ release triggered by inositol trisphosphate (IP₃)-sensitive Ca²⁺ stores. This is often initiated by α1-receptor stimulation of IP₃ production.
 - c. Ca²⁺-induced Ca²⁺ release from intracellular stores (also triggered by caffeine, blocked by ryanodine).
5. Ca-triggered contraction, force development and maintenance involves calmodulin, MLCK, MLC phosphorylation, actin-myosin ATPase, latch mechanisms
6. Relaxation by Ca²⁺ removal:
 - a. extrusion by Ca²⁺ pump in the surface membrane, or by Ca²⁺-Na⁺ exchange; Ca²⁺ uptake by intracellular stores.
7. Note that contractions of smooth muscle can be associated with:
 - a. acceleration of intrinsic spontaneous activity,
 - b. depolarization with superimposed action potentials,
 - c. depolarization without superimposed action potentials
 - d. no depolarization at all (presumably, activation is associated with α1 receptor-controlled Ca²⁺ release from internal stores without involvement of voltage-gated Ca²⁺ channels). This is illustrated below in Figure 13.



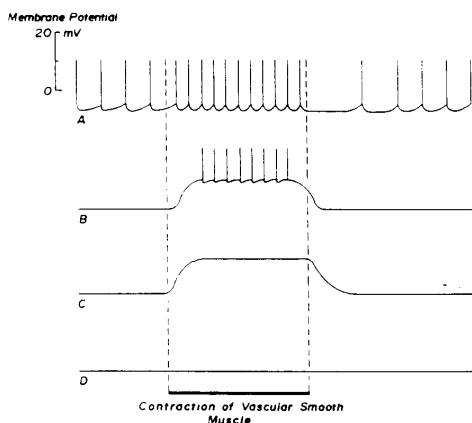


FIG. 2-28. Patterns of changes in membrane potential in vascular smooth muscle during contraction. **A:** The intrinsic spontaneous activity of the cell is augmented. **B:** Depolarization with superimposed action potentials. **C:** A sustained depolarization. **D:** No changes in membrane potential.

F. Disorders of smooth muscle function and vasoactive drugs:

Inappropriate contractions of vascular smooth muscle occur in vasospasm or hypertension. These disorders are not completely understood but may involve defects in sympathetic inputs and/or vascular smooth muscle.

III. QUESTION:

A number of clinically important agents modify contractions of vascular smooth muscle. These include:

- α_1 blockers (e.g. prazosin)
- α_2 stimulators (e.g. clonidine)
- Calcium channel blockers

How might these agents work in light of what you have learned about smooth muscle contraction?

Sodium nitroprusside



Ischemic Heart Disease

Reading:

Robbins and Cotran: Pathologic Basis of Disease, 8th edition [pp 545-559](#)

LEARNING OBJECTIVES

- A. Pathogenesis of IHD
- B. Pathology of IHD
- C. Complications of IHD

I. ISCHEMIC HEART DISEASE: EPIDEMIOLOGY

- A. Leading cause of death for both men and women in USA
- B. Causes 2/3 of acquired heart disease in the industrialized countries
- C. 500,000 people die of IHD every year in the USA
- D. The rate of IHD death decline 50% since 1963 because of better treatment and prevention
- E. IHD follows the epidemiology of atherosclerosis

II. MYOCARDIAL ISCHEMIA: PATHOGENESIS

- A. Myocardial ischemia originates from an imbalance of oxygen supply and demand.
- B. Primarily caused by coronary artery stenosis (fixed) and/or sudden occlusion decreasing coronary blood flow.
- C. Can be worsened by:
 1. Decreased systemic blood pressure or hypoxemia.
 2. Increased heart rate increases demand and lessens the perfusion (by shortening the relative time of diastole when coronary perfusion occurs).
 3. Some myocardial conditions (e.g. hypertrophy) that increase oxygen demand.

III. IHD: FOUR SYNDROMES

- A. Angina pectoris: When ischemia is less severe and does not cause death of cardiac muscle.
 1. Three variants:
 - a. stable angina
 - b. Prinzmetal angina
 - c. unstable angina



- B. Myocardial infarction (MI): When the duration and severity of ischemia is sufficient to cause death of heart muscle. "Heart attack" usually means this.
- C. Sudden cardiac death
- D. Chronic IHD with heart failure

IV. ANGINA PECTORIS (SEE ANGINA LECTURE)

- A. Stable angina pectoris
 - 1. Chest pain lasting a few seconds to < 15 min.
 - 2. Precipitated by physical or emotional stress.
 - 3. Relieved by rest or nitroglycerine.
- B. Unstable angina pectoris
 - 1. Angina increasing in frequency & duration.
 - 2. Precipitated without stress
 - 3. Not relieved by nitroglycerin or rest
- C. Prinzmetal angina pectoris: Angina at rest due to coronary artery spasm; responds to vasodilators.

V. FIXED CORONARY ARTERY STENOSIS

- A. More than 75% stenosis can lead to symptomatic ischemia induced by exercise (typical angina)
- B. With such "critical stenosis," compensatory coronary vasodilation is no longer sufficient to meet even moderate increases in myocardial demand.
- C. >90% stenosis can lead to inadequate coronary blood flow even at rest.
- D. You can get an Acute Myocardial Infarct with fixed stenosis, but usually in a restricted subendocardial pattern, when there are other factors that create an imbalance of myocardial oxygen supply and demand.

VI. IHD: ACUTE CORONARY SYNDROMES

- A. These are the forms of IHD that require quick intervention.
 - 1. Unstable angina
 - 2. Myocardial infarction
 - 3. Sudden cardiac death
- B. Caused by acute changes in coronary artery atherosclerotic plaques: superficial erosion, ulceration, rupture, or hemorrhage, usually with superimposed thrombosis.



VII. SUDDEN DEATH

- A. Unexpected death within 1 hr of onset of symptoms or without symptoms.
- B. Kills >300,000 people per year in the USA.
- C. Usually a lethal arrhythmia: asystole or ventricular fibrillation.
- D. Most often due to IHD (80-90% with critical stenoses). May be due to an Acute Coronary Syndrome, but not necessarily. Survivors of Sudden Cardiac Death often have IHD but not AMI.

VIII. UNSTABLE ANGINA

- A. Partially occlusive ACS without infarction.
- B. Caused by combinations of changed plaque morphology, thrombus, and vasoconstriction leading to severe but transient reductions in blood flow.

IX. ACUTE CORONARY PLAQUE CHANGE

- A. Usually are conveniently located where interventional cardiologist can reach them by catheter.
- B. Predominate within the first several centimeters of the LAD and LCX and along the entire length of the RCA.
- C. Major secondary epicardial branches are also involved (i.e., diagonal branches of the LAD, obtuse marginal branches of the LCX, or posterior descending branch of the RCA).
- D. The preexisting culprit lesion is often not a severely stenotic and hemodynamically significant lesion prior to its acute change (85% had initial stenosis < 70%).

X AMI INCIDENCE

- A. 1.5 million AMI in US / year.
- B. 500,000 deaths from AMI
- C. 250,000 DOA from AMI.

XI. SUBENDOCARDIAL MI

- A. Subendocardial zone is defined as the inner half of the ventricular wall; the portion most poorly perfused.
- B. Subendocardial MI due to acute partial coronary artery occlusion or imbalance of oxygen supply and demand usually with fixed coronary stenosis.
- C. In cases of global hypotension, resulting subendocardial infarcts are usually circumferential.



- D. Most myocardial infarcts are transmural.

XII. AMI SIZE AND PATTERN DEPEND ON:

- A. The location, severity, and rate of development of coronary atherosclerotic obstructions.
- B. The size of the vascular bed perfused by the obstructed vessels
- C. The duration of the occlusion
- D. The metabolic/oxygen needs of the myocardium at risk
- E. The extent of collateral blood vessel
- F. The presence, site, and severity of coronary arterial spasm

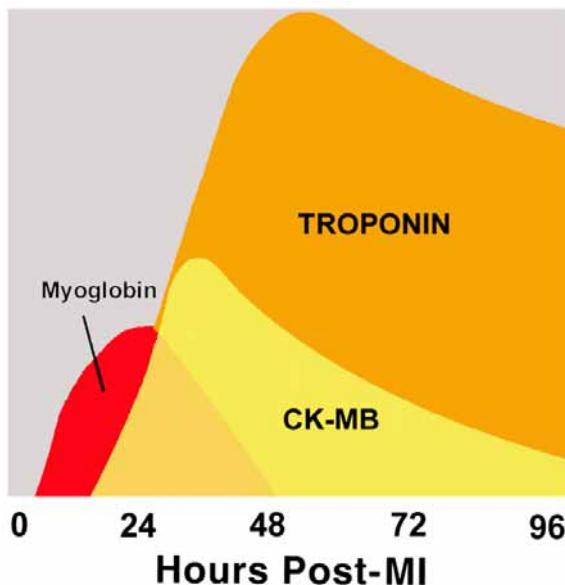
XIII. MYOCYTE CHANGES WITH MI

- A. Seconds: Onset of ATP depletion
- B. <2 min Loss of contractility
- C. 20–40 min Irreversible cell injury
- D. >1 hr Microvascular injury

XIV. SERUM MARKERS TO DIAGNOSE MYOCARDIAL INFARCTION

- A. Oldest, rarely used:
 1. AST - aspartate transaminase
 2. LD (LDH) - lactate dehydrogenase
 3. LD isoenzymes
- B. Older but still used :
 1. CK (CPK) - creatine kinase
 2. CK isoenzymes (CK-MB)
 3. CK-MB isoforms
- C. Current:
 1. Myoglobin
 2. Cardiac-specific troponin





XV. SERUM MYOGLOBIN

- A. Small cytosolic protein in skeletal and cardiac muscle.
- B. Rapidly released into the blood following myocyte injury.
- C. In AMI, abnormal in 2 hours and returns to normal in 24 hours.
- D. Very sensitive but not specific (because it will also be elevated in skeletal muscle damage).
- E. Most useful in ruling out recent myocardial infarction.

XVI. SERUM TROPONINS

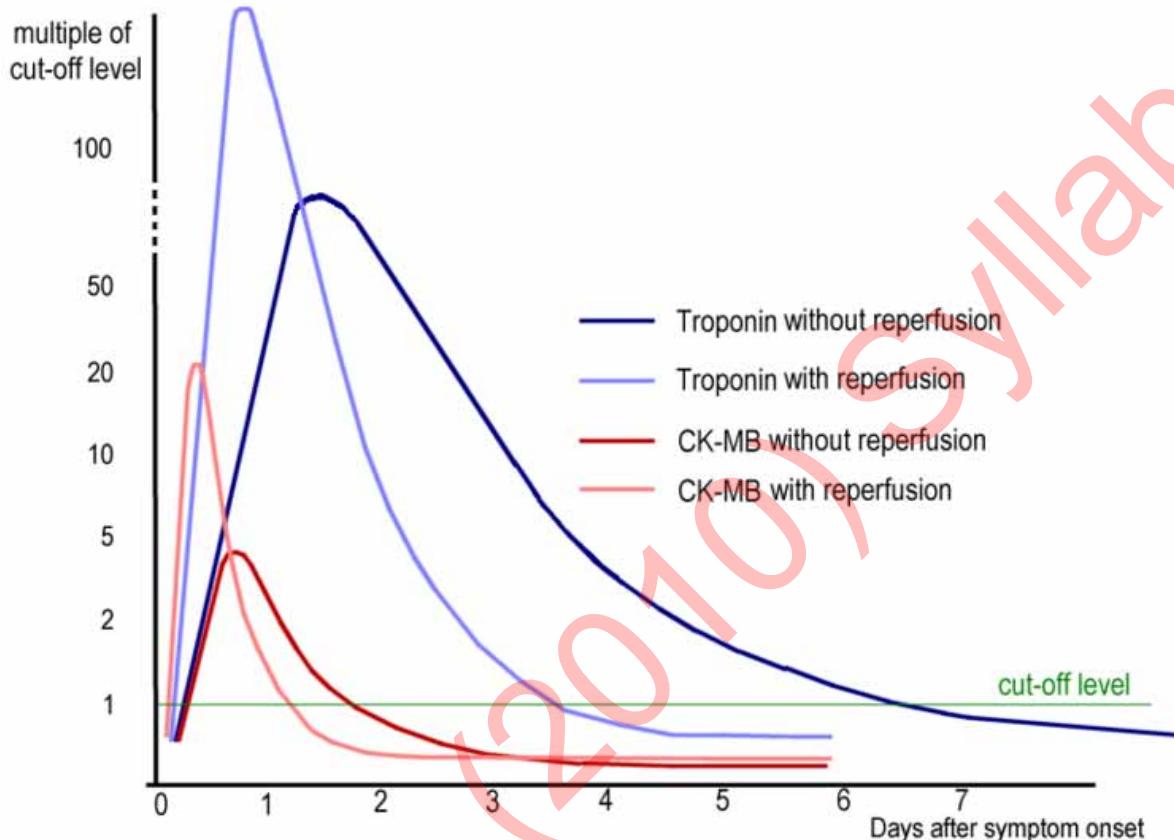
- A. Troponin is a triad of proteins found in muscle:
- B. troponin-C, -T, and -I.
- C. TnC is the same in both cardiac and skeletal muscle.
- D. TnT and TnI have cardiac and skeletal muscle-specific versions.
- E. TnT may be more sensitive than TnI because there may be a greater percentage of free TnT in cardiac myocytes.
- F. Some variability in which tests are used in clinical labs

XVII. ADVANTAGES OF CARDIAC TROPONIN OVER CK-MB:

- A. Rises simultaneously with CK-MB but lasts longer (4 to 10 days). A marker for both early- or late-presenting patients.
- B. Cardiac Tn is more specific for cardiac muscle than CK-MB. It is not affected by skeletal muscle damage. Suitable for monitoring peri-operative or trauma patients.



- C. More sensitive than CK-MB. Even when CK-MB and ECG findings are normal, a small increase in Tn level is indicative of ischemic disease.



XVIII. "STUNNED" MYOCARDIUM

- A. Prolonged post-ischemic myocardial dysfunction.
- B. Critical abnormalities in cellular biochemistry and function of cardiomyocytes salvaged by reperfusion.
- C. May persist for as long as several days.

[Note: "Hibernating" myocardium has chronically depressed function from persistent low perfusion]

XIX. HISTOPATHOLOGY OF AMI

- A. ½-4 hr Elongated, wavy cardiomyocytes
- B. 4-12 hr Beginning coagulation necrosis; edema; hemorrhage
- C. 12-24 hr Ongoing coag. necrosis; pyknosis of nuclei; myocyte hypereosinophilia; marginal contraction band necrosis; beginning neutrophilic infiltrate



- D. 1-3 d Coagulation necrosis, with loss of nuclei and striations; interstitial infiltrate of neutrophils
- E. 3-7 d Beginning disintegration of dead myofibers, dying neutrophils; early phagocytosis of dead cells at infarct border
- F. 7-10 d Well-developed phagocytosis of dead cells; early formation of fibrovascular granulation tissue at margins
- G. 10-14 d Well-established granulation tissue with new blood vessels and collagen deposition
- H. 2-8 wk Increased collagen deposition, with decreased cellularity
- I. >2 mo Dense collagenous scar

XX. CLINICAL COURSE OF M.I.

- A. 30 %: uneventful, benign recovery.
- B. 70 % one or more complications
 - 1. In-hospital death rate: 10%
 - 2. Overall mortality for non-DOA: 20 % in first year
 - 3. Recurrence of MI is common
- C. 20% of MI are silent

XXI. POST-MI COMPLICATIONS

- A. Contractile Dysfunction: Common, Early, Proportional to size of infarct; 10% with cardiogenic shock. Papillary MM involvement causes mitral regurgitation.
- B. Arrhythmias: Heart block and ventricular arrhythmias; Early or late; led to advent of CCU.
- C. Pericarditis: Common but of variable severity; Starts at 2-3 days post-MI. Epicardial manifestation of underlying myocardial inflammation.
- D. Myocardial Rupture: Most frequent when much necrosis with little fibrosis: 3-7 days post-MI (mean 5 days, range 1-10 days) Free wall, septum, and papillary involvement lead to different Sx.
- E. Aneurysm: Late complication; hypokinetic vs. dyskinetic; will not rupture
- F. Infarct “Expansion” = stretching of the current infarct tissue
- G. Infarct “Extension” = new nearby necrosis
- H. Mural Thrombus with potential thromboembolism
- I. Late Heart Failure = Chronic IHD



XXII. CHRONIC ISCHEMIC HEART DISEASE

- A. Progressive heart failure as a consequence of ischemic myocardial damage.
- B. The term Ischemic cardiomyopathy is often used by clinicians
- C. Usually due to late post-MI cardiac decompensation, but may also be diffuse myocardial dysfunction.
- D. Comprises half of cardiac transplant recipients.

Last Year's (2010) Syllabus



Valvular Heart Disease

Reading:

Robbins and Cotran: Pathologic Basis of Disease, 8th edition [pp 560-571](#)

LEARNING OBJECTIVES

- A. Functional classification of valve disease
- B. Clinical features of valve disease
- C. Review of valve disease pathogenesis

I. FUNCTIONAL CLASSIFICATION OF VALVULAR HEART DISEASE

- A. Stenosis
 - 1. Valve orifice is too narrow
 - 2. Usually from some bulky healing/scarring process
 - 3. Only a few etiologies
- B. Regurgitation
 - 1. Aka “insufficiency” or “incompetence”
 - 2. Valve does not create a sufficient closure
 - 3. Many etiologies; Can also be from distortion of supporting structures rather than valve leaflets.
- C. Mixed, with both Stenosis and Regurgitation
- D. Isolated: affecting only one valve
- E. Combined: affecting two or more valves

II. FUNCTIONAL REGURGITATION

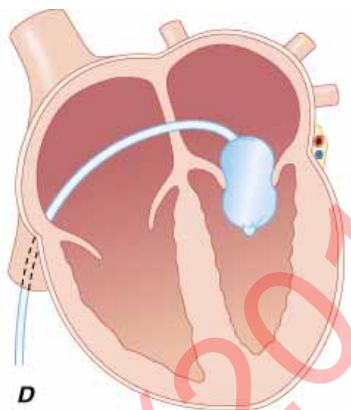
- A. dilation of the ventricle causes papillary muscles to be pulled down and outward, preventing coaptation of mitral or tricuspid leaflets
- B. dilation of the aortic or pulmonary artery, pulling the valve commissures apart, preventing full closure

III. CLINICAL FEATURES OF VALVULAR HEART DISEASE

- A. Mitral Stenosis
 - 1. Causes:
 - a. Rheumatic
 - b. Mitral annular calcification with extension onto the leaflets
 - c. SLE or rheumatoid arthritis
 - d. Endocarditis



2. MV orifice
 - a. Normal: 4-6 cm²
 - b. MS: < 2 cm².
 - c. Severe MS: < 1 cm² (often with LA pressure 25 mmHg); Mild MS: > 1.5 cm².
3. Symptoms:
 - a. Exertional dyspnea.
 - b. Increase C.O. leads to increased LA and CWP -> decreased compliance.
4. Treatments include surgeries (such as MV repair/commissurotomy or MV replacement) or PMBV: Percutaneous Mitral Balloon Valvotomy



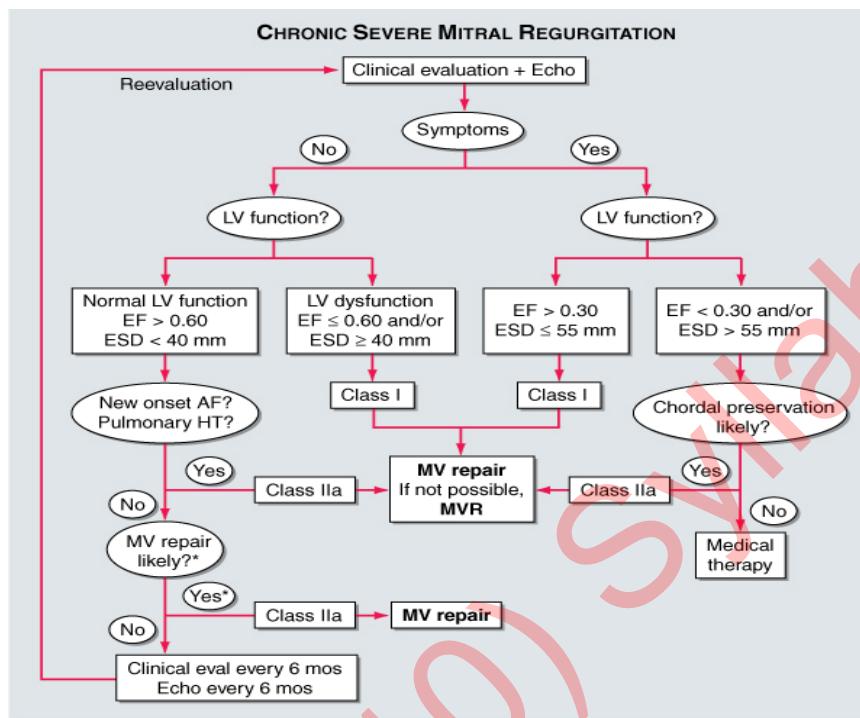
B. Mitral Regurgitation

1. Pathogenesis: Alteration of any part of MV apparatus: leaflets, annulus, chordae tendineae, papillary muscles, and subjacent myocardium.
2. Acute causes:
 - a. Acute myocardial infarct (papillary muscle rupture)
 - b. Trauma
 - c. Endocarditis
 - d. Chordal rupture.
3. Chronic causes:
 - a. Mitral valve prolapse
 - b. Rheumatic disease
 - c. Mitral annular calcification/degeneration
 - d. Congenital
 - e. Healed endocarditis
 - f. HOCM



- g. LV dilation from any cause (often ischemic). LV dilation causes annular dilation and outward displacement of papillary muscle.
- 4. Clinical
 - a. Often slowly progressive, with initial defect causing more strain and weakening, and cycle of MR ->LA & LV dilation -> more MR. "Regurg. Begets Regurg."
 - b. LV afterload is reduced, causing more complete LV emptying. A decrease in EF in these patients is a particularly bad sign of failure.
 - c. Cardiac cath. often not needed. Severe MR is defined by Echo: a regurgitant vol. >60 mL/beat, regurgitant fraction (RF) >50%, and effective regurgitant orifice area >0.4 cm².
- 5. Management
 - a. Symptoms:
 - 1) Mild and Moderate isolated MR are usually asymptomatic.
 - 2) Fatigue, exertional dyspnea, and orthopnea with chronic severe MR.
 - b. Medical Rx
 - 1) Treat Systemic Hypertension
 - 2) Treat CHF (to decrease LV dilation->MR)
 - 3) Treat atrial fibrillation, including possible anticoag.
 - c. MV repair:
 - 1) Valvuloplasty often with insertion of an annuloplasty ring.
 - 2) Avoids complications of valve replacement: thromboembolic and hemorrhagic complications with mechanical prostheses and late valve failure in the case of bioprostheses.
 - 3) Decisions about when to operate follow typical guidelines as in the flowchart below.
Flowcharts are used for all of the forms of valvular heart disease.





Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J; Harrison's Principles of Internal Medicine, 17th Edition; <http://www.accessmedicine.com>
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C. Aortic Stenosis

1. 25% of chronic valvular heart disease. 80% are men.
2. Causes:
 - a. Degenerative calcific in normal AV
 - b. Degen. Calcific in bicuspid (bicAV in 1.4% of population)
 - c. Rheumatic fever (now <10% AS).
3. Severe AS (<1cm²) can be asymptomatic for years with hypertrophied LV generating a normal stroke volume.
4. Symptoms:
 - a. Exertional dyspnea
 - b. Angina pectoris
 - c. Syncope.
5. Clinical
 - a. Echo is also useful for identifying MS and AR, which sometimes accompany AS
 - b. Coronary angiography is indicated to check CAD in patients >45 years old with severe AS who are being considered for operative treatment. 50% would benefit from CABG at the same time.



- d. 10-20% of deaths in severe AS due to sudden death (likely arrhythmia).
 - e. In severe AS, strenuous physical activity should be avoided. Avoid dehydration and hypovolemia to maintain CO
 - 6. Valve Replacement: Mechanical Valves
 - a. They are extremely durable.
 - b. They have the problem of thrombogenicity, particularly at MV.
 - c. Usually requires anti-coag Rx
 - d. Types
 - 1) Bi-leaflet (e.g. St. Jude)
 - 2) Ball-cage (e.g. Starr-Edwards)
 - 3) Tilting Disc
 - 7. Bioprosthetic Valves
 - a. They use devitalized (fixed) animal tissue: Human, pig, cow origin.
 - b. Heterograft (xenograft)
 - c. Homograft (allograft; human cadaver)
 - d. Autograft (move the PV to AV; and replace PV with mechanical)
 - e. Tissue comes from valve or pericardium.
 - f. They come (rigid) stented or (flexible) unstented.
 - g. They have less thrombogenicity but have problems of structural valve deterioration
- D. Aortic Regurgitation
- 1. Pathogenesis:
 - a. Either primary valve disease or aortic root dilation.
 - b. Aortic root disease now more common than primary valve disease
 - 2. Causes of Valvular AR:
 - a. Congenital (bicuspid)
 - b. Endocarditis
 - c. Rheumatic
 - d. Myxomatous
 - e. Traumatic
 - f. Syphilis
 - g. Ankylosing spondylitis



3. Causes of Root Disease:
 - a. Aortic dissection
 - b. Cystic medial degeneration
 - c. Aortitis
 - d. Hypertension
 - e. Marfan.
4. AR causes an increase in LV end-diastolic pressure.
5. In acute AR, the LV cannot dilate sufficiently to maintain stroke volume, there is marked elevations of LA pressures with pulmonary edema or cardiogenic shock.
6. In chronic AR there is LV dilation and then associated hypertrophy. This combination creates some of the largest hearts seen at autopsy.
7. Clinical signs can be related to the tremendous pulse pressure
8. AVR (Aortic Valve Replacement)
 - a. AVR may also require aortic root repair/replace
 - b. In "root-only" disease you can repair the root and maintain the native AV
9. Mortality Rates after Valve Surgery

Operation	Number	Operative Mortality (%)
AVR (isolated)	12,501	2.8
MVR (isolated)	3788	5.3
AVR + CAB	12,748	5.2
MVR + CAB	2683	10.3
AVR + MVR	1018	8.8
MVP	3982	1.0
MVP + CAB	4293	7.0
TV surgery	4358	9.6
PV surgery	432	5.2



- E. Tricuspid Regurgitation
 - 1. Causes: Usually functional and secondary to marked dilation of the RV...but can be due to rheumatic, endocarditis, myxomatous degeneration, carcinoid, or trauma.
 - 2. Secondary form is often reversible if RV dilation is decreased.
 - 3. Usually well tolerated clinically
 - 4. Surgery is usually repair rather than replacement and often coupled with mitral valve surgery.
- F. Tricuspid Stenosis: Rarely of clinical significance
- G. Pulmonic Valve Disease: Rarely of clinical significance
- H. Valve Pathology: Many etiologies:
 - 1. Congenital
 - 2. Traumatic
 - 3. Secondary to myocardial disease or functional heart changes
 - 4. Inherited collagen disorders (Marfan, Ehler-Danlos)
 - 5. Degenerative (calcific, myxoid)
 - 6. Immune (Rheumatic, Lupus)
 - 7. Infectious (endocarditis, syphilis)
 - 8. Thrombotic (marantic)
 - 9. Metabolic (Serotonergic)
- I. Calcific Degeneration
 - 1. Probably related to wear-and-tear, therefore mostly left-sided: AV cusps, MV annulus
 - 2. Dystrophic calcification without significant lipid deposition or cellular proliferation, a process distinct from but with some features of atherosclerosis
 - 3. Presentation at 50-60s y.o. if bicuspid; at 70-80s y.o. if merely "senile"
 - 4. Calcific AS has risk factors similar to atherosclerosis cardinal risk factors (but with less emphasis on LDL).
 - 5. Early stage (AV sclerosis) is clinically insignificant
 - 6. Involves the valve cusps themselves at areas of greatest flexion.
 - 7. Calcifications stiffen cusps and fill the sinuses of Valsalva, preventing full opening.





- J. Mitral Annular Calcification
1. Calcification starts at annulus and may spread down leaflets.
 2. Prevention of systolic annular contraction may cause regurgitation.
 3. Stiffening of leaflets may cause stenosis.
 4. Increase incidence with female, MV prolapse, or L VH
 5. Mildly increases the risk of endocarditis of MV.
- K. Mitral Valve Prolapse: Clinical
1. Mid- or Late-Systolic click with >2mm of prolapse (beyond annulus plane). 3% of adults. F>M.
 2. Most are asymptomatic.
 3. Usually cause is unknown, but associated with collagen disorders: Marfan, Ehler-Danlos, and osteogenesis imperfecta.
 4. MVP is a risk factor for MV infective endocarditis, emboli, or arrhythmias.
 5. Most common cause of isolated severe MR requiring surgical treatment.
6. Mitral Valve Prolapse: Pathology
- a. Gross:
 - 1) Usually MV only. Posterior > Anterior leaflet. Annular dilation also.
 - 2) Interchordal hooding of leaflets.
 - 3) Rupture of cords may occur.
 - b. Microscopic: Myxomatous degeneration (weakened collagen with replacement by acid mucopolysaccharide)
- L. Rheumatic Heart Disease
1. Scarring valvular disease caused by Acute Rheumatic Fever.



2. ARF caused by multisystem (Jt. Heart, skin, brain) autoimmune reaction a few weeks after Group A Strep pharyngitis (usually 5-14 yo)
3. Acute rheumatic pancarditis may progress to chronic rheumatic valvular disease. Valve dysfunction 5-20 years later.
4. ARF is common in developing countries but has greatly decreased in developed countries in the last 40 years, maybe due to hygiene, Abx, virulence drift.
5. Pathology
 - a. Valve involvement: 70% MV; 25% MV + AV
 - b. Valve leaflets are diffusely thickened by fibrosis.
 - c. In MV: 1/3 pure MS; 2/3 MS+MR
 - d. Commissures fuse, the chordae tendineae fuse and shorten, the valvular cusps become rigid.
 - e. Later degenerative changes may be a nonspecific process: Initial deformity -> further chronic injury.

M. Infective Endocarditis

1. Infection of endocardium, usually on the valve.
2. Almost always bacterial (fungus rare). The bacteriology of this will be covered in Microbiology lectures.
3. Acute bacterial endocarditis due to highly virulent bacteria.
4. Subacute bacterial endocarditis due to less virulent organisms, usually attacking a deformed valve.
5. Risk Factors
 - a. Cardiac:
 - 1) Previously deformed valves
 - 2) Prosthetic valves
 - 3) Open heart surgery
 - b. Extracardiac:
 - 1) Chronic infection
 - 2) IVDA
 - 3) Immunosuppression
 - 4) Hemodialysis
 - 5) Penetrating chest trauma
 - 6) Infected surgical procedures (e.g. dental extraction)
6. Sites
 - a. AV and MV are the most common sites of infection. Right side often involved in intravenous drug abusers.



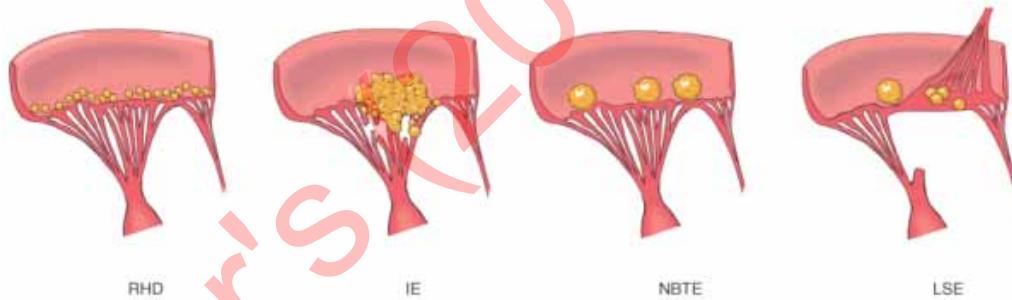
b. Sites of I.E. infection:

MV	25%
AV	25%
MV + AV	10 %
TV	10 %
Prosthetic	10 %
Congenital	10 %
Other	10 %

7. Complications

- a. Valve vegetations (composed of thrombus, organisms and leukocytes) can be a source for septic emboli to many organs.
- b. IE can destroy valve leaflet creating regurgitation and eventually heart failure.
- c. IE can spread into nearby annulus and myocardium (Ring Abscess)

8. Types of endocarditis



- a. Acute rheumatic endocarditis
- b. Infective endocarditis
- c. Non-bacterial thrombotic "marantic" endocarditis: sterile non-destructive thrombi in debilitated patients
- d. Libman-Sacks " verrucous" endocarditis (in SLE): sterile inflammatory

N. Drug-induced Valve Disease

1. Due to increased agonist activity on serotonin (5-HT 2B) receptors in valve subendocardial fibroblasts.
2. Anorectic drugs, particularly in combination (Fen-Phen) Fenfluramines augment serotonergic activity; phentermine interferes with the pulmonary clearance of serotonin.



3. Parkinson Rx: pergolide and cabergoline (dopamine agonists)
 4. Migraine Rx: Ergot medications
 5. Note: SSRI (Prozac, etc.) do NOT cause this
- O. Carcinoid Heart Disease
1. Valvular sclerosis associated with carcinoid tumors that produce bioactive molecules, such as serotonin and bradykinin.
 2. Affects the endocardium downstream from the tumor; then cleared by monoamine oxidase present in microvasculature
 3. Fibrous intimal thickenings in the right ventricle, TV, and PV.
 4. Patent foramen ovale or lung metastases allow sclerosis in left ventricle, MV, and AV.

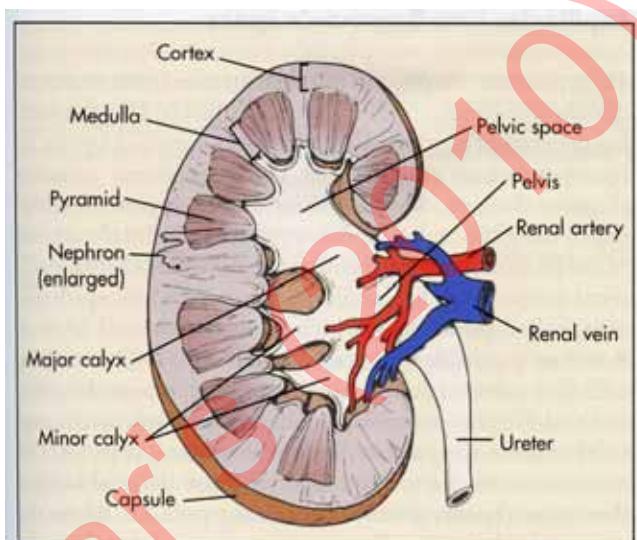


Last Year's (2010) Syllabus

RENAL CIRCULATION

I. THE ANATOMY OF THE KIDNEY

- A. The kidney may be divided into 2 layers: an outer layer called the cortex and an inner layer called the medulla. These layers are like the rings of a tree since one layer wraps around the other layer.
- B. One can consider the kidney as a pie, which is divided into slices, which are called lobes. There are 10 to 18 lobes and each lobe contains a medullary pyramid, which serves as the drainage for the kidneys, to the ureters. In the medulla, the lobes are easily separated but in the cortex distinct lobes are difficult to see.
- C. The medulla has 2 subzones or layers: the inner zone and the outer zone. The outer zone may be viewed as consisting of outer and inner stripes.

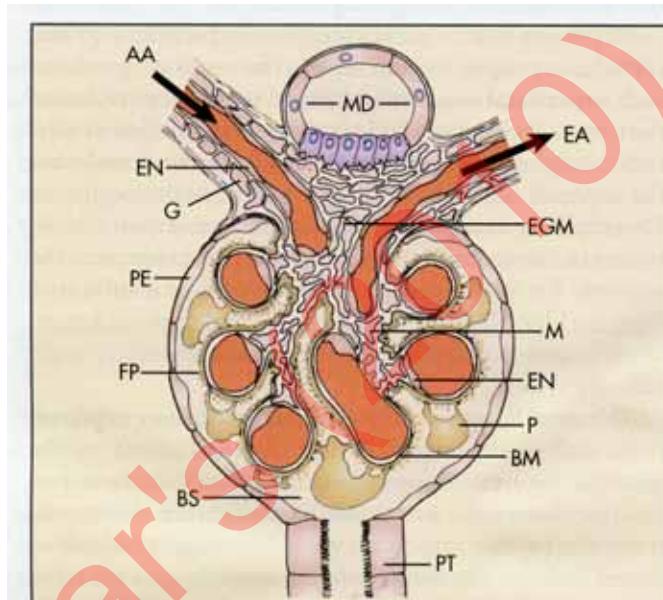


- D. Anatomy of the Kidney Learning Questions:
 1. What are the 2 layers of the kidney called?
 2. What are the separate slices of the kidney called?
- E. Answers to Anatomy of the Kidney Learning Questions:
 1. 2 Layers of the kidney are the outer layer called the cortex and the inner layer called the medulla.
 2. The separate slices of the kidney are called lobes.



II. THE RENAL CIRCULATION

- A. The circulation of the kidney is critical to its role as a fundamental excretory organ. The kidney is heavily perfused, receiving approximately 20-25% of the cardiac output. This extensive blood flow is critical to the task of clearing toxins and regulating salt and water from the blood.
- B. The renal artery has branches called the interlobar arteries, which connect from the hilum to the corticomedullary junction (CMJ). In addition, there are arcuate arteries in the zone between the cortex and medulla. There are interlobular arteries which extend toward capsular surface. There are afferent arterioles which carry the blood to each glomerulus by forming capillary loops, which rejoin to form efferent arterioles. [One should be able to note the relationship between the afferent and efferent arterioles.]



- C. The critical work of the kidneys occurs in the glomerulus and the most critical elements of the renal circulation are the glomerular capillaries. Because of the remarkable permeability of the glomerular capillaries, salt and water exchange is possible just as the pulmonary capillary permeability permits oxygen and carbon dioxide exchange.
- D. There is a step-wise sequence of elements of the renal arterial circulation that brings blood to the glomerular capillaries and the elements of the renal venous circulation that bring blood away from the glomerular circulation.

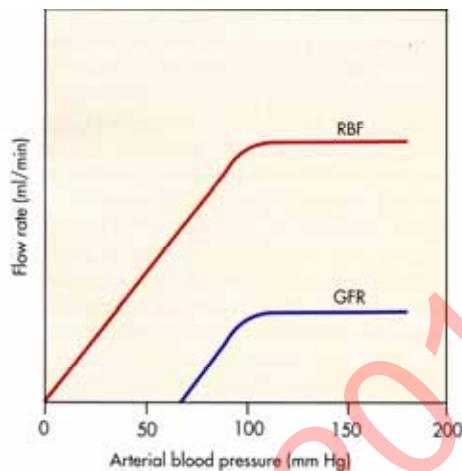


- E. The elements of the renal arterial system follow the following sequence: Renal Artery \Rightarrow Segmental Arteries \Rightarrow Interlobular Arteries \Rightarrow Arcuate Arteries \Rightarrow Afferent Arterioles \Rightarrow Glomerular Capillaries. [These elements are key to know.]
- F. The elements of the renal venous system follow the following sequence: Glomerular Capillaries \Rightarrow Efferent Arterioles \Rightarrow Peritubular Capillaries (A subset of which is called the Vasa Recta) \Rightarrow Venules \Rightarrow Arcuate Veins \Rightarrow Interlobular Veins \Rightarrow Segmental Veins \Rightarrow Renal Vein. [These elements are key to know.]
- G. The kidney plays a critical role in physiological homeostasis by regulating blood pressure and by regulating salt and water excretion and retention. The kidney must maintain blood pressure to create relatively constant perfusion of critical bodily organs such as the heart and brain despite physiological changes in the body.
- H. Learning Questions for Microcirculation of the Kidney:
1. What percentage of the cardiac output goes to the kidneys?
 2. What are the elements of the renal arterial system?
 3. What are the elements of the renal venous system?
 4. What critical roles does the kidney play in physiological homeostasis?
- I. Answers to the Learning Questions for Microcirculation of the Kidney:
1. What percentage of the cardiac output goes to the kidneys? 20-25%.
 2. What are the elements of the renal arterial system? The elements of the renal arterial system follow the following sequence: Renal Artery \Rightarrow Segmental Arteries \Rightarrow Interlobular Arteries \Rightarrow Arcuate Arteries \Rightarrow Afferent Arterioles \Rightarrow Glomerular Capillaries.
 3. What are the elements of the renal venous system? The elements of the renal venous system follow the following sequence: Glomerular Capillaries \Rightarrow Efferent Arterioles \Rightarrow Peritubular Capillaries (A subset of which is called the Vasa Recta) \Rightarrow Venules \Rightarrow Arcuate Veins \Rightarrow Interlobular Veins \Rightarrow Segmental Veins \Rightarrow Renal Vein.
 4. What critical roles does the kidney play in physiological homeostasis? regulating blood pressure and regulating salt and water excretion and retention.



III. REGULATION OF RENAL CIRCULATION

- A. The kidney must balance its role in regulating blood pressure and regulating salt and water retention. Under marked physiological changes, particularly changes in arterial blood pressure, the kidney must continue to regulate salt and water. The kidney maintains the glomerular filtrate rate as much as possible.
- B. In order to achieve a constant glomerular filtration rate, the kidney maintains a relatively constant renal blood flow.[the key principle is maintenance of renal blood flow] This phenomenon is called autoregulation.

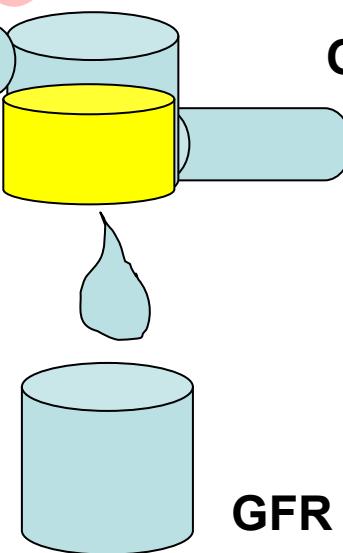


- C. Regulation of the afferent arteriole plays a particularly important role in autoregulation of both renal artery blood flow and glomerular filtration rate.
- D. The basic mechanisms of autoregulation are twofold: 1) pressure sensor or myogenic mechanism; 2) tubuloglomerular feedback. [These 2 mechanisms are important.]
- E. The pressure sensor or myogenic mechanism is quite simple: when the arterial blood pressure rises the renal afferent arteriole is stretched. Stretching of smooth muscle causes it to contract. The increased resistance largely offsets the increase in arterial pressure, causing the renal blood flow and therefore glomerular filtration rate to be constant.
- F. In the tubuloglomerular feedback mechanism, the macula densa of the juxtaglomerular apparatus (the juxtaglomerular apparatus consists of macula densa cells in the initial portion of the distal tubule and juxtaglomerular cells in the walls of the afferent and efferent arterioles) senses a change in the flow of tubular fluid, such as sodium chloride resorption. This stimulus results in a signal that modulates the renal afferent arteriolar resistance.



- When the tubular fluid flow rises, the signal will result in renal afferent arteriolar vasoconstriction.
- G. These mechanisms permit the autoregulation of renal blood flow and glomerular filtration rate to be constant despite changes in arterial blood pressure.
 - H. There are several basic principles of autoregulation [one should know how vasoconstriction and vasodilatation affect renal blood flow and glomerular filtration rate]:
 1. We focus on how much the glomerulus gets and at what pressure;
 2. Vasoconstriction of afferent arterioles means less flow gets to glomerulus and also less pressure;
 3. Vasoconstriction of efferent arterioles means there is increased pressure within the glomerulus (“back-up” effect); since overall resistance to flow is increased, the overall renal blood flow rate is decreased.
 - I. When there is vasoconstriction of either the afferent or efferent arterioles, the renal blood flow declines. However, the effect of vasoconstriction on glomerular filtration rate will differ depending on whether the site of vasoconstriction is in the afferent or efferent arterioles.
 - J. We can consider the afferent arterioles as the input and the efferent arterioles as the output. The perfusion pressure in the glomerulus determines the glomerular filtration rate (see Figure).

Input = Afferent

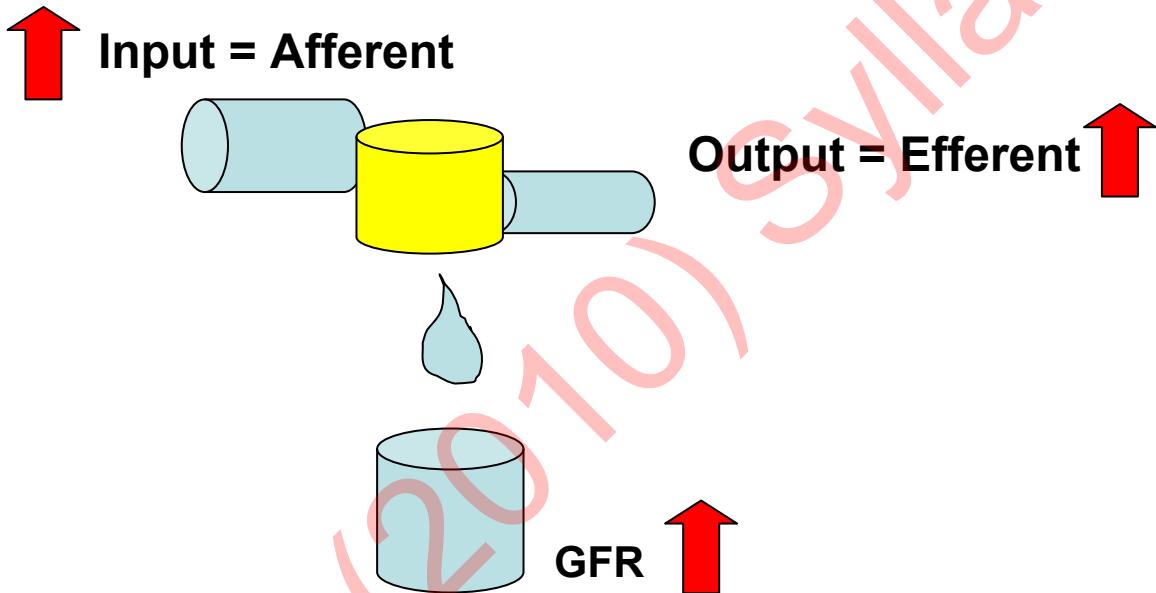


Output = Efferent



- K. If there is vasodilatation, which we can consider as less vasoconstriction, in the afferent arterioles, we see that the renal blood flow increases. ($V=IR$ is the analogy of less resistance results in increased flow when the pressure or potential difference is constant.) (See Figure below.) Since there is increased renal blood flow, the glomerular filtration increases also. It may be helpful to think of blood backing up from the efferent arterioles since the flow has increased.

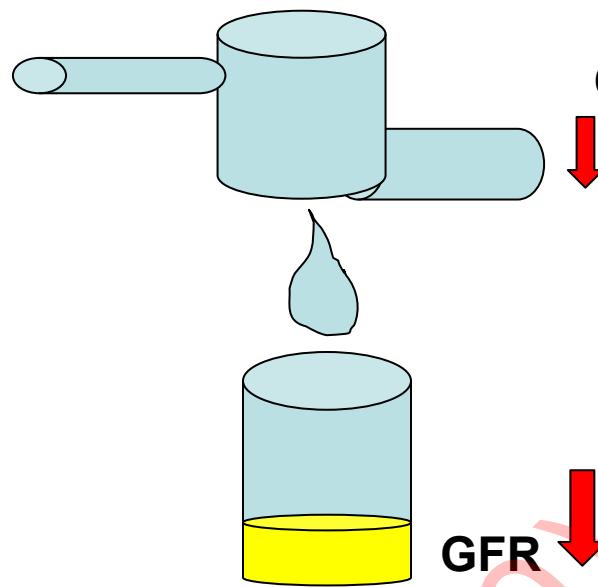
Less Afferent Vasoconstriction



- L. If there is increased vasoconstriction of the afferent arterioles, there is decreased renal blood flow and the corresponding glomerular filtration decreases. (See Figure below) [One notes that changes in vasoconstriction of the afferent arterioles produces changes in the renal blood flow and the glomerular filtration rate. The renal blood flow and the glomerular filtration rate either increase or decrease together.]



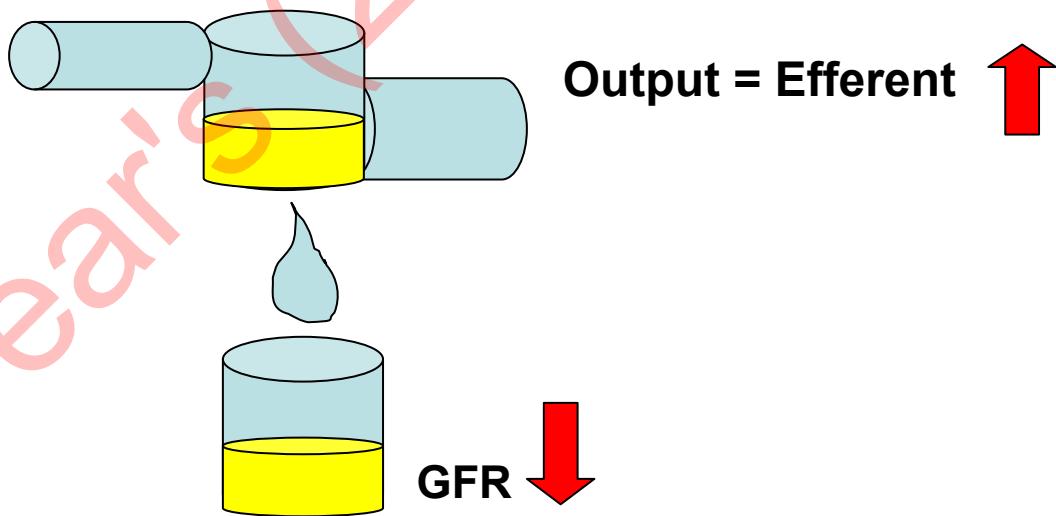
Input = Afferent



Output = Efferent

- M. On the other hand, if there is vasodilatation of the efferent arterioles, there is increased renal blood flow. One can think of the flow as backing up less in the glomerulus and thus the glomerular filtration rate decreases.

Input = Afferent

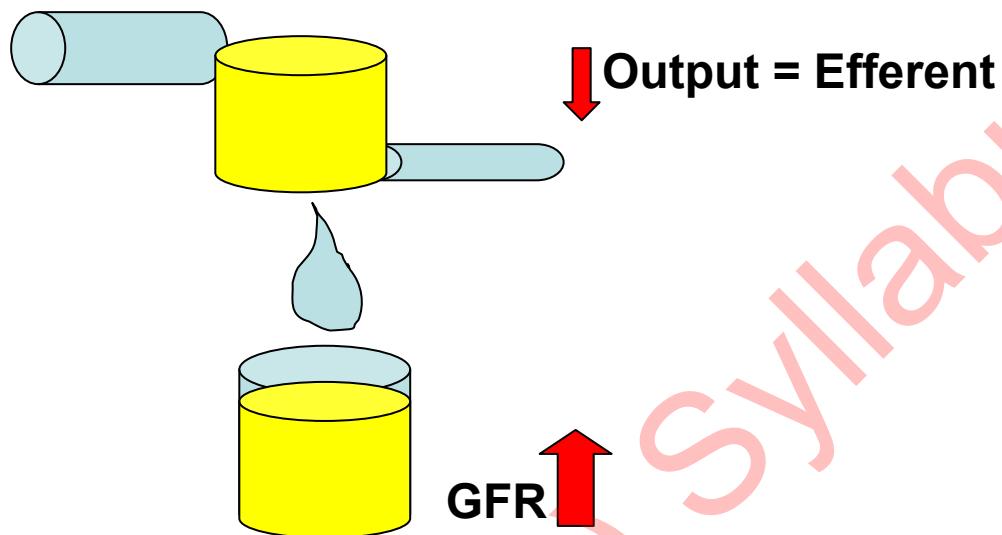


Output = Efferent

- N. If the vasoconstriction of the efferent arterioles increases, the renal blood flow decreases. Since the input is constant, the backup in the glomerulus can be thought of as increasing. As a result, there is increased glomerular filtration rate.

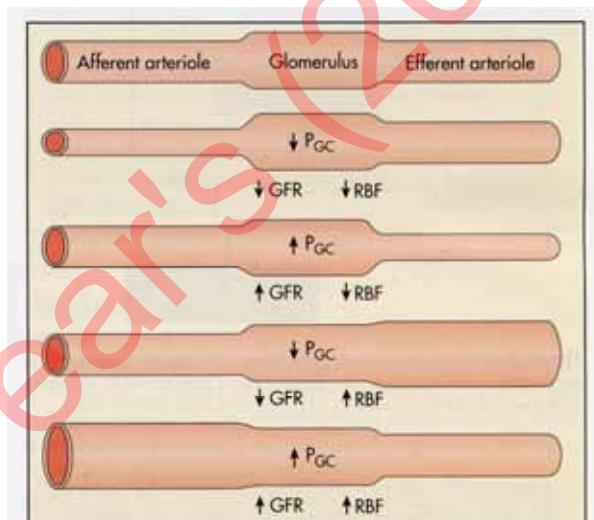


Input = Afferent



- O. The following Figure summarizes well the role of vasoconstriction or vasodilation of the afferent or efferent arterioles on renal blood flow and glomerular filtration rate. [It is important to be able to describe each of these effects]

IV. SUMMARY OF REGULATION



- A. Regulation of Circulation Learning Questions:
1. What are the 2 basic mechanisms of autoregulation?
 2. What are the effects of increased afferent arteriolar vasoconstriction on renal blood flow and GFR?
 3. What are the effects of decreased afferent arteriolar vasoconstriction on renal blood flow and GFR?



4. What are the effects of increased efferent arteriolar vasoconstriction on renal blood flow and GFR?
 5. What are the effects of decreased efferent arteriolar vasoconstriction on renal blood flow and GFR?
- B. Answers to Regulation of Circulation Learning Questions:
1. What are the 2 basic mechanisms of autoregulation?
 - 1) Pressure sensor or myogenic mechanism;
 - 2) Tubuloglomerular feedback.
 2. What are the effects of increased afferent arteriolar vasoconstriction on renal blood flow and GFR? Decreases both renal blood flow and GFR (go in same direction.)
 3. What are the effects of decreased afferent arteriolar vasoconstriction on renal blood flow and GFR? Increases both renal blood flow and GFR (go in same direction.)
 4. What are the effects of increased efferent arteriolar vasoconstriction on renal blood flow and GFR? Decreases renal blood but increases GFR (opposite directions).
 5. What are the effects of decreased efferent arteriolar vasoconstriction on renal blood flow and GFR? Increases renal blood flow but decreases GFR (opposite directions).



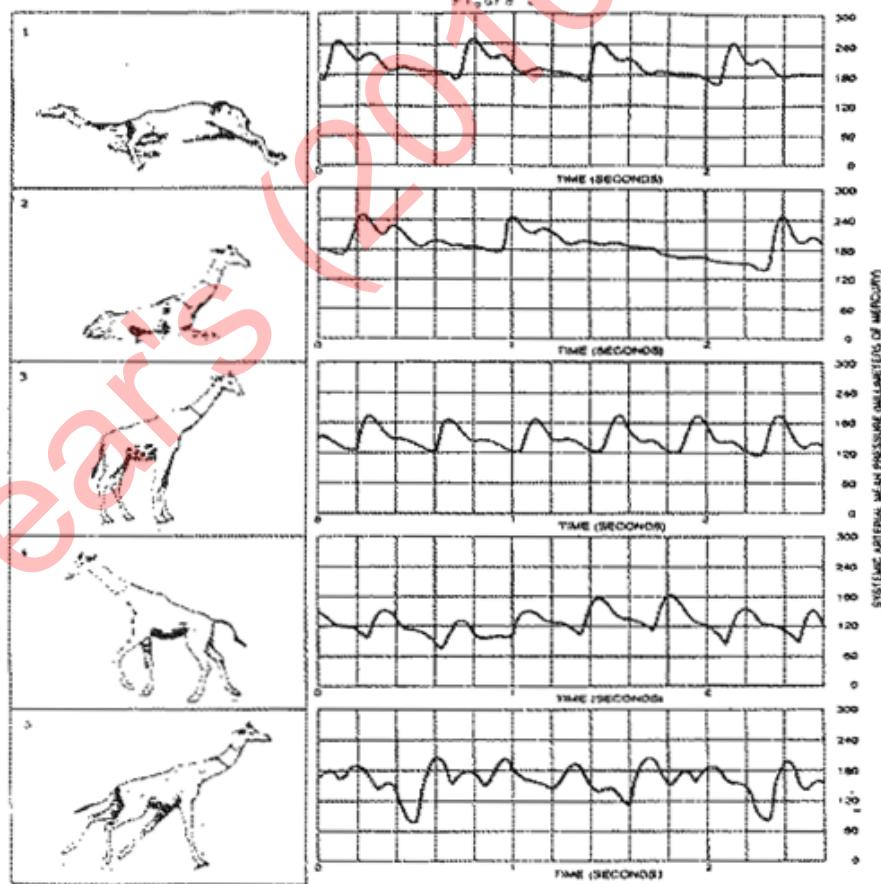
Last Year's (2010) Syllabus

HYPERTENSION

ARTERIAL PRESSURE: DETERMINATION, REGULATION AND HYPERTENSION

I. INTRODUCTION

Arterial pressure is maintained within the CV system to assure adequate flow to all tissues under varying conditions of rest, posture, activity and stress (i.e. fever, hemorrhage). Cerebral perfusion requires that pressures are kept at levels compatible with the upright stance in man and other mammals. The sensing of systemic arterial pressure and filling pressures in the atria are essential components for the regulation of cardiovascular hemodynamics and, when functioning properly, keep resting cardiac output in man from exceeding approximately 4.5 L/min/M² of body surface area and keep mean arterial pressure from falling below approximately 60 mm Hg. In other species the principles are the same but absolute values -- as in the giraffe where blood pressure is kept at 240/180 -- may differ. (Fig.1).



PRESSURE AND HEARTBEAT vary in accordance with the activity of the giraffe. Where the animal is lying down (1), with its heart and its brain at the same level, the blood pressure in the carotid artery ranges from 100 to 140 mm. Hg. (millimeters of mercury). The heart rate, with four major pulsations in 2.5 seconds, is about 60 beats per minute. As the animal raises its head (2) the blood

pressure stays much the same but the heart rate slows temporarily. Standing (3) and walking (4) raise the heart rate to some 150 beats per minute, while arterial blood pressure falls to a range of from 90 to 150 mm. Hg. Collected (5) brings the heart rate to maximum; 120 beats per minute. El highest blood pressure in gallupping are 220 mm. Hg.; deep drops in pressure coincide with front-hoof beats.



II. MEASUREMENT

- A. Obviously, arterial blood pressure can be measured directly by measuring the height of a column of liquid above the level of the heart. This was in fact done (see "Physics of the Circulation") by Rev. Hales in the horse. Normally BP will rise with each left ventricular contraction and fall during diastole, giving different values for the peak (systolic) and nadir (diastolic). The driving force integrated over the entire cardiac cycle is the mean pressure. It will be determined by the shape of the arterial pressure curve and the relative duration of systole and diastole, to be discussed below. The phasic signal can be damped either mechanically or electrically to read the mean pressure. Present techniques allow a fluid-filled catheter to be connected to a needle or passed directly into an artery. The free end of the catheter is attached to a transducer, which translates pressure changes into changes in electrical resistance. Such measurement techniques offer continuous direct monitoring of arterial pressure. This is necessary when patients are critically ill or when powerful vasoactive drugs capable of causing rapid vasoconstriction (e.g. Dopamine, Norepinephrine, Angiotensin) or vasodilation (e.g. sodium nitroprusside, ganglionic blockers) are being administered intravenously.
- B. However, these invasive methods are uncomfortable for the patient and are unnecessary for usual clinical needs. The method of Korotkoff is utilized, which takes advantage of the fact that laminar flow through an artery is silent while intermittent forward flow produces a sound. By implanting a cuff around an extremity to a pressure in excess of systolic pressure, flow distal to the cuff ceases. When pressure in the cuff is reduced to just below systolic pressure, flow proceeds across the artery beneath the cuff for that portion of the cardiac cycle during which arterial pressure exceeds cuff pressure. This transient "spurt" gives rise to a sound which can be heard with a stethoscope placed over the artery just distal to the cuff. The flow will be intermittent as long as the falling pressure continues to exceed diastolic arterial pressure. When cuff pressure falls below diastolic arterial pressure, there will be no cessation of flow. With return of continuous flow, sounds will muffle and disappear. Thus the pressure at which sounds appear and disappear signal systolic and diastolic pressure, respectively.



Figure 2

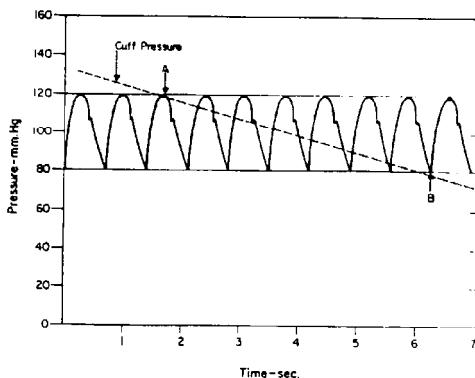


Fig. 5-11. Principle of measurement of arterial blood pressure with a sphygmomanometer. The oblique line represents pressure in the inflatable bag in the cuff. At cuff pressures greater than the systolic pressure (to the left of A), no blood progresses beyond the cuff and no sounds can be detected below the cuff. At cuff pressures between the systolic and diastolic levels (between A and B), spurts of blood traverse the arteries under the cuff and produce the Korotkoff sounds. At cuff pressures below the diastolic pressure (to the right of B), arterial flow past the region of the cuff is continuous, and no sounds are audible.

III. THE ARTERIAL PRESSURE CURVE

- A. If arterial pressure is recorded against time, a typical curve is recorded. It shows a rise to a peak, then a fall, interrupted by a notch, followed by a slight secondary rise and then further fall until the cycle starts again. The precise shape of this wave form is determined by some simple factors which will be mentioned here and by some complex considerations which are beyond the scope of this discussion (see "Physics of the Circulation, Part III"). The specific anatomy of the curving aortic arch with its proximal major branches and its distal bifurcation creates numerous loci from which the advancing wave front is partially reflected backward. This, as well as the tapering diameter of the normal aorta is responsible for the changing shape of the wave front as it travels from the aortic root to the distal arterioles.
- B. The rising arterial pressure in the proximal aorta with early systole reflects the fact that blood is being expelled into the aorta faster than it is escaping into distal vessels and tissues. The compliance of the aorta determines the rate at which pressure changes. As pressure rises in the proximal aorta, the rate at which blood is discharged peripherally increases and the relative impedance to LV outflow increases, leading to slower systolic ejection. Thus, as the pressure rises, the rate at which net volume is increasing in the aorta falls. This is reflected in the falling slope of the rising systolic pressure curve. When the pressure is at its peak, entry and exit of blood are equal. With the downslope of aortic pressure, the volume of blood in the segment of aorta in which pressure is being monitored falls. When the pressure in the proximal aorta exceeds LV pressure, the aortic valves close, there is momentary cessation of forward movement of blood, which then resumes as the elastic



walls of the aorta compress the blood in the aortic root. This closure of the aortic valves and transient interruption of flow gives rise to the dicrotic notch which punctuates the declining arterial pressure. The sound produced by this closure (5-2) separates systole (ejection) from diastole during cardiac auscultation. Pressure falls throughout diastole as blood leaves the proximal aorta and the tension in the aortic wall falls.

Figure 3

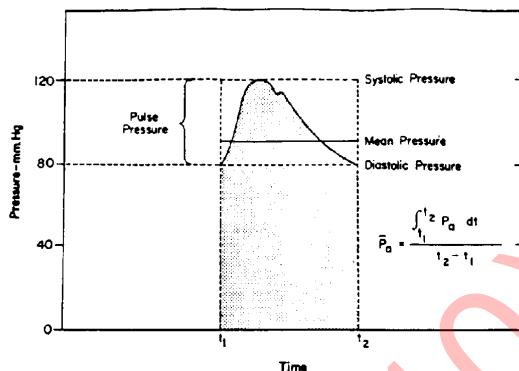


Fig. 5-4. Arterial systolic, diastolic, pulse, and mean pressures. The mean arterial pressure (\bar{P}_a) represents the area under the arterial pressure curve (shaded area) divided by the cardiac cycle duration ($t_2 - t_1$).

- C. Obviously, the more rapidly ejection volume is delivered, the more rapid will be the rate of rise and the higher will be systolic peak pressure. Additionally, enhanced cardiac contractility (e.g. exercise, excitement) or increased stroke volume (e.g. in aortic valve insufficiency or extreme bradycardia, remember, as heart rate goes down stroke volume must rise if cardiac output is to be maintained) will increase systolic pressure. Also, as aortic root compliance is reduced by atherosclerosis, age, and calcification, higher pressures are needed to distend the aorta by the same volume. Thus, systolic pressures typically rise with age.

Figure 4

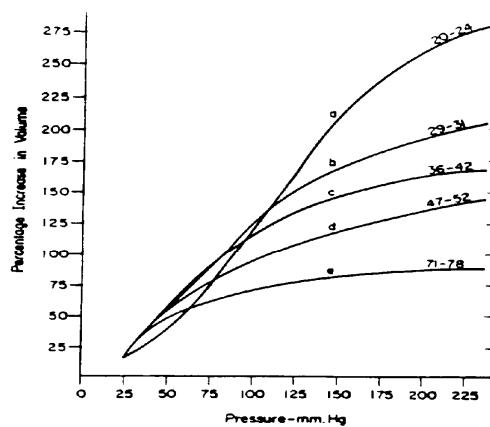


Fig. 5-3. Pressure-volume relationships for aortas obtained at autopsy from humans in different age groups (denoted by the numbers at the right end of each of the curves). (Redrawn from Hallock, P., and Benson, I. C.: J. Clin. Invest. 16:595, 1937.)



- D. Conversely, if the systolic ejection period is prolonged (i.e. in severe aortic valvular stenosis) or if marked tachycardia (with small stroke volumes) occurs, peak systolic pressures are lowered.
- E. Following the completion of ejection, blood is leaving the arteries via the major resistance vessels, the arterioles. If the arterioles are dilated and resistance is low, blood will be delivered to tissues more rapidly and the slope of arterial pressure will decline more quickly. A high peripheral resistance will do the opposite, leading to a higher diastolic arterial pressure at the time of the next systolic interruption of the declining diastolic pressure.
- F. Although "drainage" of the aorta is normally only through the arteries, certain pathological conditions allow blood to leave the aorta through a low-resistance shunt. This is the case with a patent ductus arteriosus (PDA) in which blood is shunted from the aorta to the low-pressure pulmonary circulation, causing a much faster decline in aortic pressure and a lower diastolic and mean arterial pressure. In the event of aortic valvular insufficiency, blood leaks retrograde into the LV during diastole. This similarly speeds the descent of diastolic pressure to a lower nadir than normal. The enhanced stroke volume and more rapid aortic decompression produce the characteristic high systolic and low diastolic pressure of aortic insufficiency.
- G. Regardless of the rate of decline of arterial pressure during diastole, the longer the cardiac cycle, the longer the diastolic period and thus the lower trough pressure will be. Thus severe bradycardia (i.e. 35-45/min) such as occurs in complete heart block will also have wide pulse pressure with exaggerated peak systolic and low diastolic pressures.

IV. MEAN BLOOD PRESSURE

- A. In order to quantitate flow and resistance in the CV system, we generally utilize mean flow expressed as volume/minute. Therefore mean blood pressure is used as the driving force.

1. From the analogy with Ohm's Law,

$$\text{a. Flow} = \text{PI} - \text{P2} = \text{MAP} - \text{CVP}$$

Res TPR

b. where: MAP = mean arterial pressure

CVP = central venous pressure

TPR = total peripheral resistance

2. Since normal MAP is approximately 100 mm Hg and CVP is normally 0-5 mm Hg, CVP is usually disregarded in the calculation so that

$$\text{a. Flow (liters/min)} = \text{MAP (mm HR)}$$



- Last Year's Slides
- TPR
- b. where: TPR is given in arbitrary resistance units.
- B. From Poiseuille's Law we recall that resistance (TPR) to flow is determined by length, viscosity and the reciprocal of the radius to the fourth power ($1/R^4$). Since length does not alter after growth is complete, we can rearrange the equation: MAP = Viscosity x Cardiac Output x $(1/R^4)$.

V. IMPLICATIONS OF UAP = VISCOSITY X CARDIAC OUTPUT X(L/R)⁴

- A. Although viscosity is potentially important, it is relatively constant with normal hematocrit and protein concentration in plasma, neither of which will increase appreciably over hours or days (in the event of hemorrhage, hematocrit will fall in hours, but the viscosity vs. hematocrit curve is fairly flat below the normal hematocrit of 45%) and therefore it can be excluded as a short-range determinant of arterial pressure under normal (but not pathological) circumstances.
- B. Viscosity, when it rises to abnormally high levels, is usually due to marked increase in hematocrit (the percentage of whole blood composed of erythrocytes). Although this occurs rarely in Polycythemia Vera among adults, in children it is more commonly caused by cyanotic congenital heart disease with right-to-left intracardiac shunts leading to arterial hypoxemia and secondary bone marrow overproduction of red blood cells in an attempt to maintain whole blood O₂ content. In untreated Tetralogy of Fallot, (right ventricular outflow obstruction and inter-ventricular septal defect), arterial PO₂ Of 40 torr or less may be encountered as well as hematocrits of 75-80 percent. With hematocrits of this magnitude, viscosity is elevated enough to interfere with tissue perfusion.
- C. Elevation of plasma globulins occurs with certain malignancies of lymphocytes or plasma cells. When these immune globulins increase to concentrations of 4-8 gm/dl (normal < 1.2 gm/dl), viscosity may be more than doubled with resulting changes in tissue perfusion. Nevertheless, hyperviscosity is a relatively rare contributor to arterial hypertension. Cardiac output depends upon numerous influences which include essentially:
1. Determinants of venous return:
 - a. blood volume
 - b. venous capacitance
 2. Determinants of myocardial performance:
 - a. the family of Frank-Starling curves
 - 1) contractility



- Last Year
- 2) filling pressure
- b. afterload
- D. Therefore, excessive blood volume could be expected to cause arterial hypertension and in fact this can be seen with inadvertent hypertransfusion or in the disease Polycythemia Vera, in which red cells are overproduced by the bone marrow in an unregulated fashion raising total blood volume as well as hematocrit.
- E. Small changes in venous tone could alter venous compliance and venous volume, although normal, might raise peripheral venous pressure and augment venous return, leading in turn to increased cardiac output. Conversely, inadequate venous tone, such as might occur with disease of the peripheral autonomic nerves (as in long-standing Diabetes Mellitus), after the use of drugs which block sympathetic ganglia or even severe chronic distention of peripheral veins (as in severe varicose veins) may all lead to transient failure of venous return upon assuming an upright posture. Without adequate venous return, cardiac output falls and arterial pressure also.
- F. Loss of extracellular volume in the form of excess perspiration, diarrhea or diuresis (urine loss) may be due to environmental factors (heat), intestinal disease, or inadequate renal concentrating mechanisms due to intrinsic renal disease, endocrine (adrenal, pituitary) insufficiency, or drugs (diuretics) to name several causes of dehydration and hypotension. Abrupt loss of cardiac contractility affecting a large segment of the left ventricle (40% or more) can precipitate a drastic fall in stroke volume and a fall in cardiac output severe enough to cause hypotension and shock. On the other hand, a few cases have been described of persistent hypercontractility of the heart leading to sustained supranormal cardiac output and mild (predominantly systolic) hypertension. This condition has been successfully treated with β_1 -blocking drugs.
- G. Clearly a most powerful physiologic hemodynamic determinant is the radius of the arterial vessels. Changes in arterial diameter are proportionally greatest in the small vessels with muscular walls the arterioles (see "Physics of the Circulation"). Their caliber is controlled by several factors:
1. Humoral substances
 - a. circulating norepinephrine and epinephrine
 - b. vasopressin
 - c. angiotensin II
 - d. histamine
 - e. others (pO_2 , pCO_2 , prostaglandins)



2. Autonomic control via sympathetic efferents and the relative preponderance of α and β_2 receptors
 3. Autoregulation
- H. A major pathologic abnormality of aortic resistance occurs with coarctation of the aorta. Typically this is a congenital defect leading to marked constriction of a short segment of the aorta, typically in the region of the insertion of the ductus arteriosus close to the origin of the left subclavian artery. In this circumstance pressure in the vessels leading to the head and upper extremities (including the internal mammary arteries) is elevated, while pressure in the abdominal aorta and lower extremities is reduced. Interestingly, resting flow (ml/am tissue) is maintained at normal levels both above and below the site of constriction, testifying to the functioning role of autoregulation throughout childhood.

VI. REGULATION

- A. Since efficient perfusion of the brain, heart and peripheral tissues is so important to survival, and since changes in venous volume, filling pressures and peripheral resistance can be influenced by so many activities (eating, drinking, perspiration, body temperature, excitement, exercise and inflammation), systems to maintain pressure and resistance -- and therefore flow -- must exist. Rapidly-acting regulation occurs through high pressure baroreceptors in the carotid sinus and in the aorta. They respond with changing feedback signals to distention in the carotid and aortic walls. Traffic on afferent nerves varies between systole and diastole and is targeted to medullary centers and then to the vagus nerve, influencing heart rate and --to a lesser extent -- contractility of the atria and -- even less -- the ventricles. Integration through the hypothalamus alters sympathetic activity in an integrated fashion. This is a very rapidly acting system and adjusts to changes in posture, acute blood loss and similar stimuli. (Occasionally, it may cause hypotension if the carotid sinus is compressed/deformed externally. This may happen inadvertently with a very tight collar or while shaving or, more commonly, as a diagnostic maneuver by a physician seeking to abort a tachycardia reflex by stimulating the carotid sinus reflex using carotid sinus pressure). These baroreceptor reflexes will counter acute hypertension as well as hypotension. But if hypertension is maintained, they normally adapt, and within 2-5 days they are "reset", firing in response to hypertensive pressures at the same frequency as they did to normal pressures before the change took place. Thus they play no role in reversing chronic hypertension.



- B. Low-pressure receptors are thought to exist in the pulmonary artery and the atria, functioning in part as "volume receptors." Acute increases in pressure in these (normally low pressure) structures cause systemic vasodilation and may also stimulate an increased output of urine by the kidneys.
- C. If cardiac output is increased and peripheral resistance does not alter, then increased capillary hydrostatic pressure would occur with increased transcapillary fluid transfer, as predicted by Starling's Law of diffusion. The loss of intravascular volume would gradually reduce venous volume and venous return and would tend to return cardiac output toward normal.
- D. This mechanism is more typically recognized in reverse. When hemorrhage occurs, venous return and cardiac output fall, hypotension occurs despite arteriolar vasoconstriction and intracapillary hydrostatic pressure falls, leading to leaking of interstitial fluid into capillaries, restoring plasma volume. (However, since red cell volume cannot be replaced until production increases days later, the ratio of red cells to whole blood falls with this internal "transfusion" of interstitial fluid and hematocrit falls over a period of hours -- the classical finding in hemorrhage.)
- E. Humoral response to hypotension occurs within minutes to an hour. Hemorrhage or serious hypotension is accompanied by a release of vasopressin by the posterior pituitary gland. This peptide, formed in the hypothalamus, has a potent vasoconstrictor effect and also, in its role as antidiuretic hormone (ADH), decreases the excretion of water by the kidney, conserving intravascular volume.
- F. Abrupt decline in the renal arterial perfusion pressure is a potent stimulus to the release of renin from the granules of the juxtaglomerular cells of the kidney. Renin, an enzyme, enters the circulation where it cleaves a decapeptide, Angiotensin I, from a circulating alphaglobulin protein molecule. During its passage through the pulmonary circulation, Angiotensin I is converted by the enzymatic cleavage of 2 amino acids to an octapeptide, Angiotensin II. Angiotensin II is an extremely potent peripheral arteriolar vasoconstrictor and causes a rise in peripheral vascular resistance. It also acts to stimulate release of aldosterone from the adrenal cortex. Aldosterone is a very potent mineralocorticoid which, by its action on the kidney, leads to retention of Na⁺ and water, thus conserving total body fluid volume, and with it, venous return.



- G. Autoregulation, since its exact mechanism is unknown, plays a less well understood role in response to acute hypotension or fall in flow. In the short run, its tendency to vasodilation probably is inadequate to overcome the rise in resistance mandated by the previously mentioned negative feedback responses. The latter act to maintain total peripheral resistance high enough to permit adequate perfusion of the heart and brain.
- H. On the contrary, if cardiac output is increased above normal, evidence exists that autoregulation may gradually increase peripheral resistance over a period of a week or more, leading to an increased afterload and a fall in cardiac output back to normal levels at the expense of persistent hypertension. Such a course of hemodynamic events has been shown in anephric patients made hypervolemic. (In anephric patients both renal volume control and renin production are absent.) Much interest now focuses on such a sequence (i.e. initial elevation of cardiac output followed by autoregulating elevation of peripheral resistance leading to sustained hypertension with a normal cardiac output) as a mechanism for essential hypertension. Such a sequence might also be the basis for development of hypertension occurring with tumors of the adrenal cortex leading to overproduction of aldosterone (primary hyperaldosteronism) which could induce hypertension initially through volume mechanisms.

Figure 5

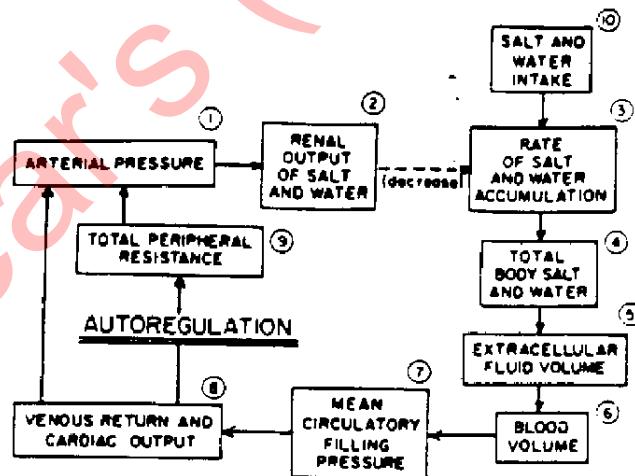


Figure 22-2. A block diagram of the renal-body fluid mechanism for long-term control of arterial pressure.



- I. The renal response to arterial pressure is to alter the amount of urine produced. Normally urine production rises or falls very steeply with very small changes in mean arterial pressure (i.e. one liter/day at 100 mm Hg to four liters/day at 106 mm Hg). Although the physiology of mechanisms of the renal response will not be discussed in this section, it can be readily understood that any nonrenal cause of increased renal arterial pressure will be met by net volume loss (unless volume intake rises in parallel fashion). If volume intake is unchanged from control blood pressure levels, volume loss will exceed volume intake until mean BP returns to the level at which it began. This control mechanism has a long term guarantee of BP maintenance. Similarly, one can anticipate that if renal diuretic response to rises in arterial pressure is blunted (i.e. the curve of urine output in response to arterial pressure is shifted to the right or the slope is diminished), then any volume increment will be associated with considerably greater mean pressure, or any stimulus causing increased pressure will need a more sluggish restorative diuretic response. Or in a larger sense, renal disease may be expected to be an etiology for hypertension. In fact, this is the case. Most renal diseases leading to loss of renal mass and blunted volume control responses are often associated with hypertension.

Figure 6

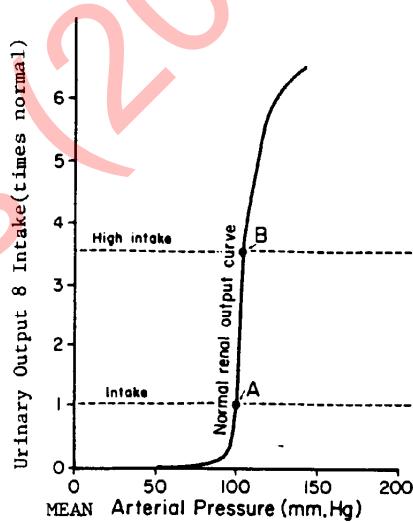


Figure 22-5. Graphical procedure for predicting the steady-state long-term arterial pressure level by equating the renal output curve with the fluid and salt intake level. (See explanation in the text.)



- J. If one renal artery is partially constricted, not only is renal water excretion in that kidney diminished, but renin is released, leading eventually to elevated plasma levels of renin and angiotensin. These substances, in turn, elevate peripheral arterial resistance and, by their action on the other kidney, prevent it from excreting Na^+ and water normally in response to the hypertension. Thus a state of persistent hyperreninemia and hypertension is maintained. Hypertension in this situation may be reversible if the unilateral renal artery constriction is corrected. The clinical finding of a bruit (murmur) over a kidney in combination with severe hypertension raises this diagnostic possibility at the bedside.

Figure 7

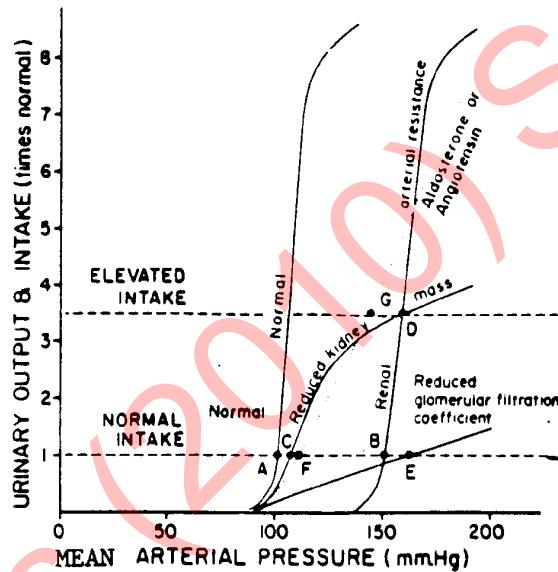


Figure 22-7. Abnormal urinary output curves and graphical analysis of the long-term level of arterial pressure in various hypertensive states caused by the abnormal renal function.

- K. A variation on this theme is the unilateral constriction of a renal artery and the removal of the contra-lateral kidney. Once again renin is released and angiotensin leads to hypertension, while at the same time the renal parenchyma, initially ischemic is conserving fluid. As volume is progressively increased, venous return and cardiac output rise, autoregulation raises peripheral resistance and the ischemic kidney's perfusion is maintained by a systemic hypertension which returns the ischemic kidney's perfusion to normal, leading to reduction of renin production to normal. The patient is left with normal cardiac output, normal renin and angiotensin levels but with increased peripheral resistance and hypertension.



L. The importance of the kidney in hypertension has been repeatedly verified since the early experiments with renal artery constriction by Goldblatt. The subsequent discovery and characterization of renin, Angiotensin I and II, and aldosterone have strengthened the physiological basis for this renal-hypertensive linkage. Similarly, the studies of renal responsiveness to altered perfusion pressure with altered rates of urine production by Guyton and others have done the same. Nevertheless, the precise role of the kidney in essential (primary) hypertension is not entirely clear, and low, "normal" and high levels of circulating renin are encountered in essential hypertension without demonstrable renal pathology. Since essential hypertension accounts for approximately 95% of hypertension, more work is needed before the majority of cases of arterial hypertension are completely understood.

VII. HYPERTENSION

- A. When used clinically, "hypertension" refers to a level of arterial pressure at rest which is greater than necessary to provide adequate safeguards for perfusion of the body. Since BP is distributed in a statistically "normal" fashion in the population, this definition is arbitrary. Although the level is age-related, in the adult BP greater than 140/90 is considered to be the threshold for hypertension. This definition reflects the need to alert the physician to the fact that risks associated with hypertensive CV disease (e.g. congestive heart failure, stroke, other) increase as diastolic, or systolic pressures rise above these levels.
- B. Usually, hemodynamic measurements indicate that fixed hypertension in the adult is associated with a normal cardiac output and increased peripheral resistance. Some measurements in younger individuals with labile (not fixed) hypertension have shown elevated cardiac output with "normal" resistances during periods of hypertension, raising the question of whether this supranormal output state is the earliest physiological abnormality.
- C. Once hypertension has been identified, it is logical to search for definitive, reversible causes. These involve -in most patients who are otherwise normal and ambulatory -an effort to exclude anatomical resistance such as coarctation of the aorta (by comparing BP in the arms with that in the lower extremities) and humoral sources of elevated peripheral resistance, such as physiological active tumors of the adrenal medulla (pheochromocytoma) or adrenal cortex (hyperaldosteronism and Cushing's syndrome). Unilateral renal artery stenosis can be excluded in an individual with 2 kidneys by finding a low circulating renin level. A high renin level is consistent with renal artery stenosis, but not diagnostic of it. It may reflect intrarenal ischemia



- which is almost always present in far advanced and severe symptomatic ("malignant") hypertension, (perhaps due to spasm of numerous renal arterioles). Hypervolumic or hyperviscosity states are extremely rare and, when present, are usually associated with other chemical and laboratory findings.
- D. Unfortunately, 95% or more cases of hypertension in the general population remain without a definitive cause (primary or essential hypertension). Since most cases fall in the "mild" category and can be controlled with readily available drugs, a search for underlying causes is now usually reserved for those patients who are young, whose hypertension is very resistant to usual medication or to patients with clinical clues suggesting one of the above -mentioned conditions
1. The consequences of prolonged hypertension can be identified at 3 sites: 1) Cardiac 2) Large Arteries and 3) Small Arteries.
- E. The increased cardiac work determined by the higher pressure at time of onset of ejection (arterial diastolic pressure) rising to peak systolic pressure requires increased myocardial O₂ delivery. With the development of myocardial hypertrophy in response to increased pressure, the need for O₂ is augmented. Over a prolonged course of severe hypertension the myocardial effort fails, ejection fraction falls, ventricular diastolic filling pressures rise and myocardial dilatation occurs. This sequence of events defines the hemodynamics of left-sided congestive heart failure, an important complication of hypertension.
- F. The ventricular combination of pressure load, hypertrophy and dilatation (through the Laplace relationship) all augment left ventricular O₂ demand and make the myocardium more vulnerable to ischemic lesions (angina pectoris, myocardial infarction).
- G. The elevated mean pressure within the larger arteries is traumatic to the endothelial cells and plays an important role in accelerating atherosclerosis. (The pulmonary arteries which contain blood with the same cholesterol content as aortic blood but at much lower pressures are free of atherosclerosis unless pulmonary hypertension occurs, in which case pulmonary arterial atherosclerosis occurs.) In addition, the increased mean (and pulsatile) pressure increases aortic wall tension. Gradual distension of the aorta may occur. At any given pressure, any increase in radius of the aorta increases wall tension so that a positive feedback loop occurs, whereby the wall tension -and the aortic distention -- increase at a faster rate as the aneurysm (dilated segment) enlarges. In the brain, arteries are thinner-walled than elsewhere, and defects in continuity of the arterial muscular media



may occur at arterial branch points. These loci may burst in hypertensives, leading to hemorrhagic stroke and loss of function or death.

- H. When hypertension is severe, it may enter a phase of severe elevation of pressure (e.g. 250/150) which is accompanied by severe vasospasm. Such vasospasm at the arteriolar level leads to ischemic foci in many organs. In the kidney it leads to acute renal failure and multiple ischemic areas which in turn cause increased renin release, further raising blood pressure and peripheral resistance. In the brain, the weaker blood vessel walls, although also showing vasospasm (actually visible in the ocular fundus where smaller retinal artery branches --visible with the ophthalmoscope -- are of arteriolar size and show focal spasm) are less able to resist the higher pressures and edema formation occurs. Combinations of edema and focal hemorrhages are seen in the optic fundus (remember, that the retina, through the optic nerve, is an extension of the brain) and in sections of the brain at post-mortem when individuals die secondary to malignant hypertension.
- I. The treatment of hypertension is rationally based upon attempts to reduce venous return, to reduce myocardial contractility and to cause arterial vasodilatation. The use of diuretic agents causes enhanced urinary loss of Na⁺ and H₂O and thus reduces venous return and cardiac output. (However, a new equilibrium volume of input vs. output is usually established and measurement of body weight and cardiac output do not allow a definite agreement on the mechanism of the chronic antihypertensive action of the diuretics.)
- J. The β-receptor blockers, by their competition at β1 receptors in the heart, cause reductions in cardiac output and have been used with great success to treat hypertension. However, their blockade of β2 receptors in the periphery might be expected to leave α receptors unopposed, thus tending to raise arterial pressure. (The time course of action of β-blockers on blood pressure and on receptors is not entirely synchronous, raising questions of whether other, less well understood mechanisms are the cause for the β-blockers antihypertensive effect.)
- K. Agents that act directly on blood vessel walls to relax smooth muscle (e.g. Ca⁺⁺-antagonists, nitrates, sodium nitroprusside) cause a direct lowering of peripheral resistance and of blood pressure. Other substances counteract the sympathetic nervous system at the central or peripheral level to lower peripheral resistance. Newer agents are now available which block peripheral angiotensin by competition (Saralasin) or by inhibition of angiotensin converting enzyme (Captopril), blocking the conversion



of Angiotensin I to Angiotensin II. Such agents can be used as physiologic probes to determine the relative role of the renin-angiotensin system in the genesis of hypertension in a single patient.

- L. Ultimately the test of any therapeutic program is its antihypertensive effect balanced against its economic and biologic cost. As may be imagined, fatigue (due to low cardiac output, excessive diuresis and potassium loss), postural hypotension (syncope) and interference in other autonomically regulated functions (leading to impotence) may compromise the desirability of any therapeutic program.

VIII. SUMMARY

- A. The determinants of blood pressure are complex. On a stroke-by-stroke basis, stroke volume, cardiac contractility, aortic compliance, heart rate and peripheral resistance all play parts in the shape and magnitude of the cyclic arterial pressure curve. These determinants change with age, activity and super imposed pathologic events affecting the heart, its valves and the circulatory system.
- B. Mean blood pressure over longer periods is affected by mean cardiac output and total peripheral resistance. Because the resistance is proportional to $1/R^4$, very small changes in arteriolar radius, under the control of interacting influences such as the sympathetic nervous system, circulating Angiotensin II, other hormones and autoregulation can cause major changes in blood pressure.
- C. Any change is sensed by short and longer-acting feedback regulatory systems -- which normally act to maintain arterial pressure at a level compatible with optimal cardiac output to all organs, but particularly the brain -- in an upright posture. The carotid sinus responds on a beat-to-beat basis and offers protection from abrupt postural variations. It "resets" after several days at higher pressure and is therefore not a useful defense against chronic hypertension.
- D. Longer-acting regulation depends upon the kidney, which through the renin-angiotensin system, can provide significant rise in peripheral resistance in response to hypotension of the renal circulation. Conversely, long-term systemic hypertension can ensue if a kidney is ischemic secondary to pathologic stenosis of the renal artery.



- E. Autoregulation may be involved if the hypertensive state is brought about by increased cardiac output. A rise in peripheral resistance (afterload) would then return output and perfusion to normal at the price of persistent hypertension. 'Most cases of hypertension are label led "essential" because no definite pathophysiologic sequence of events has been identified. The consequences of sustained hypertension are the development of myocardial hypertrophy and eventual congestive heart failure, the increased rate of atherosclerosis of large and medium- sized arteries, as well as the tendency for distention and rupture of those vessels, and finally, malignant hypertension with severe arteriolar vasospasm, loss of vision and cerebral edema.
- F. Drug treatment of hypertension is addressed to the physiologic determinants when no primary cause can be found and removed. Diuretics, β 1-blockers and vasodilators compose the majority of effective agents and respectively lower venous return, myocardial contractility (output) and peripheral arterial resistance.



Last Year's (2010) Syllabus

MYOCARDITIS AND PERICARDITIS

Kumar, 7th ed., pp. 383 – 385, 393

Suggested Reading: Robbins, 8th ed., pp. 414 – 415, 416 - 419

PREFACE TO MYOCARDITIS AND PERICARDITIS

Myocarditis and pericarditis are both important but uncommon diseases of the heart. It is important to have covered this area but a great deal of emphasis is not necessary compared with other cardiac diseases such as valvular and coronary artery disease.

LEARNING GOALS

- A. You should know that myocarditis can be Infectious, Idiopathic (?viral) and Toxic. (It is not necessary to know ALL of the causes of myocarditis and pericarditis.)
- B. You should know what pericarditis is, the main causes:
 1. Non-infectious - (uremic)
 2. Infectious
 3. Traumatic
- C. You should know the physiologic effect of pericardial effusions and also that of chronic, healed pericarditis.

I. MYOCARDITIS

Definition:

1. Myocarditis is inflammation of the muscular part of the heart. The statistical incidence of this disease is around 5% on autopsy studies. It is thought, however, that clinically the incidence is much higher and that in many cases the disease is subclinical and can regress and the patient recover fully. There is some circumstantial evidence only that myocarditis may lead to cardiomyopathy.

Classification:

1. Myocarditis can be classified as:
 - a. infectious
 - b. idiopathic
 - c. myocarditis in collagen diseases, and
 - d. myocarditis due to physical agents, chemical poisons, drugs and metabolic disorders.



A. Myocarditis caused by infectious agents:

1. Myocarditis can be caused by bacterial, rickettsial, viral, protozoal and parasitic, fungal and spirochetal agents. All of these agents can cause an inflammatory reaction in the heart; however, it is unusual unless the patient is very debilitated or has overwhelming infections, is under immunosuppressive agents or has AIDS. In myocardial lesions associated with infectious diseases, the inflammation may be due to an actual invasion of the myocardium by the organisms or to the action of their toxins, although it is possible that an allergic mechanism is responsible in some cases.
2. Gross: The gross appearance of the heart in acute myocarditis is not distinctive, but usually the myocardium is pale and flabby and the chambers are dilated. Abscesses may appear as small yellow or streaky foci occasionally become confluent. Some of the abscesses may be surrounded by a hemorrhagic zone.
3. Microscopic: The inflammation may be focal or diffuse. In some cases small abscesses may form in the myocardium such as in staphylococcal bacterial endocarditis while interstitial inflammation is minimal. In other instances, nonsuppurative inflammation of the connective tissue is the predominant change with a cellular infiltrate consisting of Lymphocytes, plasma cells, eosinophils, histiocytes and sometimes neutrophils. The interstitium may be edematous. Sometimes abscesses may develop in the myocardium as a result of certain fungal infections.
4. Some infections produce granulomatous inflammation of the myocardium such as tuberculosis, which may be nodular or miliary or even diffuse. Sarcoidosis is not proved to be an infectious disease but is mentioned here because it resembles lesions of noncaseating forms of tuberculosis.
5. Myocarditis has been described in protozoal diseases in which Chagas' disease and toxoplasmosis are examples. In Chagas' disease the inflammation in the myocardium is usually intense, mixed and myocyte necrosis may be prominent. Toxoplasmosis caused by toxoplasma gondii may present with pseudocysts containing the organisms in the muscle fibers without inflammatory reaction or the free organisms in the myocardium provoking a mixed inflammatory reaction.
6. Some helminthic parasites that affect the heart are Trichinella spiralis, and Echinococcus granulosus . Inflammatory reaction is a response to the larvae although



these are not easily seen in the lesions. Hydatid cysts caused by tapeworms can also occur in the myocardium. The primary hydatid cysts of the heart tend to rupture into the lumen of a cardiac chamber or into the pericardial sac. Fungus infection of the heart has increased with the advent of immunosuppression. The fungi most commonly seen in the heart are blastomycosis, actinomycosis, cryptococcosis, coccidioidomycosis, histoplasmosis, aspergillosis and candida. Syphilitic myocarditis can also occur.

7. Myocarditis has been reported in a variety of viral disease including all of the common infections: polio, chicken pox, flu, infectious hepatitis, mumps, infectious mononucleosis, and infections caused by Coxsackie B virus. The microscopic picture in viral lesions is similar and consists of interstitial infiltration by Lymphocytes and neutrophils with focal myocyte necrosis. Later the Lymphocytes and histiocytes predominate and there is connective tissue proliferation.

B. Idiopathic Myocarditis:

1. As the name suggests, there is no known cause for this type of myocarditis although it is strongly suspected that it may be viral in origin. In this case the inflammation is often a pancarditis. There is often rapidly progressive myocardial failure or sudden death. The gross appearance of the heart shows chamber dilatation and sometimes hypertrophy. Mural thrombi may also occur. Two forms are usually described: the diffuse type, without the formation of granulomas and the granulomatous type. The diffuse type consists of an interstitial inflammatory infiltrate which may be mixed at first but is usually predominantly mononuclear. Focal myocyte damage is usually present. With the advent of the endomyocardial biopsy the diagnosis of idiopathic myocarditis is being made more often. Unfortunately, this diagnosis is often confused with "look-a-likes" which can appear to be myocarditis but are, in fact, inflammatory infiltrates due to other causes. For this reason myocarditis is often over-diagnosed by endocardial biopsy. It is generally felt that this condition will lead to idiopathic dilated cardiomyopathy if the patient survives the acute phase; however, we have no good direct proof that this is so at this time.
2. In the granulomatous variety throughout the myocardium there are small or large granulomas without caseation and containing giant cells. Myocyte necrosis may be extensive.



The giant cells are of the foreign body and Langerhans types but some giant cells of myogenic origin may also be present.

C. Myocarditis in Collagen Diseases:

1. Myocarditis may occur in rheumatic fever, rheumatoid arthritis and lupus erythematosus. In polyarteritis nodosa there is a necrotizing vasculitis. There may be thrombi in the vessels and secondary ischemic changes. Microscopic changes in the heart muscle have been reported in dermatomyositis and scleroderma. In these cases there is fibrous tissue replacement of the myocardium without a significant inflammatory component.

D. Myocarditis Due to Physical Agents, Poisons, Drugs and Metabolic Disorder:

1. Myocarditis may be seen in response to cardiac trauma as in car accidents where there might be an infiltrate of neutrophils. Irradiation of the heart causes an acute inflammatory reaction with damage to small vessels. Many poisons and drugs will cause both toxic and hypersensitivity myocarditis. These drugs are listed in Tables 1 and 2. As you can see some of them are quite commonly used drugs, such as tetracyclines, immunosuppressives, and antihypertensives. The list of drugs thought to be responsible for causing myocarditis is added to daily so no account of them can be totally up to date. Hypersensitivity (allergic) myocarditis have lesions which are not dose or time dependent and may occur any time during delivery of the drug. These lesions regress when the drug is stopped. Systemic signs of fever and rashes may also be present. In general, hypersensitivity myocarditis is manifested morphologically with an interstitial inflammatory infiltrate which includes many eosinophils. Heart size is usually not markedly affected in acute hypersensitivity myocarditis. Toxic myocarditis and vasculitis induced by drugs is dose related and the effects are cumulative. The inflammatory infiltrate surrounding the damaged myocytes is predominantly that of neutrophils although a mixed infiltrate may also be seen. Toxic myocarditis also evokes an acute necrotizing vasculitis with hemorrhage. Toxic myocarditis may result in focal scars of the myocardium.

The anthracycline drugs, particularly adriamycin, also may cause an acute myocarditis-pericarditis syndrome; however, these drugs usually cause a chronic myocardial damage which will not be described here.



Table 1. Drugs associated with toxic myocarditis

Arsenicals	Anthracyclines
Plasmocid	Lithium compounds
Paraquat	Catecholamines
Barbiturates	Quinidine
Antihypertensives	Cyclophosphamide
Amphetamine	Theophylline
Fluorouracil	Phenothiazines
Histamine-like drugs	

Table 2. Drugs associated with hypersensitivity myocarditis

Sulfonamides	Streptomycin
Isoniazid	Sulphonylurease
Penicillin	Methyldopa
Thiazide diuretics	Phenylbutazone
Diphtheria toxoid	Horse serum
Tetanus toxoid	

E. Clinical features:

1. The clinical features of an acute myocarditis usually include a history of a recent flu-like illness with fever, myalgias, fever and shortness of breath. On examination the patient usually has an enlarged cardiac silhouette and heart failure.

II. PERICARDITIS

Definition:

1. An inflammation of the epicardium and/or the parietal layer of the pericardium. It may be classified as acute, subacute or chronic. Usually, however, it is designated according to its anatomic features, such as (1) serous, (2) serofibrinous, - (3) fibrinopurulent, (4) purulent, and (5) hemorrhagic. Pericarditis also may be idiopathic (non-specific) or due to acute bacterial infection, uremia, or associated with myocardial infarction, rheumatic, neoplastic or traumatic.
2. The pericardium normally consists of 30-50 cc of thin straw colored fluid. In some conditions such as heart failure an excessive serous transudate may occur into the pericardium slowly or rapidly. In this case there are usually no adhesions



following the mechanical or physiological withdrawal of the fluid from the sac. Hemopericardium in which blood enters the pericardial sac may be caused by trauma, such as a knife wound, myocardial rupture or coronary artery rupture. It is rare for hemorrhagic diatheses to cause hemorrhage into the pericardium. More recently the use of the cardiac biopsy may result in perforation of the ventricle and hemopericardium. Hemorrhage into the pericardium may cause tamponade which is a clinical emergency. Blood should be removed from the pericardial sac rapidly to allow diastolic expansion of the heart and also to prevent organization of the blood.

- A. Serous pericarditis: This may be due to non-bacterial inflammation, rheumatic fever, systemic lupus erythematosus (SLE), viral or tuberculous infection. It is sometimes a result of tumor metastases in the pericardium. This type of pericardial effusion rarely causes adhesions.
- B. Serofibrinous and fibrinous pericarditis: This is the most frequent type and commonly occurs in uremia, rheumatic fever or infarction. Occasionally it is due to bacteria or a viral infection. The fibrin may become organized with obliteration of the pericardial sac. Clinically, this type of pericarditis may cause pain and result in a loud friction rub.
- C. Suppurative or purulent pericarditis: This is due to bacteria, mycotic or parasitic organisms. Sometimes it is also due to direct invasion of tuberculosis or pneumonia from the lung. This type of pericarditis leads to granularity of the serosal surface with occlusion and organization into a dense thickened pericardial sac which may even be calcified. Clinically, there is usually spiking fevers and chills due to the infection.
- D. Hemorrhagic pericarditis: A hemorrhagic pericarditis is one in which blood is present in addition to the features of one of the other inflammatory exudates. The causes include tuberculosis, severe acute infections and neoplastic (tumor) involvement of the pericardium. A rare occurrence is a pericardial effusion containing cholesterol which is associated with myxedema.
- E. Healed Pericarditis: Pericarditis results in chronic adhesive (obliterative) pericarditis, or chronic constrictive pericarditis. Chronic adhesive pericarditis consists of adherent pericardium and it usually causes no embarrassment of the heart thus differing from chronic constrictive pericarditis. Chronic constrictive pericarditis is a result of healing of inflammatory exudate and is characterized by marked fibrous thickening of the pericardium which becomes so rigid that it mechanically interferes with heart action and the



circulation. The pericardial cavity may be completely or partially obliterated. The main effect of this is interference with diastolic action of the heart. The heart is usually therefore smaller in size. Pick's disease is a syndrome consisting of chronic constrictive pericarditis with severe venous congestion of the liver that may lead to fibrosis and ascites (note: there is another Pick's disease in the brain!).

III. ETIOLOGIES OF HUMAN MYOCARDITIS

A. INFECTIOUS

1. **BACTERIAL:** Diphtheria, Tuberculosis, Legionella, Salmonella, Brucella, Clostridium, Meningococcus
2. **RICKETTSIAL:** Q Fever, Rocky Mountain Spotted Fever, Scrub Typhus
3. **VIRAL:** Coxsackievirus (A&B), Echovirus, Influenza, CMV, Mumps, EBV Herpes Simplex, HIV
4. **FUNGAL:** Aspergillus, candidiasis, Histoplasmosis, Cryptococcus
5. **SPIROCHETAL:** Borrelia (Lyme)
6. **PROTOZOAL & METAZOAL:** Trypanosomiasis, Toxoplasmosis, Malaria, Schistosomiasis, Trichinosis

B. NONINFECTIOUS

1. **CARDIOTOXIC DRUGS:** Cocaine, Catecholamines, Adriamycin
2. **HYPERSensitivity DRUG REACTIONS:** Antibiotics, diuretics, etc.
3. **SYSTEMIC ILLNESS:** SLE, Collagen Vascular Diseases, Sarcoidosis

IV. ETIOLOGY OF PERICARDITIS

- A. **TRAUMA:** Pericardiectomy, Direct or Indirect Trauma, Catheter Perforation, Pacemaker Placement
- B. **INFECTIONS:** Viral, Bacterial, Fungal, Protozoan, Rickettsial
- C. **RADIATION**
- D. **AMYLOIDOSIS**
- E. **TUMORS:** Primary and Metastatic
- F. **SARCOIDOSIS**
- G. **COLLAGEN VASCULAR DISEASES:** Rheumatic Fever, SLE, Rheumatoid Arthritis, Polyarteritis Nodosa, Scleroderma, etc.
- H. **ANTICOAGULANTS:** Heparin, Warfarin



- I. MYOCARDIAL INFARCTION: Acute MI, Postmyocardial (Dressler's) Syndrome
- J. IDIOPATHIC THROMBOCYTOPENIC PURPURA
- K. DRUGS: Procainamide, Hydralazine
- L. DISSECTING ANEURYSM
- M. INFECTIVE ENDOCARDITIS WITH ABSCESS

Last Year's (2010) Syllabus



CARDIOMYOPATHIES AND TUMORS OF THE HEART

Kumar, 8th ed., pp. 409 – 412, 417.

PREFACE TO CARDIOMYOPATHIES & TUMORS OF THE HEART

Cardiomyopathies are an important subject since this disease may occur in infants and throughout the normal life span. The subject has not received a great deal of attention in textbooks because the etiology of this disease is not yet clear and also, up until recently, there has not been any good treatment. With the advent of new diagnostic procedures, such as DNA probes to try and sort out the etiology and with cardiac transplantation being a feasible method of treatment this subject is now becoming more relevant and of greater importance. It is now likely that there would be questions on this subject in the National Boards. This lecture covers not only idiopathic cardiomyopathies, but also specific heart muscle disease (secondary cardiomyopathies) and so covers a great deal of cardiac pathology. Much of this subject is covered in Kumar et. al. and a few books also listed at the back of the handout. The subject will also be dealt with in the Cardiovascular Pathology Laboratory.

Tumors of the heart are very rare and only one or two are important for you to remember, such as myxomas and secondary metastases to the heart.

GOALS

At the end of this lecture I would expect you to know:

- A. The pathology of the three main types of idiopathic cardiomyopathies and their physiologic effect.
- B. To understand the basic pathology of myxomas, rhabdomyomas and METASTATIC HEART DISEASE ONLY.

Definition:

- A. Cardiomyopathy is a condition affecting primarily the myocardium unassociated with significant narrowing of the extramural coronary arteries, or systemic hypertension, or anatomic valvular disease, or congenital malformation of the heart and vessels or intrinsic pulmonary parenchymal, or vascular disease. In other words, the diagnosis depends partly on the exclusion of other common types of heart disease. These forms of myocardial disease (cardiomyopathies) are described in diverse journals; moreover, definitions are often sketchy or controversial; the diagnosis is often made by exclusion of the usual causes of cardiac failure; and



finally, the incidence of these forms of cardiac disease in the general population is not well known, in part due to confusion in the terminology and classification of these disorders.

- B. It has been recently proposed by the Task Force on Cardiomyopathies, World Health Organization, and the Scientific Council on Cardiomyopathies, International Society and Federation of Cardiology, that nomenclature for these disease entities be made more specific and less ambiguous. According to the new classification, the term cardiomyopathy should be used to describe the group previously known as "primary cardiomyopathy" or "heart muscle disease of unknown cause," and that "secondary cardiomyopathy" should be replaced by the term "specific heart muscle disease." For example, a disease entity in which a viral agent is the proposed etiologic factor should be referred to as "viral heart muscle disease" and not "viral cardiomyopathy."

I. PATHOLOGICAL CLASSIFICATION OF CARDIOMYOPATHIES

- A. PRIMARY CARDIOMYOPATHY (Idiopathic):
1. Dilated type (congestive)
 2. Hypertrophic type
 - a. With subaortic stenosis (IHSS)
 - b. Without subaortic stenosis
 3. Obliterative type
- B. Endomyocardial fibrosis (E.M.F.)

II. PRIMARY CARDIOMYOPATHIES

Cardiomyopathies are accompanied by cardiomegaly and severe functional impairment of the myocardium. Most series show a predilection for males.

- A. Dilated type of cardiomyopathy:
1. The cause of this cardiomyopathy is uncertain but a viral etiology is suspected. In this type, the heart is enlarged, the ventricles markedly dilated and the clinical signs are those of systolic pump failure. The morphological changes are nonspecific, but include interstitial fibrosis and long attenuated myofibers. Actual necrosis and inflammatory exudate are rare. Intracardiac mural thrombi are often seen because of depressed cardiac output and stasis. Once symptoms begin, one-half of the patients are dead within a year and two-thirds within two years. The cause of death is heart failure, embolization, or terminal ventricular arrhythmias.



2. Treatment:
a. The only treatment is heart transplantation.
- B. Hypertrophic cardiomyopathy:
1. (also known as ASH, asymmetric septal hypertrophy and IHSS, idiopathic hypertrophic sub-aortic stenosis). The majority of patients with this condition come under observation during the third or fourth decade of life, although the congenital nature of the disease is supported by numerous reported cases of IHSS in infancy and childhood, and the occasional association with other congenital abnormalities and Friedreich's ataxia. The ultrastructural changes seen are reminiscent of the early stages of myocardial embryogenesis. Familial incidence is common and the inheritance is autosomal dominant. In this condition, the interventricular septum is thicker than the left ventricular free wall and the ventricular cavities are reduced in size. There is fibrosis of the L.V. outflow tract. The septal myocardium shows pathognomonic features of severely disorganized multidirectional myocytes. The clinical signs are of diastolic pump failure. Sudden death frequently occurs. Gradually the terms "idiopathic subaortic stenosis" and "obstructive" cardiomyopathy are dwindling in usage and importance, reflecting the realization that hypertrophic cardiomyopathy is essentially a disease of heart muscle rather than an outflow tract obstruction. The understanding of the importance of the diastolic dysfunction manifested by impaired relaxation and irregular filling represents an advance in knowledge of this disease.
 2. Treatment:
a. Includes myomectomy of the outflow tract.
- C. Postpartum cardiomyopathy:
1. This cardiomyopathy manifests itself during pregnancy or within three months following the puerperium. The myocardial changes are similar to that in patients with idiopathic dilated cardiomyopathy occurring in non-puerperal states.
 2. Alcoholic, anthracycline-related, selenium deficiency also cause end stage cardiomyopathies.
- D. Endomyocardial disease or fibrosis (EMF):
1. (Obliterating Restrictive Cardiomyopathy). A disease of unknown etiology characterized by severe focal endocardial fibrosis of one or both ventricles, with underlying subendocardial fibrosis with or without associated



eosinophilia. The fibrosis is predominantly in the inflow tracts of the ventricles and the apices. Mural thrombi often overlay the fibrous plaques. This disease is prevalent in Africans and is sometimes called "Uganda" disease. Clinically this disease presents a "restrictive" pattern of heart function.

SPECIFIC HEART MUSCLE DISEASE

(Secondary Cardiomyopathy in old terminology)

- | | |
|--|---|
| A. Infiltrative: | Amyloid, sarcoid, giant cell, calcium, 1° neoplasm, 2° neoplasm, glycogen, lipids and mucopolysaccharides. |
| B. Inflammatory: | Viral (Coxsackie B&A, echovirus, influenza, infectious mononucleosis), parasitic (trichinosis), protozoal (Chagas', amebic, toxoplasmosis), rickettsial, spirochetes and treponemata. |
| C. Metabolic | Hyper- or hypothyroidism, pheochromocytoma, nutritional (or endocrine): (Beri-Beri and alcoholism), Cushing's disease. |
| D. Neuromuscular: | Progressive muscular dystrophy, Friedreich's ataxia, myotonic muscular dystrophy. |
| E. Collagen Diseases: | Scleroderma, dermatomyositis, systemic lupus erythematosus, rheumatoid arthritis |
| F. Toxins, drugs and physical: | Adriamycin, emetine, carbon tetrachloride, phosphorus, radiation, Adriamycin, emetine, carbon tetrachloride, phosphorus, cobalt, others |
| G. Hypersensitivity and immunologic causes | |

III. SPECIFIC HEART MUSCLE DISEASE

A. Infiltrative:

Amyloidosis is the only common condition in this category and cases fall into two distinct groups: 1) Classical primary type which occurs in patients 45-70 years of age, in which cardiomegaly is prominent and amyloid is plentiful in other organs. 2) Senile cardiac amyloid in 10 % of patients over 70 years of age and is usually confined to the heart. In glycogen and lipid storage diseases, mucopolysaccharidoses and oxalosis enzyme deficiencies are present, while in hemachromatosis the deficiency is in iron absorption. Calcium deposition occurs in generalized metabolic abnormalities in which the serum calcium is high, or in localized areas of degenerative myocardium.



B. Inflammatory:

Inflammatory myocardial disease (myocarditis) has been reported with almost every known pathogenic organism. Coxsackie viruses group B, and to a lesser extent, Group A, are implicated most commonly. Fungal infections are rare and occur typically in immunosuppressed patients. Of the protozoal diseases, toxoplasma myocarditis is well recognized and Chagas' disease (T. Cruzi) is common in South America. Giant cell granulomatous reactions are of unknown etiology, but mycobacteria may be a cause.

C. Metabolic:

Thyrotoxicosis causes cardiac dilation and hypertrophy. "Myxedema heart" is associated with cardiomegaly and a mucinous degeneration of the myocardium. Excessive deposits of adipose tissue are found in patients with hyperadrenocorticism. Focal myocarditis and fibrosis have been observed in patients with pheochromocytoma. In beri-beri (thiamine deficiency) the heart is enlarged and the myocardial institum edematous and focally fibrotic.

D. Neuromuscular Diseases:

In Friedreich's ataxia there is a reported incidence of cardiac involvement in 90% of the cases. The heart is enlarged with hypertrophy of both ventricles and there is a diffuse, reticular fibrosis with a non-inflammatory retrogressive alteration of myofibrils. There is approximately 50% of patients with progressive muscular dystrophy under myocardial changes with diffuse myocardial fibrosis, but with only minor changes in myocytes. In myotonic muscular dystrophy, 60% of patients have cardiac enlargement and failure in which myocyte atrophy and fatty infiltration may occur.

E. Collagen Diseases:

All collagen diseases may affect the myocardium. Rheumatic fever, rheumatoid arthritis, and systemic lupus erythematosus often have a greater effect on the cardiac valves than the myocardium. Scleroderma may cause myocardial fibrosis. Myocardial involvement in dermatomyositis is rare.

F. Toxins and Physical Forces:

Trauma (contusions) and radiation are well recognized causes of myocardial cell damage or interstitial myocardial fibrosis, or both. Many drugs, such as digitalis, isoproterenol, ephedrine, antibiotics and emetine, damage myocardial cells. The anti-neoplastic drug Adriamycin and its analogs may produce cardiotoxicity in large



doses. Cobalt, arsenic, antimony, fluoride, mercury and lead alter myocardial structure and function.

G. Hypersensitivity and Immunologic Cardiac Diseases:

The evidence for the existence of immune mechanisms in myocardial disease to date is inconclusive. The presence of the various anti-heart antibodies, whether circulating or bound to the myocardium, does not necessarily provide a mechanism for an immune disorder of the heart. Several reports of heart-reactive antibodies in patients with cardiomyopathy have shown gamma and immunoglobulins, as well as Complement, bound to the myocardium. Some drugs, e.g., isoniazid, may produce hypersensitivity reaction.

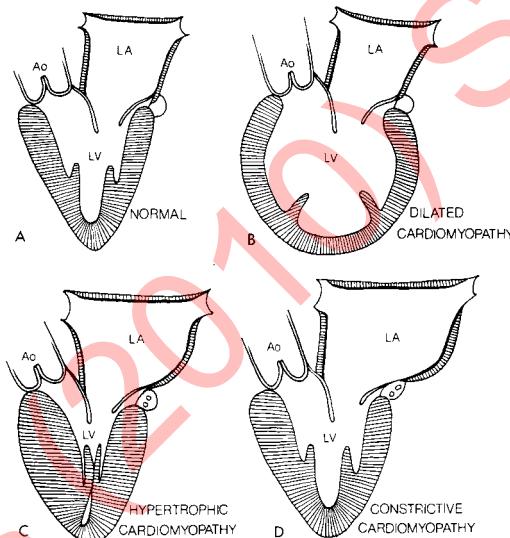


Figure 1: Diagram illustrating the various types of cardiomyopathies, compared to the normal, discussed herein. In the hypertrophic type of cardiomyopathy the left ventricular cavity is small, and in the constrictive variety, as illustrated by amyloidosis, the left ventricular cavity is of normal size. In the dilated type the largest circumference of the left ventricle is not at its base but midway between the apex and base.

IV. REFERENCE

1. Roberts WC and Ferrans VJ: Pathologic Anatomy of the Cardiomyopathies: Idiopathic dilated and Hypertrophic types. Human Path 6:287, 1985.



--Atrial Myxoma-- NEOPLASMS OF THE HEART

INCIDENCE:

Primary neoplasms of the heart are very rare (an incidence 0.02%).

Please note: The tumors are listed for completeness but only myxomas and rhabdomyomas are clinically important.

In common with tumors elsewhere in the body, tumors of the heart pericardium may be classified as benign or malignant.

I. BENIGN:

A. Myxomas:

An exophytic tumor which may fill a cardiac chamber or prolapse through one of the A-V valves. Usually single, they may be multiple occupying multiple chambers. 95% involve atria with 3-4 times predilection for the L.A.

Microscopically: Islands of gland-like structures in sea of mucin.

B. Rhabdomyomas:

1. May be intramyocardial or project into a cavity. Associated with tuberous sclerosis. Rhabdomyomas are circumscribed but they are not encapsulated. Usually seen in infancy or early childhood.
2. Microscopically: Irregular vacuolization of cell cytoplasm producing "spider cells."

C. Lipomas:

1. The most common site is the L. ventricle and the right atrium. Tumor is circumscribed, sessile, polypoid or intramuscular and are often symptomless.
2. Microscopy: Composed of mature fat cells.

D. Fibromas (Fibrohistiocytomas):

More often occur in the interventricular septum of the anterior wall of the left ventricle. They are nonencapsulated and consist of interlacing bundles of fibrous tissue of varying cellularity. Hemangiomas, Lymphangiomas and mesotheliomas also occur.

E. Teratomas:

Exceedingly rare (see Williams GEC: Teratoma of the Heart. J Path Bact 82:281,1961).



F. Tumors of the heart valves:

Fibromas, myxomas, hamartomas and papillary tumors have a predilection for heart valves. One variety is polypoid or flat and occurs in children and the other is papillary and occurs in adults.

II. MALIGNANT

A. Sarcomas:

Either of smooth or skeletal muscle, appear to be the commonest cardiac malignant tumors. Fibrosarcomas, fibromyxosarcomas are exceedingly rare.

- B. Malignant vascular tumors (angiosarcomas), Kaposi's sarcoma, malignant hemangioendothelioma and malignant hemangiopericytomas have been reported.
- C. Primary lymphoma: Involvement may be diffuse, nodular or rarely as an endocardial polypoid growth.
- D. Rare examples of primary cardiac neoplasms include granular cell myoblastoma, neurogenic sarcoma, ganglioneuroma and malignant mesenchymoma.

III. METASTASES

Secondary deposits from malignant-neoplasms elsewhere in the body are the commonest tumors seen in the heart, outnumbering primary benign or malignant cardiac lesions at least 30-fold. Of all patients with disseminated malignant disease, up to 15 percent have cardiac lesions. The commonest primary sites of origin are carcinomas of the lung, breast, large bowel and stomach, followed by malignant lymphoma. While metastases are often asymptomatic, patients may present with cardiac failure, arrhythmias or a pericarditis.

Frequency of Metastases to the Heart
from Various Tumors

Melanoma	50%	Leukemia	36%
Bronchogenic carcinoma	41%		
Breast	20%	Sarcoma	12%

(Remember: melanoma is much less common than lung carcinoma!)

IV. TUMORS OF THE HEART

A. ENDOCARDIAL / INTRACAVITARY TUMORS

1. Myxomas
2. Fibroma, Lipoma, Angioma
3. Teratoma



4. Metastatic Neoplasms (Lung, Kidney, Thyroid)
 5. Osteosarcoma (Atrium or Mitral Valve)
 6. Papillary Fibroelastoma
- B. MYOCARDIAL TUMORS
1. Rhabdomyoma
 2. Fibroma, Lipoma, Hemangioma
 3. Teratoma
 4. Angiosarcoma
 5. Malignant Lymphoma
 6. Metastatic Tumors (Lung, Breast, Kaposi's Sarcoma)
- C. PERICARDIAL TUMORS
1. Lipoma
 2. Malignant Mesothelioma
 3. Metastatic tumors (Lung, Breast, Melanoma)
 4. Leiomyosarcoma



Last Year's (2010) Syllabus

Endothelium and Coronary Circulation

I. VASCULAR ENDOTHELIUM: A MULTIFUNCTIONAL INTERFACE

- A. The entire circulatory system is lined by a continuous, single-cell-thick layer --- the vascular endothelium. Despite its microscopic dimensions (often less than 1 micron in thickness), this living membrane is a multifunctional organ whose health is essential to normal vascular physiology and whose dysfunction can be a critical factor in the pathogenesis of vascular disease. Anatomically, the endothelium forms the physical boundary separating the intravascular compartment from all of the tissues and organs of the body. Biologically, this interface supports a number of vital functions.
- B. First and foremost, the endothelium comprises a “container” for blood. As long as this cellular membrane remains intact and is functioning normally, a non-thrombogenic surface is presented to the circulating blood, thus allowing it to remain fluid and perform its nutritive functions unimpeded by intravascular clotting. Physical disruption of the endothelial lining, even on a microscopic scale, elicits an immediate hemostatic response, involving localized activation of the coagulation cascade and the adherence and aggregation of platelets, an adaptive reaction that serves to limit blood loss at sites of injury. Conversely, acute or chronic impairment of the non-thrombogenic properties of the intact endothelial lining (a form of endothelial dysfunction, see below) can be an important predisposing factor for intravascular thrombosis.
- C. Because of its unique anatomical location the endothelium also functions as a selectively permeable barrier. Macromolecules encountering various regional specializations of the endothelium, including cell surface glycocalyx, cell-cell junctional complexes, microvesicles, transcellular channels and subendothelial extracellular matrix, are enhanced or retarded in their movement from (or into) the intravascular space. Selectivity of this barrier function typically reflects the size and/or charge of the permeant molecule, but may also involve active metabolic processing on the part of the endothelial cell. Enhanced permeability to plasma macromolecules, such as albumin, is a hallmark of acute inflammation, and, in the case of lipoproteins, is an important part of atherosclerotic lesion development. Pathophysiologic stimuli, as well as therapeutic drugs, that can modulate this endothelial function thus have potential clinical relevance.



- D. Another functionally important consequence of the location of the endothelium is its ability to monitor, integrate and transduce blood-borne signals. Through expression of cell surface receptors for various cytokines (IL-1 α , β , TNF- α , IFN- γ , TGF- β), growth factors and other hormones (e.g., basic FGF, VEGF/VPF, insulin and insulin-like growth factors), as well as bacterial products, (e.g., Gram-negative endotoxins and related binding proteins), and their intracellular coupling, via second messenger cascades, to the metabolic and transcriptional generation of other biological effector molecules, endothelial cells function as important tissue response regulators. At every site in the circulatory system they are sensing and responding to the local pathophysiological milieu, and can help propagate these responses transmurally, from the intimal lining into the walls of larger vessels (e.g., coronary arteries), or from the luminal surface of capillaries directly into the interstitium of adjacent tissues (e.g., myocardium). As will be considered in more detail below, this sensing and transducing function extends beyond classical humoral stimuli to the biotransduction of distinct types of mechanical forces generated by pulsatile blood flow (e.g., fluid shear stresses, circumferential wall stress and transmural pressure).
- E. Endothelium is capable of generating a diverse array of biologically active substances, including lipid mediators, cytokines, growth factors and other hormone-like substances, many of which serve as important biological effector molecules, influencing the behavior of multiple cells and tissues. Some act directly within their cell of origin in a so-called autocrine mode, whereas others act on adjacent cells (within the vessel wall or in the blood) in a paracrine mode. And, yet other endothelial-derived mediators, such as hematopoietic colony-stimulating factors (GM-CSF, M-CSF) are secreted into the circulation to act at a distance, analogous to classical hormones. In addition to being the source of cytokines, growth factors and hormones, the endothelium also is an important target of their actions. Indeed, the capacity for the endothelium to undergo, local or systemic, "activation" in response to such stimuli, with resultant dramatic changes in functional status, is an important aspect of its biology and pathobiology. First demonstrated in the case of MHC-II histocompatibility antigen upregulation by T-lymphocyte products¹², and then extended to the induction of procoagulant tissue factor activity and endothelial-leukocyte adhesion molecules by inflammatory cytokines and bacterial endotoxin, the phenomenon of "endothelial activation" has become an important paradigm for modulation of endothelial phenotype. It provides a conceptual model that encompasses both physiological adaptation and pathophysiological dysregulation.



- F. Given its interface location, integrating and transducing capability, and the vast repertoire of its biologically active products, the endothelium plays a pivotal role in a series of "pathophysiologic balances. In each, endothelial-derived agonists and antagonists dynamically interact in the regulation of important processes that can have both local and systemic ramifications, such as hemostasis and thrombosis, vascular tone, vascular growth and remodeling, and inflammatory and immune reactions. At any given time, factors influencing the activation state or functional integrity of the endothelium determine the relative set-points of each of these balances. For example, the intact, unactivated endothelial lining is non-thrombogenic, because the net activity of antithrombotic factors, such as prostacyclin, thrombomodulin, cell surface heparin-like glycosaminoglycans and ecto-ADPases, exceeds that of the various pro-thrombotic factors potentially also generated by the endothelium. The controlled expression of certain of these pro-thrombotic factors in response to local vascular trauma (e.g., thrombin-induced von Willebrand factor release) can function adaptively, as part of a response-to-injury reaction; conversely, decreased production of anti-thrombotic factors (e.g., prostacyclin, tissue plasminogen activator) may contribute to intravascular thrombosis and vital organ damage.
- G. Similarly, imbalances in endothelial-derived smooth muscle relaxants versus endothelial-derived vasoconstrictors can influence local circulatory dynamics, as well as systemic blood pressure. Indeed, the endothelium is the source of some of the most potent naturally occurring vasoactive substances known, including nitric oxide and related substances (originally described as an EDRF, or "endothelium-dependent relaxing factor", by Furchtgott and Zawadski) and endothelin-1, a novel peptide that resembles the lethal toxin in the venom of certain vipers whose bite can induce coronary vasospasm. Other factors in this endothelial vasomotor balance include prostacyclin, angiotensin II (generated by angiotensin converting enzyme at the luminal interface) and platelet-derived growth factor. The latter substance can be generated by endothelial cells and, in addition to its mitogenic properties, also is a potent smooth muscle contractile agonist.
- H. Under normal conditions, the cells of the vessel wall are essentially growth quiescent, but following experimental endothelial denudation, a burst of medial smooth muscle migration and division is triggered, which then subsides as endothelial regeneration occurs. This well orchestrated wound healing response presumably reflects not only the localized generation or release of growth stimulators but also a transient, relative deficiency in endothelial-derived growth inhibitors. The resultant intimal hyperplasia is very similar to that which occurs in early atherosclerotic lesions. The



more complex issues of sustained smooth muscle hyperplasia, secondary to immune-mediated endothelial damage in transplant-associated arteriosclerosis, or in the post-angioplasty setting, as well as the interplay of angiogenic and anti-angiogenic factors in neovascularization phenomena in ischemic myocardium and peripheral tissues may also reflect imbalances in endothelial-derived growth regulators.

- I. Taken together, the above overview provides a working concept of the vascular endothelial lining as a dynamically mutable, multifunctional interface that can actively participate in a number of biologically important interactions. In the next section, we will examine how certain types of pathophysiologic stimuli can provoke endothelial dysfunction, and explore some of the consequences for the pathogenesis of vascular disease.
- II. **MYOCARDIAL OXYGEN DEMAND AND SUPPLY**
 - A. Since the primary function of the coronary circulation is to supply the heart's metabolic needs, any discussion of the physiology of the coronary circulation must begin by emphasizing the unusually close relationship between myocardial metabolism and perfusion. This relationship is illustrated schematically in Figure 1. The left-hand side of the balance represents myocardial oxygen demand. Since the heart has a limited and short-lived capacity for anaerobic metabolism, its metabolic needs can be considered solely in terms of oxidative metabolism. The major determinants of myocardial oxygen demand include wall stress, contractile state, and heart rate. According to Laplace's law, wall stress is directly proportional to blood pressure and radius of curvature and inversely proportional to wall thickness. Systolic blood pressure is often used as an estimate for myocardial wall stress, and increases in blood pressure are associated with similar increases in wall stress. Contractility, which includes the velocity and magnitude of myocardial contraction, is the second major determinant of myocardial oxygen consumption. In the intact heart, sympathetic stimulation, and catecholamine or calcium administration can result in a substantial increase in myocardial oxygen consumption related to the increased contractility. Heart rate is the final important determinant of myocardial oxygen demand, and there is a direct relationship between heart rate and myocardial oxygen consumption. The role of heart rate is probably related to the increased number of contractions per minute, although increases in heart rate are associated with increased contractility as well.



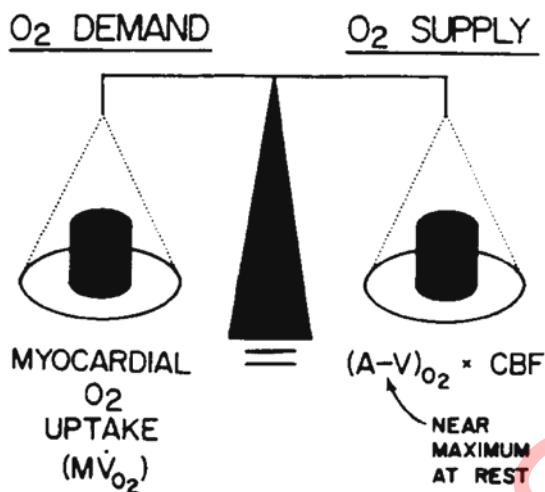


Figure 1. Schematic representation of the normal balance between myocardial oxygen demand and supply. $(A-V)_{O_2}$ = arterial-venous oxygen difference; CBF = coronary blood flow. From Klocke FJ, Coronary blood flow in man, Prog Cardiovasc Dis, 19:117, 1976.

- B. The right-hand side of the balance in Figure 1. represents myocardial oxygen supply **and**, according to Fick's law, can be expressed as the product of coronary blood flow and the coronary arterial-venous oxygen difference. One of the unique features of the coronary circulation is its high degree of oxygen extraction under basal conditions. Coronary sinus blood is typically only 20-30% saturated, making it difficult for the heart to adjust to increasing metabolic needs by increasing oxygen extraction. Therefore, changes in myocardial oxygen consumption require changes in coronary flow which are similar in both direction and magnitude. The ability of the myocardium to regulate its flow according to its oxygen requirements is known as autoregulation, and coronary flow can increase 3-6 fold in response to increasing oxygen demand. In the absence of disease coronary blood flow is tightly coupled to changes in metabolic requirements of the myocardium.
- C. To understand factors modulating coronary flow, it is necessary to consider in some detail the relationship among coronary flow, driving pressure, and vascular resistance. The hydraulic equivalent of Ohm's Law, $Q=AP/R$, has traditionally been used to express the relationship between coronary flow (Q), and the parameters which modulate it, i.e. driving pressure (AP) and resistance (R). Driving pressure is usually taken as the difference between arterial pressure and right atrial pressure, but the latter is low in the normal circulation, and the equation is often simplified to $Q=Pa/R$, where Pa = aortic pressure.



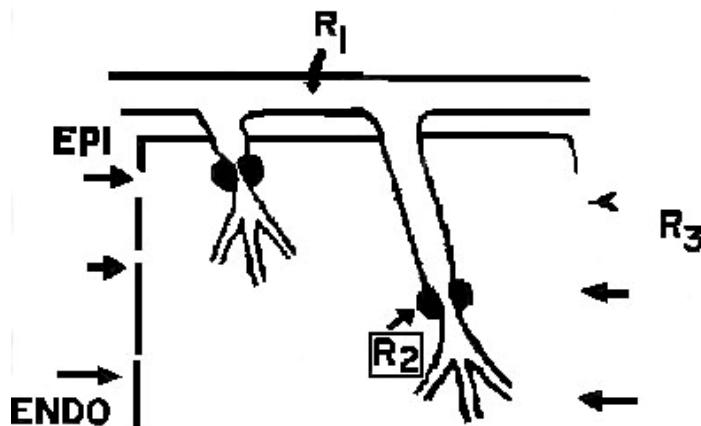


Figure 2. Diagram of a transparent segment of myocardium illustrating the different components of resistance in the normal situation. R₁ = basal viscous

- D. Coronary vascular resistance (R) has been modeled to be the sum of three physiologic components which are illustrated in Figure 2. R₁, or basal viscous resistance, originates in the large and medium-sized arteries and arterioles and relates to the cross-sectional area in these vessels. It is the minimum possible resistance of the system during diastole with the coronary bed fully dilated and is constant over long periods of time. R₂, or autoregulatory resistance, is the major component of resistance and is thought to result from vascular smooth muscle tone in the arteriolar walls. This component of resistance is normally 4-5 times larger than R₁. Changes in its magnitude can occur in a single cardiac cycle in response to changes in myocardial metabolic requirements, with maximal vasodilatation occurring in as little as 15-20 seconds. R₂ has traditionally been considered the primary mechanism which allows coronary flow to change in response to changing myocardial oxygen demand. R₃ or compressive resistance, is due to compression of myocardial vessels and results from intramyocardial pressure. Compressive resistance varies during a single cardiac cycle and is especially large during systole. All three of these functional components of coronary vascular resistance can vary regionally, temporally, and transmurally, and this will be discussed subsequently.



III. TEMPORAL AND TRANSMURAL HETEROGENEITY OF CORONARY FLOW

- A. Figure 3 illustrates the effects of cyclical changes in R₃ on overall flow and resistance in the coronary bed during a single cardiac cycle. Note that overall coronary resistance is 3-4 fold greater in systole than in diastole and results from increased compressive resistance (R₃) during systole when intramyocardial forces are large. As a result, there is a marked difference in systolic and diastolic flow, and, in fact, only 15-20% of the total flow to the left ventricle occurs during systole. This is not the case for the less muscular right ventricle which receives a large proportion of its blood flow during systole as well as diastole (see Figure 4.)

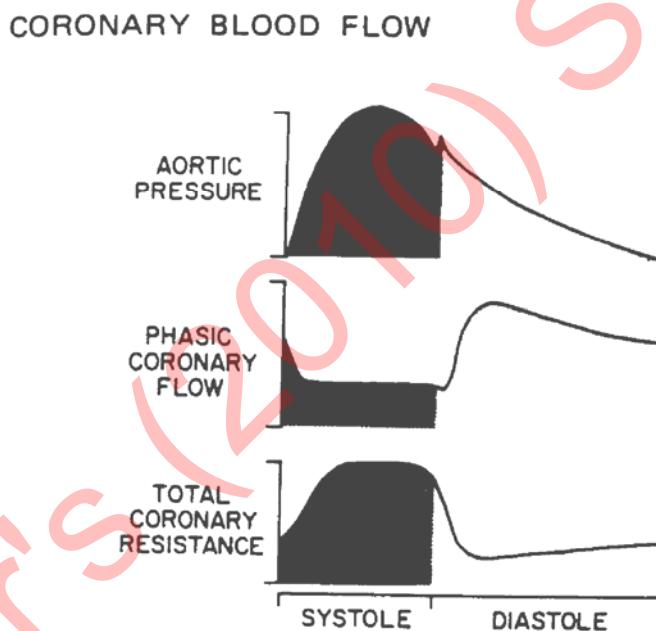


Figure 3. Tracings of recordings of aortic pressure, coronary flow, and calculated coronary vascular resistance from a conscious animal. Resistance is appreciably greater during systole than diastole because of the compressive component of resistance. From Klocke FJ, Coronary blood flow in man, Prog Cardiovasc Dis, 19:1 17, 1976.

- B. An additional important factor which is not illustrated in Figure 3 is the variation in the magnitude of R₃ across the myocardial wall. This variation is a consequence of the normal transmural distribution of intramyocardial pressure during systole (Figure 2). While its detailed pattern remains unsettled, R₃ is definitely greater in the subendocardium than it is in the subepicardium. The normal transmural gradient in R₃ implies that a disproportionately low fraction of coronary flow reaches the subendocardium during systole, and, in fact, it may cease entirely in the inner-most layer of



the myocardium. This situation has important consequences for the autoregulatory component of resistance. (R₂) since overall flow per gram of tissue is normally equal in all transmural layers of the left ventricle, averaging 75-100 ml/min per 100 grams of tissue. To counteract this diminished subendocardial perfusion during systole, a correspondingly greater amount of flow needs to be delivered to the inner layers of the left ventricle during diastole. This is accomplished by a selective reduction of autoregulatory tone (R₂) in the subendocardium, allowing it to be perfused at a higher rate than the subepicardium during diastole.

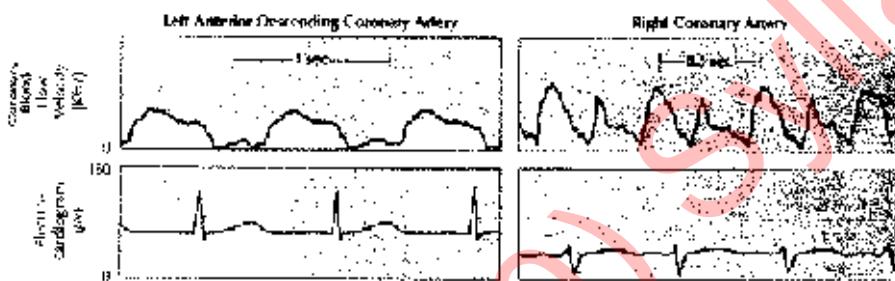


Figure 4. Phase coronary blood flow velocities during open heart surgery. The systolic component of coronary blood flow is much greater in the vessels supplying the right as compared to the left ventricle. (from Marcus, Hospital Practice, 1986)

- C. Therefore, the subendocardial arterioles are relatively vasodilated in the basal state, permitting the subendocardium and subepicardium to receive the same overall flow rates. Figure 5 shows an expansion of Ohm's Law which has been applied to different portions of the myocardium during systole and diastole. This figure illustrates that, while systolic compressive resistance is greater in the subendocardium than in the subepicardium, autoregulatory resistance is normally less, thereby allowing the subendocardium to make up its relative systolic flow deficit during diastole.

IV. CORONARY RESERVE

- A. Figure 5 also allows the concept of coronary reserve to be examined. As mentioned previously, the autoregulatory component of resistance (R₂) exhibits a substantial degree of tonic constriction under basal conditions. During periods of increased myocardial oxygen demand, this arteriolar tone can decrease sufficiently to allow flow for the entire cardiac cycle to increase 3-6 fold. The normal circulation, therefore, possesses a reserve capacity for vasodilation which is of pivotal importance during stress, exercise and in pathological states. Figure 5 illustrates that coronary reserve is not uniform across the myocardial wall, but is less in the subendocardium than in the subepicardium. A portion of this potential reserve is required to overcome the effects of



compressive resistance (R_3) in the subendocardium, which is therefore more vulnerable to ischemia than is the subepicardium.

	<u>SYSTOLE</u>	<u>DIASTOLE</u>
SUBEPI-CARDIUM	$\dot{Q} = \frac{\Delta P}{R_1 + R_2 + R_3}$	$\dot{Q} = \frac{\Delta P}{R_1 + R_2 + R_3}$
SUBENDO-CARDIUM	$\dot{Q} = \frac{\Delta P}{R_1 + R_2 + R_3}$	$\dot{Q} = \frac{\Delta P}{R_1 + R_2 + R_3}$

Figure 5. Application of Ohm's Law to different portions of the myocardium in systole and diastole. \dot{Q} = coronary flow; ΔP = driving pressure; $R_{1,2,3}$ = viscous, autoregulatory, and compressive components of coronary resistance.

- B. The ability of the autoregulatory component of resistance (R_2) to regulate local myocardial blood flow according to its oxygen requirements allows two additional points to be discussed. First is the autoregulation curve which is shown in Figure 6. In this figure, coronary flow is plotted as a function of arterial pressure. When myocardial oxygen demand is constant, flow is constant over a wide range of perfusion pressures. This is known as the autoregulatory range and extends from 60-140 mmHg. Within this range of pressures, changes in arteriolar tone (R_2) can maintain flow constant in the face of a reduction in driving pressure. At an arterial pressure of about 60 mmHg, the arterioles are maximally vasodilated, and further decrements in arterial pressure are associated with a decrease in coronary flow. Autoregulatory resistance also explains the occurrence of myocardial reactive hyperemia, i.e., the excess blood flow which follows a period of arterial occlusion. Figure 7 is a record of aortic pressure and coronary flow in a conscious animal and illustrates the hyperemic response following a brief period of coronary artery occlusion. The volume of flow of which the heart is deprived by the interval of coronary occlusion is known as flow debt; it is calculated as the product of control flow rate and the duration of the occlusion. Reactive hyperemic flow is the volume of flow in excess of the control rate and is equal to the difference between the total reactive hyperemic flow and control flow. Experimental studies indicate that flow debt is usually greatly overpaid, and the repayment of flow debt, i.e. the ratio of hyperemic flow to control is typically 300-400%.



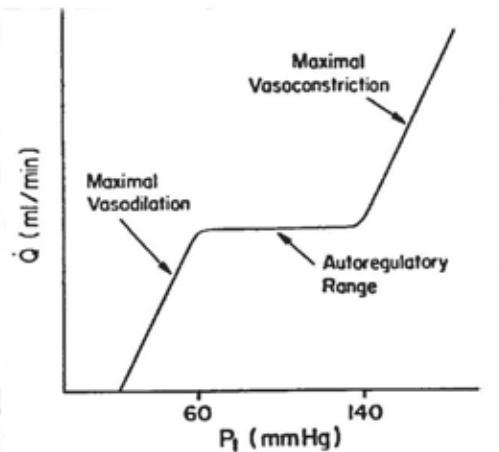


Figure 6. The autoregulation curve. Note that coronary flow (Q) is independent of arterial inflow pressure (P_1) when the latter is between 60 and 140 mmHg.

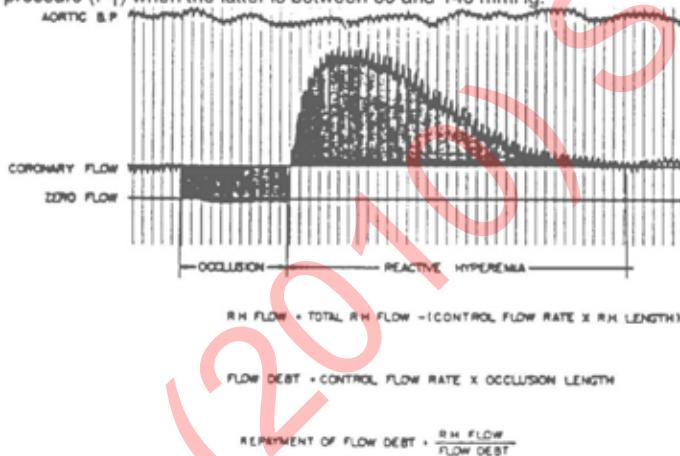


Figure 7. Myocardial reactive hyperemia. Each time line indicates a 1-sec. interval. R.H. = reactive hyperemia. From Olsson , Myocardial reactive hyperemia, *Circ Res*, 37:263,1975.

- C. The myocardial reactive hyperemic response is predictable in that the volume of hyperemic flow is determined by both the duration of coronary occlusion and the control flow rate. The peak flow rate during reactive hyperemia increases with increasing length of occlusion up to occlusions lasting 15-30 seconds, longer occlusions do not increase the magnitude of peak flow, indicating that this degree of ischemia causes maximum vasodilation of the coronary bed (i.e. R_2 is at a minimum) in order to further discuss autoregulatory resistance, it is necessary to consider those factors which regulate coronary blood flow.

V. CONTROL OF CORONARY BLOOD FLOW

- A. Coronary vascular smooth muscle is subject to neural, humoral, metabolic, and myogenic and endothelial influences, all of which may modulate autoregulatory resistance (R_2). Studies of neural mechanisms for adjusting coronary resistance have suggested the presence of direct adrenergic innervation involving both constrictor and dilator mechanisms (see Table 1). The former predominates,



and there is an alpha-adrenergic mechanism which normally exerts a tonic vasoconstriction influence on coronary vascular smooth muscle; it serves as a restraint on the ability of the coronary bed to vasodilate during stress. Both beta-adrenergic (Beta-2) vasodilatory influences as well as cholinergic vasodilatory influences have been demonstrated in animals, but their role in regulating the tone of the resistance vessels in man is unclear. The interactions of cholinergic stimulation and the endothelium will be discussed later.

Autonomic Receptors that Influence Various Classes of Coronary Vessels

<u>Receptors Activated</u>	<u>Large Conduit Vessels</u>	<u>Small Resistance Vessels</u>	<u>Coronary Collateral Vessels</u>	<u>Endo-Epicardial Ratio</u>
B ₁	Dilate	?	Dilate	?
B ₂	No effect	Dilate	Small dilator effect	No change
alpha ₁	Constrict	> 50 µm constrict < 50µm dilate*	No effect	No change
alpha ₂	Dilate	> 50 µm constrict < 50 µm dilate*	No effect	No change
muscarinic ₁ and muscarinic ₂	Dilate **	Uniform dilate	?	Perfusion response to ACh increased

* Not certain if this is alpha 1 or 2. **via EDRF release

Table 1. Autonomic control of coronary blood flow. (from Marcus, Hospital Practice, 1988)

- B. The myogenic hypothesis for control of coronary perfusion was originally proposed by Bayliss in 1902. According to this theory, blood vessels are intrinsically able to respond to changes in intraluminal arterial pressure. Increases in blood pressure increase the distention of the blood vessel which in turn stimulates contraction of the vascular smooth muscle. Similarly, decreases in arterial pressure result in vasodilation. In this way, decreases in perfusion pressure are met with a decrease in resistance, allowing flow to remain constant (c.f. autoregulatory range in Figure 6). Recent studies suggest that in certain vascular beds, possibly including human coronary arteries, the vasoconstriction observed in conductance arteries in response to increasing intraluminal pressure may be due to the release of endothelial-derived



constricting factors (EDCFs), rather than intrinsic smooth muscle "myogenic" tone.

- C. Of all factors considered to be involved in the control of autoregulatory resistance, metabolic factors appear to play the largest role. For a substance to be proved an important mediator of the coronary dilatation associated with increased myocardial O₂ consumption, it must fulfill several criteria: 1) have potent vasoactive properties, produced endogenously in the vicinity of coronary resistance vessels, 2) must be able to be released in a cardiac cycle and have maximal effect in < 20 seconds, 3) infusion should mimic metabolically induced dilatation and blockade must prevent metabolically induced vasodilatation, 4) changes in concentration in the vicinity of resistance vessels should precede and parallel changes in metabolically induced dilatation.
- D. Numerous agents, including adenosine, prostaglandins, oxygen tension, carbon dioxide tension, lactic acid, hydrogen, potassium, phosphate, and pH have, at one time or another, been proposed as "the" metabolic regulator of resistance. All of these agents are endogenously produced potent vasodilators that fulfill at least some of the above criteria. However, none of these substances satisfies all of the criteria and none has been established as the primary biochemical coupling agent between increased myocardial O₂ demand and coronary vasodilation. After the release of a 20-second coronary occlusion, a prolonged hyperemic response occurs. During the dilator phase the myocardial concentration of C₀₂, hydrogen, potassium and oxygen are nearly opposite of what might be expected if they were the mediator of the vasodilator response. Blockade of adenosine or prostaglandins does not dramatically attenuate this hyperemic response. Although adenosine was at one time considered the primary biochemical mediator of metabolic autoregulation, adenosine blockers do not alter the close coupling between myocardial perfusion and myocardial O₂ consumption during exercise. Thus, none of the current candidates survive intense scrutiny. The search continues for this elusive messenger that couples myocardial oxygen consumption and coronary vascular resistance.



VI. IMPORTANCE OF ENDOTHELIUM IN CONTROL OF CORONARY ARTERIAL TONE

- A. During the last 7-8 years it has been recognized that the coronary endothelium is a dynamic organ which plays an important role in the regulation of coronary artery tone, particularly in the epicardial (conductance) vessels. In 1981 Furchtgott reported the important observation that relaxation to acetylcholine in rabbit aortas is dependent upon an intact endothelium. Since that time it has been shown that normal coronary endothelium in animals and in humans releases an endothelium-derived relaxing factor or factors (EDRFs) in response to a variety of pharmacologic and physiologic stimuli (see Figure 8).

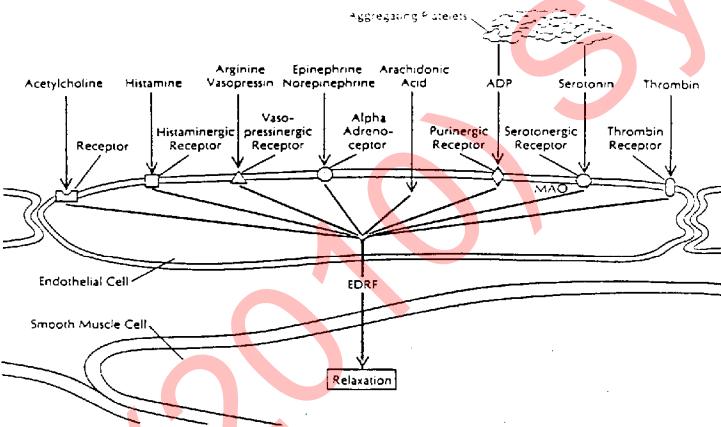


Figure 8. In response to increasing blood flow and a wide variety of biochemical stimuli, coronary endothelium may release EDRF, leading to smooth muscle relaxation. The local release of EDRFs and/or EDCFs may have powerful effects on the tone of underlying smooth muscle (from Vanhoutte, Hospital Practice, 1988).

At least one of these EDRFs appears to be nitric oxide, and mediates smooth muscle relaxation via a mechanism analogous to the nitrovasodilators (activation of guanylate cyclase -, increased cGMP etc.). The importance of these observations are that in areas of endothelial injury or dysfunction humoral substances (e.g., serotonin released from aggregating platelets) may provoke coronary vasoconstriction rather than dilatation, resulting in spasm and ischemia. Recent studies have also suggested that increases in coronary blood flow (e.g. during exercise) cause epicardial coronary dilatation that is mediated by flow-mediated release of EDRF. Both flow-mediated and muscarinic endothelium dependent relaxation in human epicardial coronary arteries appears to be impaired in the setting of atherosclerosis, and may be a contributing factor in resting and/or exercise-induced ischemia.

- B. Finally, as mentioned briefly in a preceding section, there has been increasing interest in endothelium-derived constricting factor(s) (EDCFs). It appears that there are at least two such agents which may participate in the autoregulation process and may also be



released in pathologic settings such as hypoxemia or reperfusion of chronically occluded coronary arteries.

VII. PATHOPHYSIOLOGY IN CORONARY ARTERY DISEASE

- A. Figure 9 utilizes the functional model described above to contrast the normal pattern of perfusion with that encountered in coronary artery disease. The left-hand portion of the figure represents a segment of myocardium perfused through a normal coronary artery, while the right-hand portion illustrates an adjacent segment perfused through a diseased vessel. The effect of partial occlusion has been represented as an increase in the magnitude of viscous resistance (R_1). This increase in (R_1) is accompanied by a compensatory decrease in autoregulatory resistance (R_2): the myocardium calls on its normal vasodilatory reserve to maintain total resistance, and therefore, total flow at the normal level.
- B. The effects of partial coronary artery occlusion on coronary perfusion are complex. Figure 10 illustrates flow across mild and severe stenoses (upper and lower panels, respectively). As shown schematically in the upper panel, flow is altered only slightly by a mild stenosis (i.e. 10-20% arterial narrowing); the flow is laminar and "reattaches" to the vessel wall downstream of the stenosis. The relationship between pressure drop across the stenosis and flow across the stenosis is linear, and there is little energy loss across the stenosis. With more severe stenoses, however, flow separates from the vessel wall downstream of the stenosis, and local turbulence results. A significant amount of energy is lost, and pressure drop across the stenosis is proportional to the second power of flow.
- C. Figure 11 examines in more detail the relationship between degree of stenosis and coronary perfusion. The left-hand panel illustrates that stenosis resistance is proportional to the square of the severity of the stenosis. Changes in lesion severity associated with mild lesions (e.g. 10-20% stenoses) are associated with only small increases in coronary vascular resistance. On the other hand, rather remarkable increments in resistance can occur with minimal progression of a stenosis in the 80-90% range.



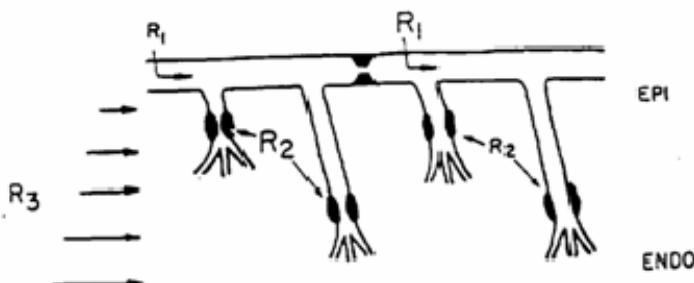


Figure 9. Schematic diagram of a segment of myocardium illustrating the different magnitudes of the components of coronary resistance in the normal situation (left-hand portion of diagram) and in coronary artery disease (right-hand portion of diagram). Epi - subepicardium; endo = subendocardium; R_{1,2,3} - viscous, autoregulatory, and compressive components of coronary resistance. From Klocke, FJ, Coronary blood flow in man, *Prog Cardiovasc Dis*, 19:117, 1976.

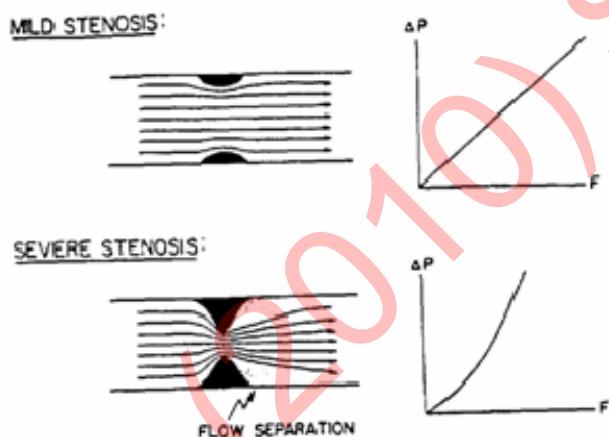
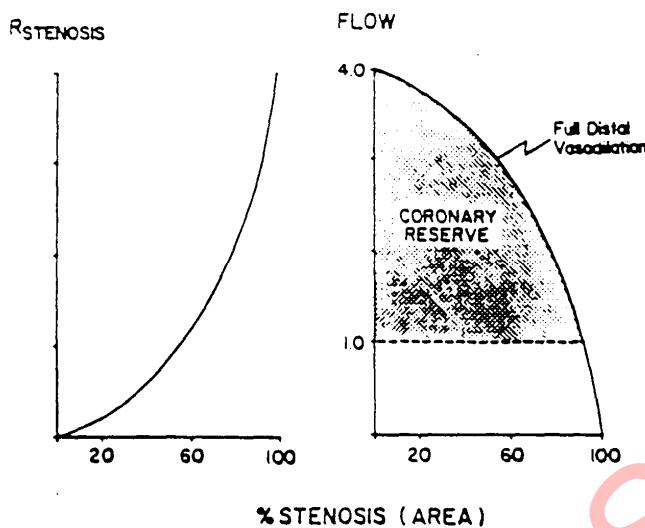


Figure 10. Velocity profiles and pressure-flow relationships for mild and severe stenoses. ΔP = pressure drop across the stenosis (mmHg), F = flow across the stenosis (ml/min). From Klocke FJ and Ellis AK, Control of coronary blood flow, *Ann Rev Med*, 31:489, 1980.





The right-hand panel of the figure schematically summarizes the relationship between coronary flow and percent stenosis in the intact coronary bed. Basal flow is designated by an arbitrary value of 1.0, and available coronary reserve is represented by the shaded area above this value. The normal situation is represented by 0% stenosis, and coronary reserve is taken as four-fold. As a stenosis develops, reserve begins to be compromised, although with a 10-20% stenosis significant reserve nonetheless exists. The degree of compromise increases significantly at higher degrees of stenosis, and coronary reserve is exhausted at about 85% obstruction. When the degree of stenosis is in this range, large reductions in flow are produced by small additional increments in the degree of obstruction. With stenoses greater than 85%, basal flow becomes compromised, and myocardial ischemia occurs even at rest.

VIII. PREDICTION OF MYOCARDIAL OXYGEN DEMAND AND PERfusion

- A. As mentioned previously, prevention of myocardial ischemia requires a balance between oxygen requirements on one hand and oxygen supply on the other. While this balance is true for the heart as a whole, it is also true for each region of myocardium, and regional variations in both oxygen requirements and local flow may explain why ischemic lesions tend to occur in certain parts of the heart. There is a convincing body of evidence which suggests that both naturally occurring and experimentally produced infarcts are often confined to, or more marked in, the subendocardial muscle of the left ventricle. Coronary reserve is exhausted earlier in the inner layers of the heart under most conditions. Once reserve has been exhausted, further increases in oxygen requirements will result in ischemia, reflecting the inadequacy of flow despite full utilization of coronary reserve mechanisms.



- B. Over the years, attempts have been made to try to define hemodynamic indices which would predict when subendocardial ischemia is likely to occur. The myocardial supply-demand ratio is one such index which allows the adequacy of blood flow to the subendocardium to be estimated. As illustrated in Figure 12, DPTI, the diastolic pressure-time index, is the area between the arterial and left ventricular pressure curves during diastole. It reflects myocardial oxygen supply and represents the average time and driving pressure available for perfusing the myocardium; this is particularly true for the subendocardium which is perfused only in diastole. The denominator of the ratio, SPTI, the systolic pressure-time index, is the area under the left ventricular pressure curve during systole and reflects myocardial oxygen demand. When the DPTI:SPTI ratio (normally 1.5 at rest) falls below 0.4, coronary reserve is ordinarily exhausted, and local perfusion, especially in the subendocardium, may fall short of oxygen requirements.

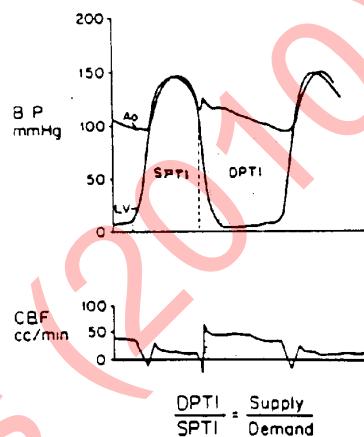


Figure 12 Upper panel: superimposed left ventricular (LV) and aortic (Ao) pressure tracings. The shaded area is the difference between the two pressures in diastole--the diastolic pressure-time index (DPTI). The area under the LV pressure tracing during systole (but not including isovolumic relaxation) is taken as the systolic pressure-time index (SPTI). Lower panel: recording of coronary flow. The shaded area indicates diastolic flow and accounts for 75-85% of flow for the entire cardiac cycle. From Vincent WR, Buckberg GD, and Hoffman JIE, Left ventricular subendocardial ischemia in severe valvar and supravalvar aortic stenosis, *Circulation*, 49:326, 1974.



IX. CONCLUSION

In summary, myocardial viability requires a balance between oxygen supply and demand. Coronary reserve is the ability of the arterioles to vasodilate in response to increasing metabolic demands and results in increased coronary flow. Coronary reserve is not uniform in all areas of the heart and is less in the subendocardium than in the subepicardium due primarily to increased compressive forces (R3) in the subendocardium. As a result, the subendocardium is less able to increase flow to meet increasing metabolic demands and is particularly susceptible to the development of ischemia, particularly in the setting of obstructive coronary artery disease. The concept of diastolic and systolic pressure-time indices allows prediction of circumstances in which subendocardial ischemia is likely to occur. The importance of the coronary endothelium in regulating coronary artery tone and responses to increased flow and/or pressure is becoming increasingly recognized.

X. REFERENCES

1. Berne and Levy, *Cardiovascular Physiology*, 1986. 5th Ed., Chapter 10.
2. Marcus ML, The regulation of myocardial perfusion in health and disease. *Hospital Practice*, pp.105-132, July 1988.
3. Vanhoutte PM, The endothelium and control of coronary arterial tone, *Hospital Practice*, pp.67-84, May 1 1988.

XI. CORONARY BLOOD FLOW -- CLINICAL CORRELATES

Ischemia/Angina = A supply/demand mismatch

Augmenting Supply:

A. MECHANICAL

1. Intraaortic counterpulsation devices (IABP)
 - a. Diastolic augmentation
2. Coronary Angioplasty (PTCA)
 - a. Balloon Angioplasty
 - b. Directional atherectomy
 - c. Laser Angioplasty
3. Coronary bypass surgery (CABG)
 - a. Vein grafts
 - b. Internal mammary artery grafts

B. PHARMACEUTICAL

1. Nitrates/ Calcium Channel Blockers
 - a. Potentially dilates R1 and R2 resistance vessels
2. Aspirin



- a. Mitigates platelet aggregation/ coronary thrombosis
- 3. Cholesterol reducing agents
 - a. Potential plaque regression

Reducing Demand:

- A. PHARMACEUTICAL
 - 1. HEART RATE: Beta blockers (Propranolol, metoprolol, atenolol)
 - 2. CONTRACTILITY: Beta Blockers, Calcium channel blockers
 - AFTERLOAD: Nitrates, anti-hypertensive medications
 - PRELOAD: Nitrates, diuretics
- B. MECHANICAL
 - 1. Intraaortic balloon pump
 - 2. Cardiopulmonary bypass



Last Year's (2010) Syllabus

ANGINA PECTORIS

I. WHAT IS IT?

- A. A clinical syndrome first defined by Heberden: "But there is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, which deserves to be mentioned more at length. The seat of it, and sense of strangling, and anxiety with which it is attended, may make it not improperly be called angina pectoris."
- B. They who are afflicted with it, are seized while they are walking, (more especially if it be up hill, and soon after eating) with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to increase or to continue; but the moment they stand still, all this uneasiness vanishes.
- C. In all other respects, the patients are, at the beginning of this disorder, perfectly well, and in particular have no shortness of breath, from which it is totally different. The pain is sometimes situated in the upper part, sometimes in the middle, sometimes at the bottom of the sternum (os sterni), and often more inclined to the left than to the right side. It likewise very frequently extends from the breast to the middle of the left arm."

II. WHAT CAUSES THE PAIN?

- A. Specifically this is unknown.
- B. Pain fibers probably do not originate from the myocardium. They may arise from coronary vascular structures.
- C. The nerve roots which innervate the heart C-4 to T-6 are the same ones which receive innervation from the cutaneous dermatomes serving the neck, shoulders, arms and upper and mid-chest. We assume that this is the reason why myocardial ischemic pain is usually referred to those areas.
- D. The myocardial site of ischemia is not related to the location of pain perceived by the patient, and ischemia may be entirely painless, manifesting itself by conduction disturbances, increased ventricular automaticity or altered mechanical function of the heart.
- E. We know from experience with patients who have undergone myocardial transplantation and who have no host-graft nervous connections that ischemia, and even myocardial infarction, may take place painlessly.



III. BLOOD SUPPLY

- A. The origin of the coronary arteries is normally in the aorta just distal to the aortic valve. The right coronary ostium feeds the right coronary artery (RCA) which travels rightward in atrioventricular (AV) groove, sending branches to the thin walled right ventricle (RV) until it reaches the posterior interventricular septum; it then usually sends a major branch, the posterior descending artery (PDA) from the AV groove, along the diaphragmatic surface of the heart in the interventricular groove toward the apex. Branches from the PDA ascend within the IV septum and may serve as a source of collateral vessels from the RCA to the left coronary system.

The left coronary ostium opens onto the left main coronary artery (LMCA) which rapidly bifurcates and forms the left anterior descending artery (LAD) and the left circumflex artery (LCx). The LAD descends along the anterior interventricular septal groove toward the apex, sending perforating branches into the septum and diagonal branches along the anterior surface of the left ventricle (LV).

The LCx artery travels along the left AV groove and sends obtuse marginal branches to the lateral and inferior segments of the LV. Occasionally the PDA arises from the distal LCx and not from the RCA. When this occurs, the coronary arteries are described as a "left dominant" system. In man, the RCA is "dominant" in 90% of cases. "Dominance" is primarily an anatomical term and does not imply that left-sided lesions in a right-dominant system are mild.

- B. Disease of the coronary arteries is usually focal rather than diffuse. Strategically located lesions, particularly in the LMCA, can be very important sources of morbidity and mortality.

The most common disease of the coronary arteries is atherosclerosis and its location is primarily in the epicardial portions of the myocardial arteries. These vessels are muscular arteries and are capable of intense vasoconstriction. After the vessels penetrate the myocardium, they branch repeatedly and form end-arterioles with relatively little intercommunication. Such communication can take place to produce collateral channels permitting perfusion of areas which are ischemic due to narrowing of their usual anatomic source of supply.

Because the subendocardium and its "appendages", the papillary muscles, are most distant from the coronary ostia, they are also the most susceptible to ischemia.



- C. Flow through ventricular muscle differs from flow to most other organs of the body. When the ventricles are in systole, the pressure generated by the myocardium is applied not only to the chambers but also to the blood vessels which traverse the myocardium.

For the left ventricle, the lateral compression of the intramyocardial arteries during systole will approximate the pressure in the aorta and the net driving pressure across the LV coronary circulation will be low or zero. This means that LV coronary flow will be primarily diastolic. Since the pressure in the LV during diastole will be applied passively to the myocardium, it will oppose the pressure driving blood anterograde. Any resistance in the coronary arteries (stenoses) will act as hydraulic resistances. Therefore:

$$\text{LV Flow} = (\text{Ao SBP} - \text{LV SBP}) + (\text{Ao DBP} - \text{LV DBP})$$

(Cor. Vasc. Resist.) (Cor. Vasc. Resist.)

systole

diastole

$$\text{LV Flow} = (0) + (\text{Ao DBP} - \text{LV DBP})$$

(Cor. Vasc. Resist.) (Cor. Vasc. Resist.)

systole

diastole

Where LV=left ventricle, CVR=Coronary vascular resistance, Ao=aorta, S=systolic, D=diastolic, BP=mean blood pressure during that portion of the cardiac cycle designated.

- D. Similarly for the RV:

$$\text{RV Blood Flow} = (\text{Ao SBP} - \text{RSVP}) + (\text{Ao DBP} - \text{RVDP})$$

(Cor. Vasc. Resist.) (Cor. Vasc. Resist.)

systole

diastole

Since peak RV SBP is normally only 20-25 mm Hg, (while aortic pressure fluctuates normally between 80-120 mm Hg) RV flow continues in systole as well as diastole. Since RV muscle mass and therefore oxygen demand is less than that of the LV, RV ischemia and infarction is a much more uncommon event.

- E. Pressure in the atria (normally < 15 mm Hg peak) is sufficiently low that there is really no reason to consider them at a higher risk of ischemic injury than noncardiac tissue.

- F. Until recently, fluctuations in coronary "tone" were considered unimportant in the determination of vessel caliber. The reasoning was that autoregulation was the major factor determining vessel resistance. Therefore adjustment of vessel dilatation and constriction would always accommodate to tissue oxygen needs. In the case of fixed stenoses of coronary vessels with myocardial



ischemia distal to the narrowing, it was assumed that the coronary artery, responding to the hypoxic stimulus, would always be maximally dilated.

Recently it has been shown by arteriography, as well as indirect measurements of coronary vascular resistance, that there is a great deal of spontaneous oscillation in coronary tone in both normal and diseased vessels, and vasoconstriction may play an important and frequent role in the development of angina.

Furthermore, such vasoconstriction had, for a long time, been assumed to be related to autonomic innervation of the vessels. Although some tonic or physiologic role may be present, it is known that other mediators (i.e., histamine) and drugs (ergot derivatives) may cause intense spasm while autonomic blocking drugs (α -blockers) offer no protection from spasm. As a final note, transplanted hearts can demonstrate intense coronary spasm despite a complete lack of innervation.

IV. WHAT DETERMINES O₂ DEMAND?

- A. Basal metabolic function, temperature: minor
- B. Time-Tension Index (TTI) - Sarnoff independently varied CO, peak systolic pressure and heart rate while measuring MVO₂. Best correlation was with (mean systolic LV pressure) \times (systolic time/cycle) \times (HR) = TTI
 - 1. Since systolic time/cycle varies much less than diastolic time/cycle, one can approximate the change in oxygen demand predicted by the TTI by simply using the product of systolic BP \times HR. This is known as the "double product" and can be used as an indirect index of changing myocardial oxygen demand in a given individual. The standard treadmill exercise test uses this to determine the endpoint of exercise or to compare the effect of drugs on exercise tolerance.
 - 2. "Tension" a misnomer, since more accurate wall-tension is a function of LaPlace relationship (Tension \sim P \times r). For a given heart size, however, r will vary little over a short time.
- C. Sonnenblick emphasized the importance of velocity of contraction of muscle as a determinant of oxygen demand. He demonstrated in 1965 that by increasing the velocity of contraction (or dp/dt) with inotropic agents, while decreasing Heart Rate (electrical pacing) and systolic pressure, he could alter the indices of contractility and TTI in opposite directions. When he did so, oxygen demand followed contractility and not TTI. (Figure 1)



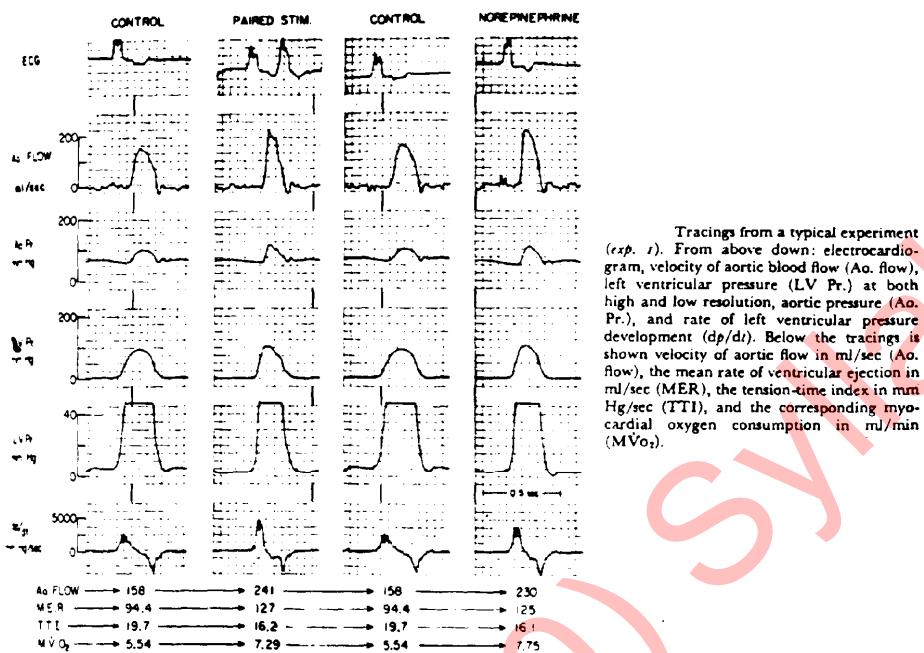


Figure 1

V. WHAT HAPPENS DURING MYOCARDIAL ISCHEMIA?

- A. Metabolic: Under normal conditions, there is a large arteriovenous oxygen extraction (AV O₂ difference) by myocardium and lactate is consumed as a source of energy. During reduction of blood flow (by arterial spasm, stenosis or increased myocardial oxygen demand relative to a fixed supply), AV O₂ difference increases with a reduction in coronary sinus oxygen content and, because of inadequate oxygen, lactate produced by glycolysis is not utilized. Coronary sinus lactate concentrations increase and may exceed circulating systemic arterial levels.
- B. Hemodynamic: Pain itself may produce autonomic discharge leading to change in heart rate. For reasons not completely understood, inferior (diaphragmatic) ischemia may produce sinus bradycardia or even atrioventricular conduction disturbances (which typically respond to atropine, a drug which antagonizes the action of the vagal neurotransmitter, acetylcholine).

Ischemia of a large segment of myocardium produces stiffness or decreased compliance, leading to a rise in end-diastolic pressure and favoring the development of an S-4 (atrial) gallop sound, as well as transient pulmonary congestion (Sometimes dyspnea may be the only sign of temporary ischemia: "painless angina").

Ischemia also causes a temporary loss of contractility, which, if severe, will lead to a fall of ejection fraction (E.F.) fall in stroke volume increased end-diastolic volume increased enddiastolic



pressure. This, too, will favor pulmonary congestion and the development of a gallop (S#3 or S4) sound.

- C. Electrophysiologic: The left ventricular subendocardium is the most vulnerable to ischemia. The ischemic myocardium, perhaps because of its inability to maintain transmembrane ionic gradients, has a lower voltage during the plateau (phase 2). Thus, electrodes overlying the ischemic area of the left ventricle will show displacement of the baseline during this phase of the cardiac cycle: ST segment depression is the hallmark of subendocardial ischemia. This finding is used to diagnose ischemia during stress (treadmill exercise) tests. (Fig.2A,B)

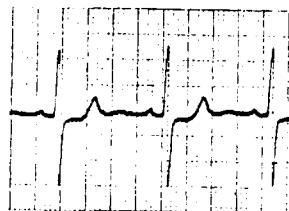


Figure 2A



Figure 2B

VI. WHAT INFLUENCES MYOCARDIAL OXYGEN DEMAND AND SUPPLY?

A. Demand:

1. Total muscle mass
2. Wall tension will rise in proportion to radius as well as pressure.
3. Heart rate
4. Ventricular systolic pressure
5. Contractility (velocity of shortening, dp/dt)

B. Supply:

1. Coronary artery resistance
 - a. Endothelial obstruction: atherosclerosis, emboli
 - b. Spasm of the arterial wall
 - c. Compression by ventricular musculature (esp. with aortic stenosis, when intraventricular pressure may exceed aortic and arterial pressure).
2. Myocardial perfusion pressure: (coronary arterial pressure minus left ventricular pressure)
 - a. Decreased aortic diastolic pressure (shock, aortic insufficiency)



- b. Increased diastolic compression of left ventricle
(increased LV diastolic pressure in CHF)
 - 3. Decreased O₂-carrying capacity of blood (anemia, CO poisoning)
 - 4. Arterial hypoxemia (high altitude, severe pulmonary disease)
- C. Obviously, common disorders may embarrass cardiac function because of simultaneous operation of several mechanisms:
- 1. Aortic stenosis may produce: muscle hypertrophy, increased systolic LV pressure, increased diastolic LV pressure.
 - 2. Aortic insufficiency may produce: LV dilatation, decreased aortic diastolic pressure, increased LV diastolic pressure and LV hypertrophy.
 - 3. Exercise will produce increased heart rate, dp/dt and blood pressure.
 - 4. Congestive heart failure will lead to LV dilatation, increased LV diastolic pressure, tachycardia.

VII. WHAT IS RATIONAL TREATMENT?

- A. Decreasing demand:
- 1. Abrupt changes in demand are almost always due to the autonomic nervous system control of heart rate, contractility and blood pressure in response to excitement or activity. The patient usually realizes very early in his disease to discontinue the physical or emotional stimulus of chest pain. Rest is the immediate treatment.
 - 2. If the attack occurs during an examination, then the physician can stimulate the carotid sinus and provoke reflex vagal discharge and a decrease in sympathetic tone. Heart rate and contractility fall, with a relief of pain.
 - 3. The use of a drug which blocks the action of norepinephrine on heart rate and contractility can provide a pharmacologic decrease in sympathetic tone. β -blockade with drugs, is now a widespread treatment for angina pectoris.
 - 4. If oxygen demand is persistently elevated, due to a pressure load (e.g., hypertension), then this can be treated specifically.
 - 5. If pre-load is reduced with fall in LV EDP and heart size and afterload is reduced with a fall in arterial pressure, then oxygen demand should fall. These are important effects of vasodilators such as nitroglycerin.
 - 6. If cardiac dilatation is present, treatment for congestive heart failure (i.e., diuretics) may decrease heart size and systolic wall stress, as well as diastolic LV pressure.



7. Adaptation: Progressive exercise leads to lower resting heart rates and lower HR response to given external work loads.
- B. Increasing oxygen supply:
 1. Severe anemia or arterial hypoxemia are relatively rare causes of angina in the industrialized counties. Transfusion of red cells or administration of oxygen (in ambient air) will be sufficient therapy in these cases.
 2. The incidence and importance of coronary artery spasm as the cause of angina is not known. It probably accounts for only a minority of instances occurring with activity. It is likely that this is considerably more frequent when angina occurs at rest. Drugs that block α -adrenergic or acetylcholine receptors do not seem to be efficacious in preventing attacks. Nitroglycerin, which acts directly on smooth muscle, is effective in aborting acute attacks. Agents, such as Nifedipine or Diltiazem, which interfere with slow calcium channels, have been very successful in preventing attacks of spasm as well as in the routine treatment of angina.
 3. When fixed lesions are present in the coronary arteries, blood supply to blocked areas depends upon collateral flow. The development of collaterals increases with time and probably is enhanced by exercise.
 4. Surgical bypass as well as angioplasty of coronary stenoses is now widely practiced and is usually 90+% effective in relieving angina pectoris.

VIII. SUMMARY

- A. Anginal pain is the result of myocardial ischemia caused by an imbalance between myocardial oxygen demand and supply.
- B. Increased demand is determined by heart rate, systolic BP and contractility.
- C. Decreased supply is typically due to obstruction or narrowing of the coronary arteries.
- D. Medical treatment is aimed at decreasing demand, preload and contractility by vasodilation and β -autonomic blockade.
- E. Surgical treatment allows bypass or reconstruction of obstructed coronary artery segments.



Drugs Used in Hypertension

Reading assignment: Katzung (10th ed), Ch. 11

LEARNING OBJECTIVES:

- A. Understand why treatment of high blood pressure (hypertension) is important.
- B. Learn the pharmacology of drugs used to treat hypertension.
- C. Understand the rationale for using particular anti-hypertensive drugs in combination.

TOPICS

- A. Diuretics
- B. ACE inhibitors
- C. Angiotension II receptor blockers
- D. Adrenergic neuronal blockers
- E. CNS-acting drugs
- F. Arteriolar vasodilators
- G. Sodium nitroprusside



Last Year's (2010) Syllabus

Shock

"Patients don't die of their disease, they die of the physiologic abnormalities of their disease." - Osler

A 62 year old man with a history of coronary artery disease and a myocardial infarction 1 year ago is admitted with confusion, low blood pressure and weak pulse with a high fever.

His vital signs are temperature 39.5 degrees, pulse 110 per minute, blood pressure 80/30 mmHg and respirations 24 per minute.

Laboratory studies reveal a high white blood count and white cells and bacteria in his urine.

Impression: Urinary track infection with septic shock.

I. SHOCK

A. Definition

1. A syndrome of failure of the heart to pump blood into the aorta in sufficient quantity and under sufficient pressure to maintain the pressure-flow relationship for adequate tissue perfusion and aerobic metabolism.

$$V = I \times R$$

$$P = F \times R$$

$$MAP = CO \times SVR$$

$$SV \times HR$$

Preload Contractility Afterload

II. HYPOTENSION

A. Pressure = Flow x Resistance

B. Blood Pressure = Cardiac Output x Vascular Resistance

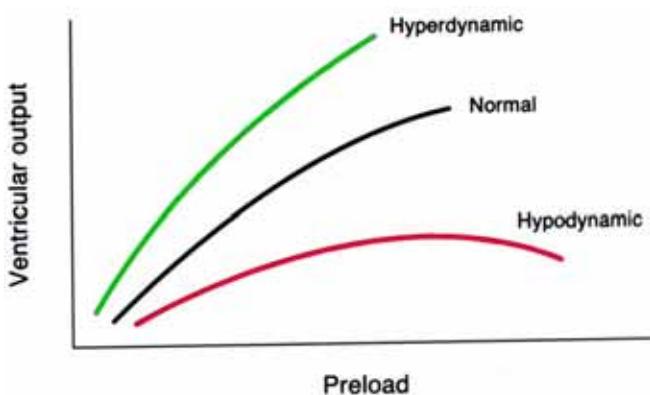
C. If hypotensive -

1. Cardiac Output falls = hypovolemia
 - a. hypocontractility
2. Resistance falls = vasodilation



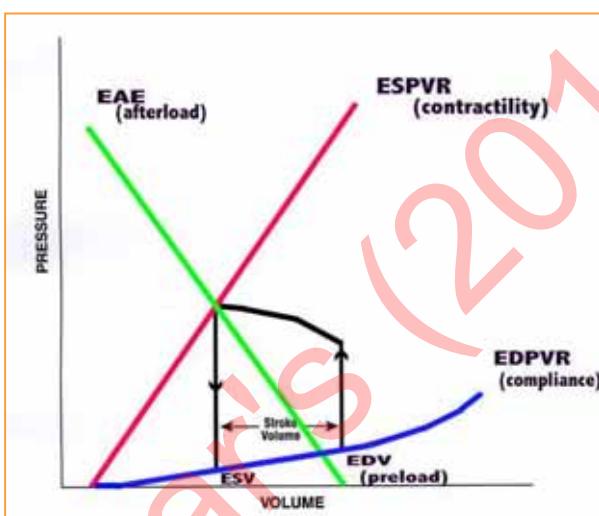
III. VENTRICULAR FUNCTION CURVES

- Ernest Starling, 1914



IV. PRESSURE-VOLUME LOOP

- Otto Frank, 1898



V. HYPERDYNAMIC SHOCK ETIOLOGIES

A. Sepsis:

1. Bacteria
2. Virus
3. Fungus

B. Inflammation

1. Cytokines:
 - a. TNF
 - b. Interleukins
 - c. Nitric Oxide
 - d. PAF



- C. Humoral:
 - 1. Kinins
 - 2. Prostaglandins
 - 3. Leukotrienes
 - 4. Histamine Complement
 - D. Splanchnic Insufficiency
 - 1. Endotoxemia
 - 2. Gram Negative Bacteremia

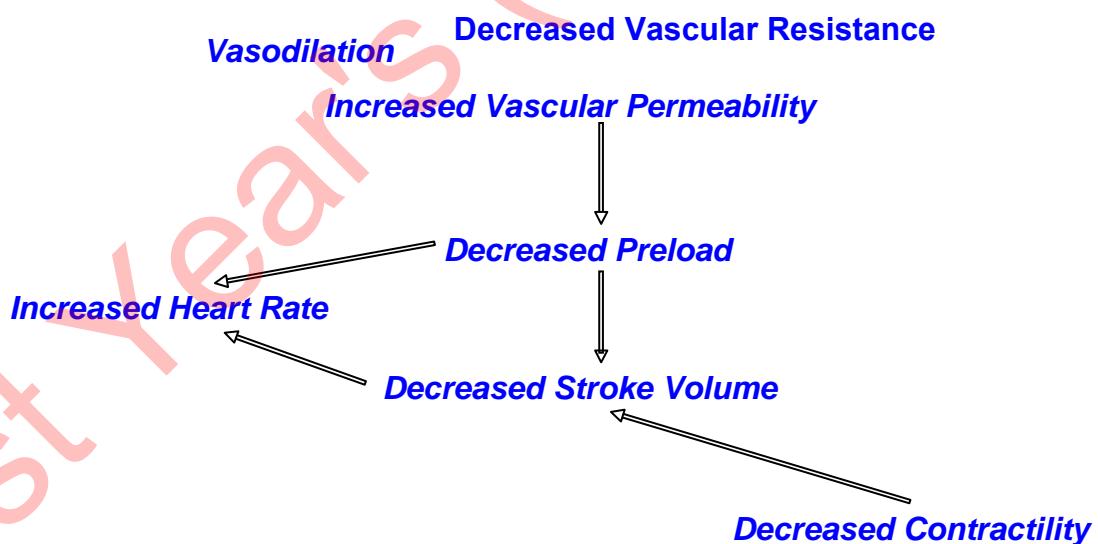
VI. HYPERDYNAMIC/SEPTIC SHOCK

- A. Manifestations

 1. Febrile
 2. Acidosis
 3. Rapid, Full Pulses
 4. Decreased Urine
 5. Increased Respirations
 6. Hypotension
 7. Warm and Moist Skin
 8. Decreased Mentation

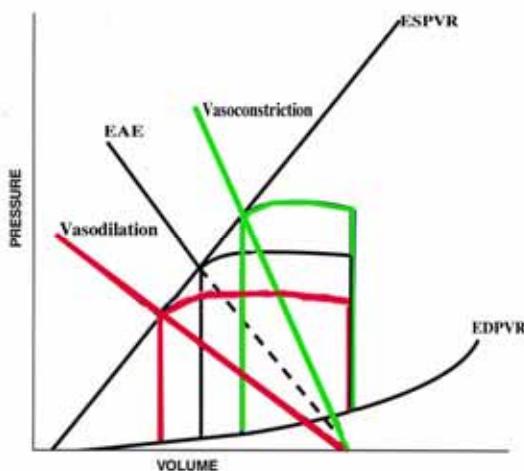
VII. HYPERDYNAMIC/SEPTIC SHOCK

- ## A. Pathophysiology



VIII. EFFECT OF ALTERATION IN VASCULAR RESISTANCE

A. Pressure-Volume Loop Representation



IX. EFFECT OF ALTERATION IN VASCULAR RESISTANCE

A. Starling Curve Representation

"Within physiologic limits we may say that the output of the heart is independent of the arterial resistance, so that whatever work is given the heart to do, it can do it without fail."

- Starling, 1918

X. HYPERDYNAMIC SHOCK - MANAGEMENT

- A. Primary Therapy
 - 1. Antimicrobials
 - 2. Surgery
 - 3. Administer Volume
- B. Secondary Therapy
 - 1. Acid-Base Stability
 - 2. Vasoactive Agents
 - 3. Inotropic Agents
 - 4. Steroids
 - 5. Activated Protein C

The patient is brought to the intensive care unit and is administered 1 liter of normal saline. Antibiotics are begun for suspected urinary track infection. Oxygen is also begun.

Monitoring is initiated and shows that he has a low vascular resistance with a mildly elevated cardiac output and low intravascular volume.

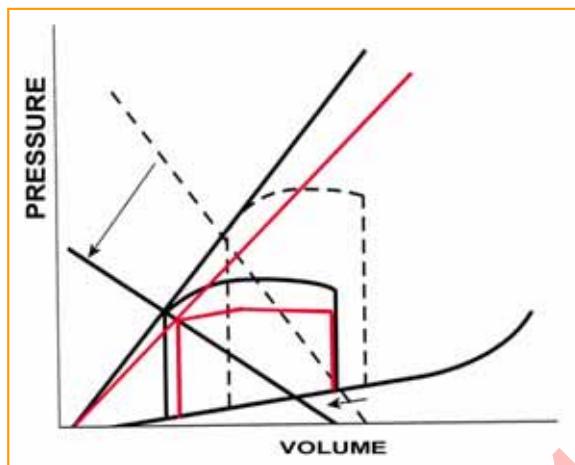
Vasodilation



Hyperdynamic cardiac response
Low preload
Acidosis

XI. HYPERDYNAMIC SHOCK

With Decrease in Preload and Hypocontractility



XII. HYPERDYNAMIC SHOCK - HEMODYNAMIC SEQUELAE

A. Reduced Preload

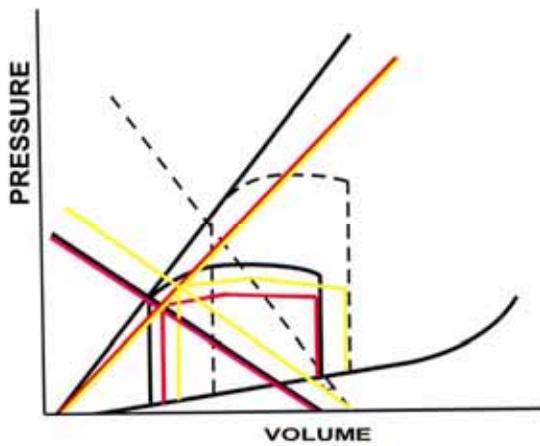
1. Increased Permeability Vasodilation
 - a. Nitric Oxide
 - b. Endotoxin
 - c. TNF
 - d. Kinins
 - e. Complement
 - f. Histamine
 - g. Prostaglandins
 - h. Leukotrienes

B. Hypocontractility

1. Diastolic Hypotension Chemical
 - a. Cytokines
 - b. Cyclic - AMP
 - c. Bacterial Toxins
 - d. Myocardial
 - e. Depressant Factor



XIII. ADMINISTRATION OF FLUID TO INCREASE PRELOAD WITH INCREASE IN STROKE VOLUME AND BLOOD PRESSURE



He is given an additional liter of normal saline and his blood pressure remains at 80/30 and he begins to have increasing shortness of breath with difficulty to maintain oxygenation.

The monitoring shows that he has adequate volume in his heart but still with vasodilation and evidence of decreased myocardial contractility.

Vasodilation

Decreased contractility with inadequate cardiac output

XIV. INOTROPIC SELECTION

A. Peripheral Vascular Effects

1. Dilators:
 - a. dobutamine
 - b. milrinone
 - c. dopexamine
 - d. isoproterenol
2. Constrictors:
 - a. dopamine
 - b. epinephrine
 - c. norepinephrine
 - d. digoxin

B. Strength of Beta Receptor Stimulation

1. Strong:
 - a. epinephrine
 - b. norepinephrine
 - c. isoproterenol



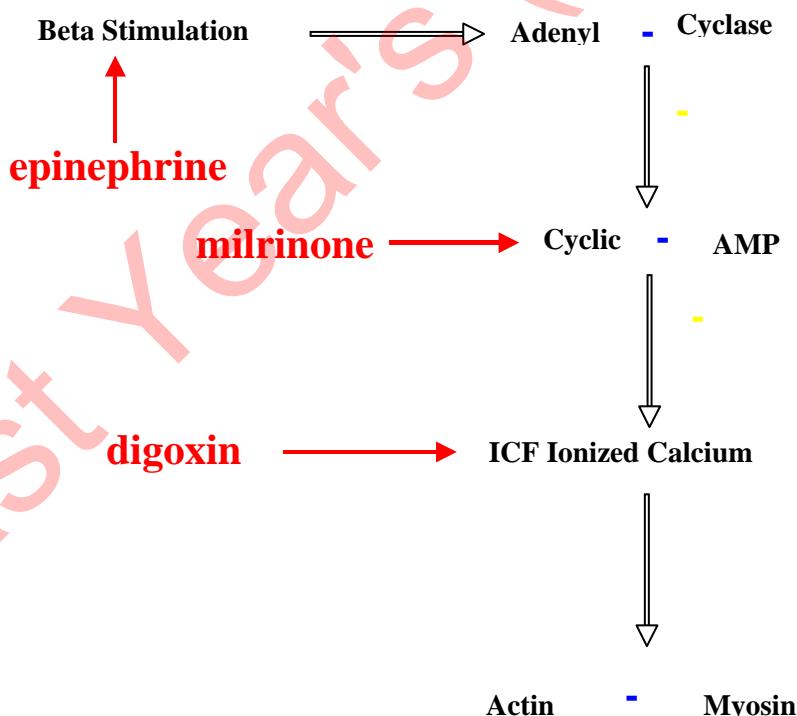
2. Weak:
 - a. dopamine
 - b. dobutamine
 - c. dexamexamine
- C. Tachydysrhythmias
 1. isoproterenol

XV. INOTROPIC SELECTION

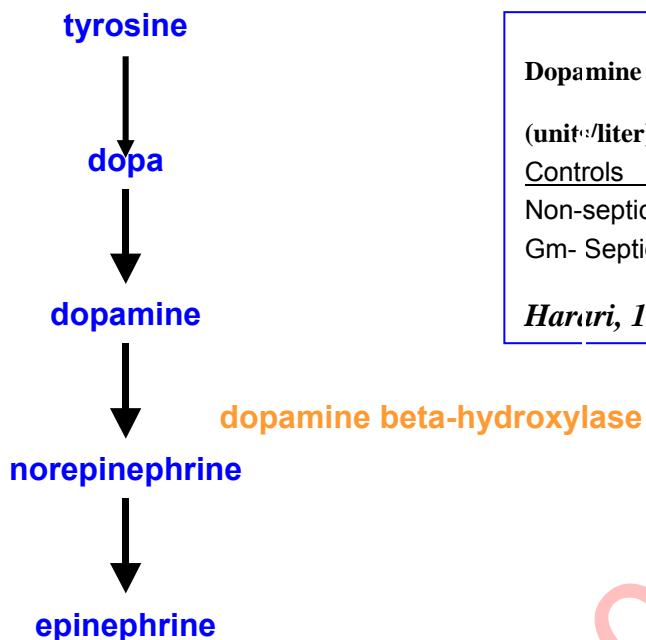
A. Mechanism of Action

1. Adenyl-Cyclase Stimulation:
 - a. dopamine
 - b. dobutamine
 - c. epinephrine
 - d. norepinephrine
 - e. glucagon
 - f. isoproterenol
2. Phosphodiesterase Inhibition:
 - a. milrinone
3. Na-K ATPase Inhibition:
 - a. digoxin

XVI. MYOCARDIAL MUSCLE CONTRACTILITY



XVII. DOPAMINE IN SEPTIC SHOCK



Dopamine Beta-Hydroxylase

(unit ⁻¹ /liter)	
Controls	21.3
Non-septic Shock	29.1
Gm- Septic Shock	7.4

Harari, 1979

XVIII. BETA RECEPTOR RESPONSIVENESS

- A. Lymphocytes from patients with GM- septic shock + isoproterenol = Cyclic-AMP
(Silverman, 1993)
- B. Lymphocytes incubated with TNF + isoproterenol =Cyclic-AMP
(Singh, 1993)
- C. Down Regulation of Beta Receptors
 - 1. Old age
 - 2. Cardiopulmonary bypass
 - 3. Bacterial Septic Shock



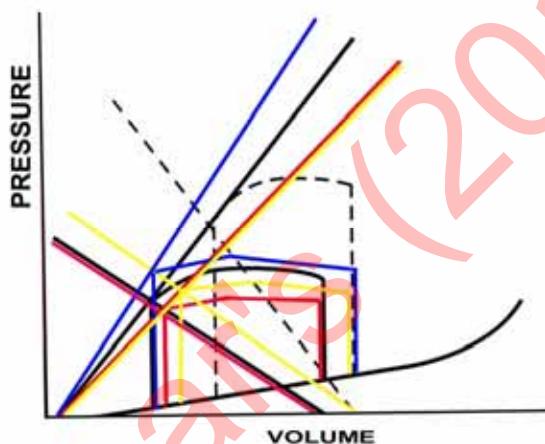
XIX. DOSE RESPONSE ANALYSIS OF EPINEPHRINE IN HUMAN SEPTIC SHOCK.

-Moran, 1993

Dose (mcg/min)	Dose* (nanog/kg/min)	Cardiac Index (L/min/m ²)	SVRI (d _{sec} ·cm ⁻⁵ ·m ²)	DO ₂ I (ml/min/m ²)
0	0	3.8	1079	481
3	43	4.2	1084	547
6	86	4.7	1039	589
9	129	4.5	1118	570
12	172	4.7	1091	615
15	215	4.1	1356	522
18	258	4.3	1448	531

* Assume 70 Kg

XX. ADDITION OF AN INOTROPIC DRUG (EPINEPHRINE/ADRENALINE) TO INCREASE CONTRACTILITY - INCREASING STROKE VOLUME AND BLOOD PRESSURE.



XXI. AN INTRAVENOUS INFUSION OF EPINEPHRINE IS BEGUN WITH INCREASE IN HIS CARDIAC OUTPUT TO A HIGH LEVEL BUT WITH PERSISTENT LOW BLOOD PRESSURE OF 85/35 MMHG.

- A. Preload is adequate
- B. Contractility has improved
- C. Vasodilation and hypotension persists

XXII. VASOPRESSOR THERAPY

- A. Hypovolemic Shock: not indicated.
- B. Cardiogenic Shock:
 1. increase diastolic coronary perfusion pressure.



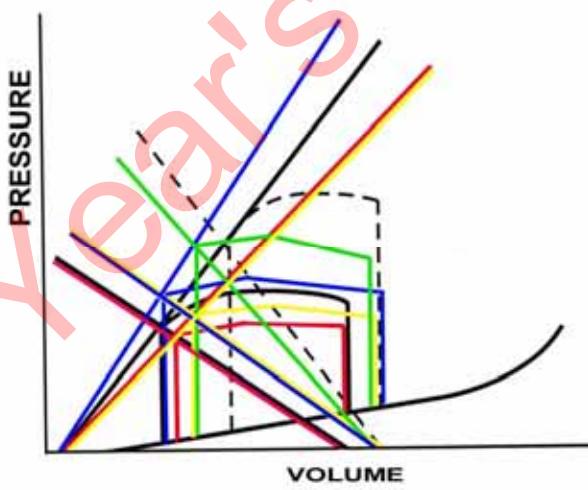
2. CPP = DP - LVEDP
 3. Beware effect on afterload and peripheral perfusion.
- C. Hyperdynamic Shock:
1. increase blood pressure in presence of elevated cardiac index.
 2. Beware organ hypoperfusion and increase in lactic acid production.

XXIII. VASOPRESSOR SELECTION

- A. Vital Organ Perfusion
- B. Tachydysrhythmias:
 1. norepinephrine
- C. Mechanism of Action:
 1. Alpha Receptor Stimulation:
 - a. phenylephrine
 - b. norepinephrine
 2. Endothelin Activation:
 - a. vasopressin
- D. Myocardial Oxygen Supply v. Demand

XXIV. ADDITION OF A VASOCONSTRICCTOR

(PHENYLEPHRINE/NEOSYNEPHRINE) TO INCREASE VASCULAR RESISTANCE AND THEREFORE BLOOD PRESSURE.



XXV. PHENYLEPHRINE IS BEGUN WITH CONTINUATION OF THE EPINEPHRINE. HOWEVER, INCREASING THE DOSE OF PHENYLEPHRINE HAS LITTLE EFFECT ON BLOOD PRESSURE.

- A. Decreased alpha receptor responsiveness



XXVI. VASOPRESSIN

- A. Produced by baro-reflex mediated secretion.
- B. Stimulates the production of endothelin
- C. Deficiency in catecholamine resistant vasodilation
- D. Effective pressor alternative with alpha resistance
- E. In-vivo coronary vasoconstriction
- F. Dosage:
 - 1. Hypotension .01-.1 u/min
 - 2. ACLS 40 units IVP

XXVII. INTRAVENOUS VASOPRESSIN IS BEGUN WHICH INCREASES THE PATIENTS BLOOD PRESSURE WITH VITAL SIGNS SHOWING A PULSE OF 88 PER MINUTE AND BLOOD PRESSURE OF 105/65 MMHG.

He remains dependent on this therapy for 12 hours and steroid administration is initiated.

Suspect decreased adrenal function

XXVIII. STEROIDS IN SEPTIC SHOCK

-Schumer, 1976

- A. 172 patients from 1967-1975
 - 1. 86 -- placebo control
 - 2. 43 -- dexamthasone 3 mg/kg
 - 3. 43 -- Methylprednisolone 30 mg/kg
- B. Mortality:
 - 1. placebo -- 38.4%
 - 2. steroids -- 10.4%

XXIX. STEROIDS IN SEPTIC SHOCK

- Bone, 1987

- A. Methylprednisolone 30 mg/kg Q6H x 4 doses
 - 1. Mortality:
 - a. Placebo -- 28%
 - b. Steroid --- 31%
- B. Steroid mortality increased if creatinine > 2.0 mg/dl
- VA Coop, 1987
- C. Methylprednisolone 30 mg/kg → 5mg/kg/hr x 9 hrs



1. Mortality:
 - a. Placebo -- 21.6%
 - b. Steroid --- 20.5%

XXX. STEROIDS IN SEPTIC SHOCK

- Bollaert, 1998
- A. Vasopressor dependent septic shock
- B. Hydrocortisone 100 mg Q8H for 5 days or reversal of shock
 1. Shock reversal at 7 days:
 - a. Placebo -- 21%
 - b. Steroid --- 68%
 2. Mortality at 28 days:
 - a. Placebo -- 63%
 - b. Steroid --- 32%
 3. Steroid responders ----- cortisol = 21 mcg/dl
 4. Steroid non-responders -- cortisol = 30 mcg/dl

XXXI. STEROIDS IN SEPTIC SHOCK

- A. Mechanisms of Enhanced Vasopressor Responsiveness
 1. Increase sensitivity of alpha and beta receptors
 2. Decrease production of inducible NO synthase
 3. Increase response of catecholamine receptors

Proposal for Use of Steroids in Septic Shock

Vasopressor dependence > 8-12 hour

Measure baseline serum cortisol level

Initiate hydrocortisone at 100 mg Q8H

Continue if cortisol level < 25 mcg/dl

A baseline cortisol level is noted to be low and he is continued on steroid administration at 100mg hydrocortisone every 8 hours.

Over the next 24 hours epinephrine, phenylephrine and vasopressin are all weaned to off with normalization of all vital signs. His acidosis resolves and all systems begin to function normally.

- B. Resolution of septic shock
- C. Effective treatment of his infection

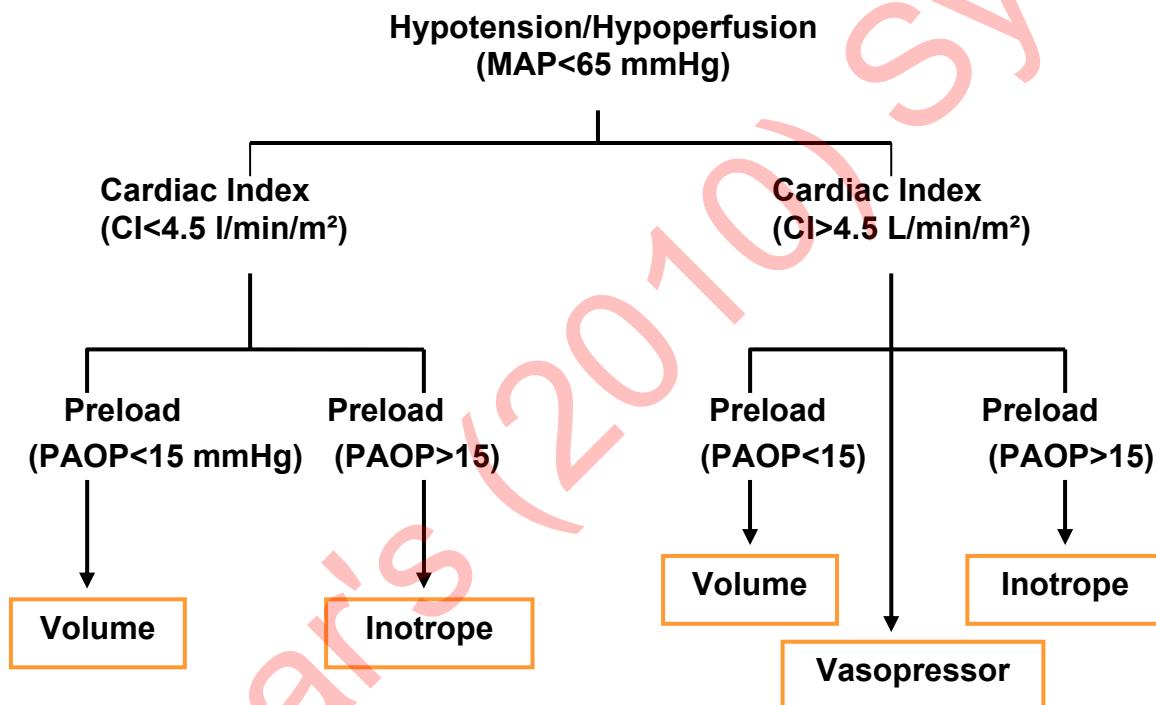
XXXII. GOALS FOR HEMODYNAMIC MANAGEMENT IN SHOCK

- A. Blood Pressure: MAP not less than 20% below normal.
- B. Inotropes v. Volume: PAOP 15 mmHg with adequate EDV.



- C. Vasopressors: Cardiac Index (CI) 4.5 l/min/m².
- D. Evidence of adequate tissue perfusion
 - 1. Acid-base balance
 - 2. Lactic Acid
 - 3. Urine output
 - 4. Capillary filling
 - 5. Skin appearance and temperature
 - 6. Oxygen delivery v. oxygen demand

XXXIII. PROPOSED ALGORITHM FOR THE MANAGEMENT OF HYPERDYNAMIC SHOCK



“The physician without physiology practices a sort of popgun pharmacy hitting now the malady then the patient, he himself not knowing which.” - Osler



Last Year's (2010) Syllabus

ADULT CARDIAC LABORATORY

CASE 1

A seventy-two year old golfer comes to you complaining of dull cramping leg pain, right slightly more than left, while walking the course. He is proud to be active and golfing, but for the last few months he has to stop several times each hole for the pain to subside. He has no leg pain at night.

His past medical history is unremarkable. He has smoked cigarettes intermittently for 55 years and is smoking 1pk/day now. He admits he doesn't watch his diet, and he is a plump 5'8" 170 lbs. His fasting total cholesterol is 180 mg/dl and BP is 140/90. He has no history of diabetes.

His physical examination is mostly unchanged from last year. He has mild prostatic hypertrophy, expected for age. His legs are warm, with good sensation, without skin changes, tenderness or palpable cords (veins or arteries), but his pedal pulses are weak. You palpate a deep non-tender midline mass in the lower abdomen, which may be pulsatile.

QUESTIONS

1. What is the differential diagnosis in this case?

2. What initial studies might you suggest for your evaluation?



3. Examine the gross specimen provided (in the “Student” cabinet in the hallway; the key for it is in M226). Describe what you see.
4. What therapies do you contemplate if his midline mass is quite large?
5. What are the possible complications of his disease?
6. What are the major risk factors for the underlying disease process? Which can be modified? How do the risk factors affect the mechanisms that drive the underlying disease process?

Last Years (2010) Syllabus



CASE 2

This 46 year-old insurance salesman with a history of hypertension and hypercholesterolemia presents to the ER with a complaint of chest pain of 1.5 hour duration. He awoke from sleep at 12:30 AM with intense precordial pain that radiated to both shoulders. This was associated with diaphoresis, but no nausea or shortness of breath. Maalox and a non-steroidal anti-inflammatory drug (NSAID) did not provide any relief. The pain was not worsened with change of position or respiration. He tried 2 sublingual nitroglycerin tablets, but they did not alleviate the pain. His risk factors included hypercholesterolemia (260), obesity (5'11", 250 lbs), hypertension (145/100) and cigarette abuse (3 pkg./day x 15 yrs). He took antihypertensive medication but admitted to poor compliance. His job was described as "high stress" and sedentary. His past medical history is unremarkable except for recent duodenal ulcers for which he was taking H2 blockers. He has no known allergies.

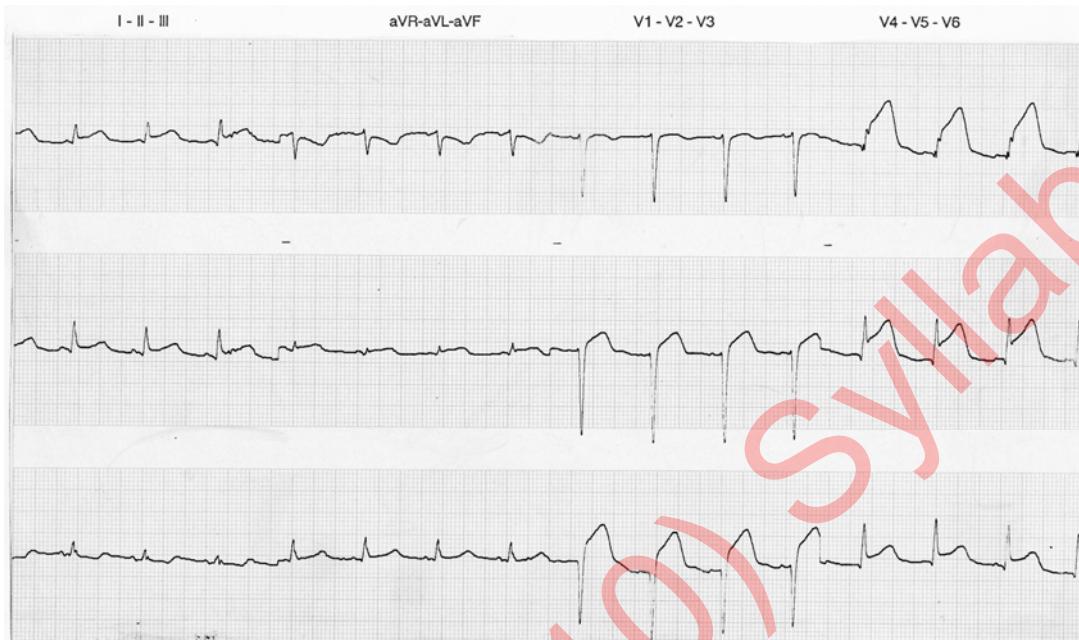
In the ER he appeared anxious and pale. Temp - 37.5 C, BP 150/100, Resp. 30 per min and Pulse 110 and regular. Physical examination was normal. The lungs were clear to auscultation. No murmurs, gallops or extra beats were detected. No cardiac enlargement was palpated. Peripheral pulses were strong and symmetrical and there was no pedal edema.

QUESTIONS

- 
 1. What is the differential diagnosis in this case?
 2. What initial studies might you suggest in the evaluation?



3. The chest X-Ray was normal except for slight cardiac enlargement. The ECG performed in the Emergency Room is shown below.



What is the diagnosis now?

4. The patient is brought to the cardiac catheterization lab and undergoes diagnostic angiography. The angiogram is available for your review (see “Lab Material” -> “Cardiac Lab 1” on the CourseWork website.) Immediately following the diagnostic procedure, the patient becomes pulseless and hypotensive. An ECG performed at that time is shown below.



- How do you interpret this ECG?
5. Advanced resuscitation was unsuccessful and he was pronounced dead. An autopsy was performed. What features do you see in the corresponding slide, #109. What is the cause of death?
 6. How might coronary atherosclerosis present? What symptoms may be reported by patients?
 7. What are the complications of myocardial infarction?
 8. Please review slide #110 from a different patient. How "old" is this lesion? (What is the estimated duration of the host reaction?)
 9. If this patient had survived, what therapeutic options would you have considered including lifestyle, medicines and invasive procedures?



CASE 3

A 24 year old woman presents to the ER complaining of severe shortness of breath and occasional hemoptysis. She can't pinpoint when her dyspnea began, but it was at least a few months ago. She regularly wakes at night, short of breath.

She presents now because she can't climb one flight of stairs without stopping to catch her breath.

In the ER, the patient was noted to be dyspneic at rest, pulse 110, BP 110/60, and afebrile. Lungs auscultation revealed bilateral rales in the bases. Heart exam showed regular rhythm with a S3. Extremities showed 2+ ankle edema.

QUESTIONS

1. What is your differential diagnosis?
 2. What initial studies would you suggest?
 3. Examine slide #134 (from a similar patient) and describe the pathologic changes.



4. An imaging study is performed [CourseWork: Inde221 -> Lab materials -> Cardiac Lab 1 -> Case 3]. What do you see? What is the diagnosis now?

5. What underlying etiologies can lead to a heart condition like this?

6. What therapeutic options might be considered? What is the long-term prognosis?

>Last Year's (2010) Syllabus



Last Year's (2010) Syllabus

CARDIAC ANESTHESIA & BYPASS

OBJECTIVES:

- A. Define the need for extracorporeal circulation and gas exchange and cardiac standstill for the performance of open-heart surgery. Introduce the role of cardiac anesthesia in the advancement of cardiac surgery.
- B. Introduce the mechanics of cardiopulmonary bypass (CPB) and the essential features of patient preparation, cannulation, initiation of CPB, and weaning off CPB. Discuss risks and benefits of procedures performed using CPB and current alternatives to CPB.
- C. Review the physiology of gas exchange and tissue oxygen delivery under cardiopulmonary bypass and introduce current thinking about optimal perfusion and organ protection.

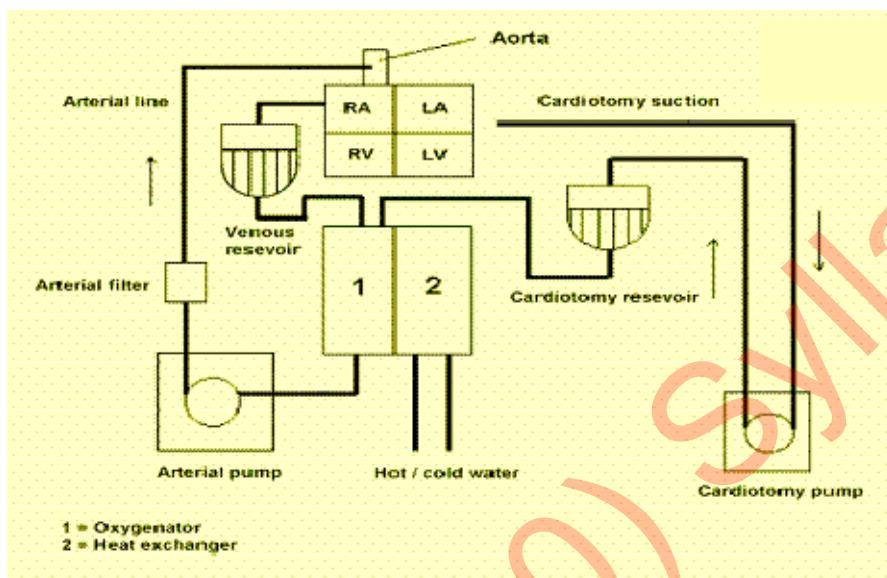
I. INTRODUCTION

For a patient undergoing open-heart surgery, diverse stresses in the perioperative period remain a major obstacle to rapid complete recovery and improvement over pre-procedure level of functioning. These include the psychological weight of anticipating a major surgery, the trespass of being connected to extracorporeal circulation/oxygenation machinery and of the surgery itself, the stress of prolonged intubation and mechanical ventilation, and post-operative pain. Even given a technically adequate surgical repair, a patient may not have the optimal outcome if these stressors are not addressed systematically by the perioperative physician. This is the role of a cardiac anesthesiologist. The advent of modern cardiac surgery was made possible by the ability to produce a still, bloodless operating field in a living patient by means of CPB, and by advances in the anesthetic management of these complex patients. One of these advances, the use of intraoperative transesophageal echo (TEE), has become an essential tool in the specialty of cardiac anesthesia.



II. CARDIOPULMONARY BYPASS (CPB)

A. General description of the CPB circuit:



The basic components of the CPB circuit are (in the order in which they meet the patient's blood): venous cannula(e) (which is/are inserted in the RA and/or vena cavae), venous reservoir, oxygenator/heat exchanger unit, arterial pump and filter, and arterial cannula (which is placed in the ascending aorta). There are variations on this arrangement but the basic design is the same. Additionally, cardiotomy suction is used to collect shed blood in the incision and return it to the CPB circuit.

1. "the heart": arterial pump:

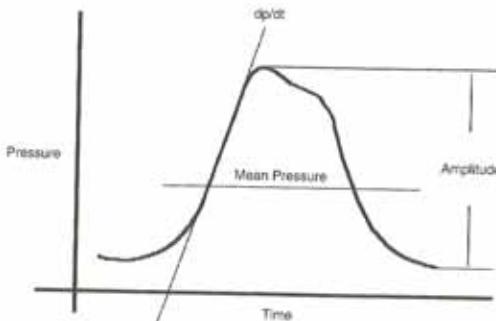
Requirements for a suitable device are: it must be able to pump fast (up to 7 L/min) and with minimal trauma to blood cells and other components, have sterile disposable blood pathway, and avoid having regions of stagnant flow.

Types of pumps are Roller (positive displacement, non-pulsatile), which is the predominant type today; Centrifugal (kinetic), which is slightly more expensive but possibly less traumatic; and Pulsatile, which is not commonly used (but see below). Potential problems include blood trauma, overpressurization, possible massive air embolism (with roller pumps); and possible retrograde flow on pump stoppage (with centrifugal pumps).

Since physiological perfusion is pulsatile, much effort was expended to research the advantages of pulsatile flow during CPB. To date, these advantages remain uncertain. Theoretically, pulsating blood flow preserves neuroendocrine mechanisms acting on the arterial tone via baroreceptor reflexes.



Hydraulic power of a pump is a sum of mean power (the product of mean pressure and mean flow) and



pulsatile power (derived from sum of pressure and flow harmonics). It is thought that the pulsatile power is better able to achieve perfusion of small vascular beds (e.g., renal glomeruli). Technically, the roller pump with accelerating and decelerating pump heads can easily achieve pulsatile flow, but the difficulty is in reproducing the truly physiological pulse architecture (shown above). Simply put, the way a roller pump pulses is different from the way the ventricle contracts.

2. “the lung”: oxygenator:

In reality, this component functions not only to oxygenate venous blood, but also to remove/add carbon dioxide and add volatile general anesthetics. In modern CPB machines, the oxygenator unit incorporates a heat exchanger, which heats or cools blood, as needed, by forced convection and conduction across a stainless steel interface. Membrane oxygenators mostly have supplanted the older Bubble oxygenators in clinical practice because, with the latter type, oxygenation and carbon dioxide removal are difficult to control independently and it is necessary to de-foam and allow time for bubble separation from blood. Membrane oxygenators contain a large surface area for gas diffusion within a compact enclosure. The gas-permeable membrane material used is, in fact, microporous, further increasing the contact surface area for gas exchange. The limiting step in oxygen delivery to RBCs is not the diffusion across the membrane but across the thickness of the blood film itself. Contrast this situation with the healthy lung, in which O₂ uptake and CO₂ elimination are limited not by diffusion, but by the ventilation-perfusion mismatch.



3. arterial cannulae

The oxygenated blood is returned to the patient via (usually) the aortic cannula, which is commonly placed first, before the venous cannula. This enables the surgeon to initiate CPB with only one cannula in place in an emergency situation in which the heart becomes submerged in blood. In this case, a suction tip placed within the pooled blood acts as a conduit for venous return to the CPB circuit (so-called sucker bypass). Surgical needs dictate the placement of the arterial cannula in other locations, such as subclavian and femoral vessels. Proper size selection is critical, as too small a diameter can lead to excessive pressure gradients and hemolysis. Small size and outflow misdirection can cause jetting effects which can injure arterial walls and break off atheroemboli. Placement of the cannula in and cross-clamping of the diseased ascending aorta are the major risk factors for perioperative strokes in surgery involving CPB.

4. venous cannulae

A single cannula may be placed in the right atrium, or, if a bloodless right heart is required, venae cavae may be cannulated separately. Venous drainage can be achieved by gravity (siphonage) or pump-assisted. It can be shown that air entrained in the venous limb of the circuit can traverse the CPB machine and enter arterial circulation, where it could contribute to gaseous microembolism to the brain. Therefore, air leaks are carefully guarded against in both limbs of the CPB circuit.

B. Anticoagulation requirement

All surfaces coming in contact with blood during extracorporeal circulation are thrombogenic. Therefore, there is an absolute requirement for full systemic anticoagulation before CPB is initiated.

Heparin is the anticoagulant used in a vast majority of cases. Heparin is a mixture of polyanionic sulfated mucopolysaccharides of different molecular weights. Heparin's activity depends on antithrombin III, a plasma protease inhibitor, which interacts with activated clotting factors II, IX, X, XI, XII, XIII. Level of systemic heparinization is monitored by measuring the activated clotting time (ACT) in the operating room. This is done by means of an in-vitro standardized clotting reaction using contact activation with a special clay. After CPB is terminated, circulating heparin is "reversed" by administering a dose of polycationic compound protamine sulfate, which forms ionic bonds with heparin and prevents further binding to antithrombin III. In summary, heparin's advantages for cardiac surgery are its low cost, long-standing experience in use, simple quantitative assay, and availability of a specific antidote.



Heparin's main disadvantages are its indirect interaction with the coagulation cascade (via ATIII) and its immunogenicity. Prolonged exposure to heparin can lead to appearance of platelet-aggregating antibodies, which, on repeated heparin exposure, can produce thrombocytopenia and a pro-thrombotic state (heparin-induced thrombocytopenia, or HIT). Patients with HIT present a challenge if they require systemic anticoagulation for CPB. Newer direct thrombin inhibitors, such as lepirudin, bivalirudin, or argatroban, have been used. Their major disadvantage is the lack of specific "reversal" agents, thus increasing the likelihood of post-operative bleeding. There are limited reports (e.g., Potzsch et al, NEJM 2000, 343:515), indicating that patients with HIT who have undetectable HIT antibodies can be safely administered heparin in a time-limited fashion for CPB.

C. Cardioplegia

While CPB provides the surgeon with the bloodless operating field, most operations also require cardiac standstill. This is achieved by means of perfusing the myocardium with a cardioplegia solution. Flaccid electromechanical arrest of the heart dramatically reduces energy consumption by the myocardium and tends to balance out the reduced supply of oxygen and energy sources to the heart during CPB. The use of cold cardioplegia also realizes the advantages of myocardial hypothermia.

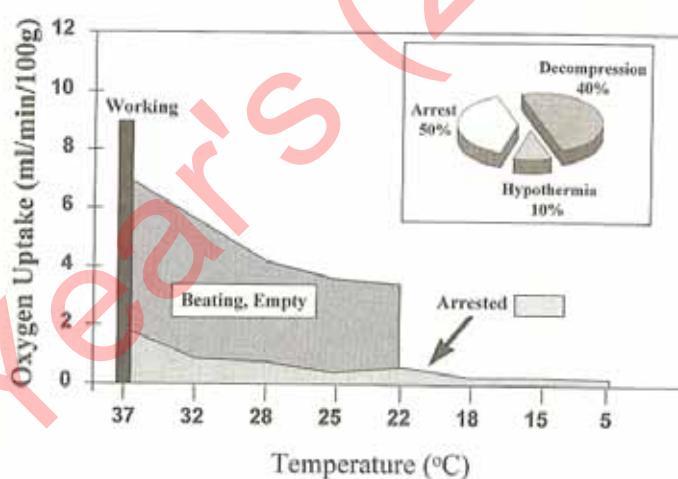


FIG. 13.9. Oxygen requirements of the continuously perfused heart at 37°C in the beating working state (dark bar) and at various degrees of hypothermia in the decompressed beating (beating empty; hatched area) and in the arrested state (stippled area) on cardiopulmonary bypass. Oxygen requirements of the working heart at 37°C are shown for comparison. Inset shows the percentage reduction in oxygen requirements contributed by ventricular decompression, total chemical asystole, and hypothermia to 10°C relative to those of the working heart. As discussed in the text, only minor reductions in myocardial oxygen demand are effected by hypothermia more profound than 22°C. (From Vinten-Johansen, Hammon JW Jr. Myocardial protection during cardiac surgery. In: Gravlee GP, Davis RF, Utley JR, eds. *Cardiopulmonary bypass: principles and practice*. Baltimore: Williams & Wilkins, 1993:155-206, with permission.)

From G.P. Gravlee, R.E. Davis, M. Kurusz, and J.R. Utley, eds. *Cardiopulmonary Bypass. Principles and Practice*, 2nd Ed.

The ionic mechanism for cardioplegia is based on the moderate elevation of extracellular $[K^+]$ to 15-20 mM, which induces a lasting depolarization of the sarcolemma, according to the Nernst equation:



$$EK = (58 \text{ mV}) \log_{10}([\text{K+}]_{\text{out}}/[\text{K+}]_{\text{in}}) \text{ at } 20^\circ\text{C}.$$

This modest depolarization (to about -65 mV) causes voltage-gated sodium channels to inactivate, rendering them unavailable for generating action potentials. A number of additives have been tried in order to enhance the cardioprotective properties of cardioplegia, e.g., adenosine, insulin, beta-blockers, but none has been shown to be convincingly superior to conventional potassium cardioplegia.

Administration of cardioplegia follows two main routes. Antegrade: following aortic crossclamping, cardioplegia is infused proximally into the aortic root from which it enters coronary ostia. The major limitation is that severe coronary artery stenosis may prevent spread of cardioplegia into at-risk myocardium. Retrograde: cardioplegia is given into the coronary sinus from which it travels retrograde via coronary veins into the myocardial capillaries. Following the removal of the cross clamp, the heart is reperfused with blood and returns to spontaneous electrical activity, although not always in sinus rhythm.

D. Weaning patient off CPB

Weaning refers to a gradual return of pumping function to the heart from the CPB machinery. This is achieved by decreasing the proportion of systemic venous return that enters the CPB circuit in concert with reducing the rate of flow of oxygenated blood from the pump into arterial circulation. Weaning proceeds from total bypass (all venous return to CPB) via stages of partial bypass. The following must be monitored and corrected in order to wean successfully:

- a. temperature - patients are rewarmed to normothermia by means of the CPB heat exchanger;
- b. acid/base status and electrolytes - essential for sustaining normal rhythm and contractility of the myocardium;
- c. rate and rhythm - patients often require defibrillation and/or pacing;
- d. preload - warm, vasodilated post-CPB patient has high fluid requirements;
- e. contractility - post-CPB hearts often need inotropic support;
- f. ventilation and oxygenation – lungs are gently reinflated to counter atelectasis, and patient is returned to mechanical ventilation.

Whenever left-sided chambers are surgically entered, there is a threat of arterial air emboli. Head-down positioning and meticulous de-airing are done, utilizing TEE guidance to reveal pockets of air that need dislodging and venting (removal).



E. Failure to wean off CPB: assist devices

If inotropic support and other variables are optimized but cardiac output is still inadequate to perfuse vital organs, several devices are available to transition the patient off CPB. Intraaortic balloon pump (IABP) augments left heart output by expanding in diastole and forcing blood into coronary and distal systemic arteries. It is placed percutaneously through the groin; the balloon resides in the descending aorta. IABP changes favorably the myocardial O₂ supply to demand ratio by decreasing the tension-time index (TTI, the time integral of the LV systolic pressure) while increasing the diastolic pressure-time index (DPTI, the time integral of central aortic diastolic blood pressure). This device is often sufficient to transition the patient off CPB. More profound ventricular dysfunction may require mechanical assistance in the form of an implanted pump, a ventricular assist device (VAD). These come in many designs and, in some cases, may be left in place for a prolonged period while the patient awaits recovery or a heart transplant. Right-heart failure resulting from pulmonary hypertension may be treated by the addition of pulmonary vasodilator inhaled nitric oxide (iNO).

F. Physiological response to CPB

Besides the purely mechanical aspects of being connected to extracorporeal circulation machinery, CPB also triggers a whole-body inflammatory response which is maladaptive, in the sense that it is not limited to the site of injury but affects the entire patient. Details of this process and the means of dealing with it are an area of active research. Neurocognitive deficits are another recognized but not fully understood side effect of CPB. In the meantime, efforts have been made to perform cardiac surgery, when feasible, without CPB. One procedure that is commonly performed either with or without CPB is coronary artery bypass grafting (CABG). "Off-pump" CABG is done on focally-immobilized beating heart, often through a small incision. Somewhat surprisingly, the most convincing studies to date show no superiority of off-pump coronary surgery to the traditional procedure in terms of patient outcomes, both cardiac and neuropsychological, or healthcare economics (ROOBY trial [Shroyer, A.L., et al. NEJM 2009]). Perhaps, the difficulty of achieving a complete and lasting coronary revascularization on a beating heart (off-pump CABG) balances out the deleterious effects of the CPB (traditional CABG). Endovascular approaches to cardiac valve repair (aortic, mitral) are being aggressively pursued as well, often enabling patients who are too frail for traditional open-heart valve replacement to reap the benefits of improved valvular mechanics and cardiac performance. Both off-pump CABG and endovascular valve-repair procedures are critically dependent on



the skill of a cardiac anesthesiologist in terms of both patient management and intraoperative TEE monitoring.

G. Tissue perfusion and oxygenation under CPB

A cardinal question for physicians taking care of patients undergoing cardiac surgery on CPB is what constitutes the optimal perfusion. In one sense, the answer is simple: it is the type of perfusion that produces the best outcome for the patients. The implication is that this type of perfusion would be most beneficial (or least damaging) to vital organs and tissues. Or, looking from the standpoint of healthcare economics, it is the type of perfusion associated with the shortest ICU and hospital stays, or the fastest return to preop functioning. The answers become complex when one looks for the single best perfusion strategy in terms of variables that are under the direct control of surgeons, anesthesiologists, and perfusionists. The types of circuits used, coatings, adjuvants (especially anti-inflammatory drugs), the use of ischemic and pharmacological preconditioning, and the degree of hypothermia are all being closely investigated.

Hypothermia, as previously mentioned, can be cardioprotective. However, deep hypothermia increases blood viscosity and can lead to sludging and even occlusion of small blood vessels. Therefore, the desire to maximize tissue oxygen delivery by increasing the hemoglobin concentration is offset by the negative rheological consequences of high Hgb. In the setting of hypothermia management of the acid/base status is non-trivial, as well, owing to the increased plasma solubility of carbon dioxide gas at lower temperatures. Should the patient's arterial blood gases be corrected to the actual patient temperature (the pH-stat strategy) or not (alpha-stat)? The strategy chosen may need to vary depending on individual patient's characteristics.

Patient's blood pressure on CPB is, approximately, a simple function of variables under our control:

$$P = (\text{pump flow}) * (\text{systemic vascular resistance}).$$

Flow is regulated by the pump setting, and SVR can be titrated with vasopressor drugs. Even in this simple scenario, the optimal parameters of blood pressure are controversial. A minimal pressure threshold likely exists, below which the brain and other important organs are taken outside of their autoregulatory range. This minimum value, moreover, varies with the patient's pre-existing hypertensive disease. Above this threshold, is higher pressure better for end-organ perfusion? Not necessarily, as higher pump flows needed to raise the pressure are more damaging to vessel walls and, accordingly, tend to increase the atheroembolic burden to end organs.



Intraoperatively, we attempt to monitor perfusion and oxygenation with a battery of measurements, such as mixed-venous O₂ saturation, blood gases, urine output, cerebral oximetry, gastric mucosal pH, etc. These indices provide suggestions as to how to improve organ perfusion in an individual patient in real time. Collected from a cohort of subjects, they can be correlated with specific postoperative outcomes of end-organ dysfunction (myocardial damage, renal failure, brain injury) or, more likely, their surrogates (cardiac enzymes leaks, increases in serum creatinine, lower neurocognitive scores, respectively). The evidence-based answers to the question of optimal perfusion are just now beginning to emerge.

Suggested Readings:

- 1) Hickey PR, Buckley MJ, Philbin DM. **Pulsatile and nonpulsatile cardiopulmonary bypass: review of a counterproductive controversy.** Ann Thorac Surg. 1983 Dec;36(6):720-37.
- 2) **Mechanical Circulatory Support.** Lewis T, Graham TR, eds. London, Boston: E. Arnold, 1995.
- 3) Hogue CW Jr, Palin CA, Arrowsmith JE. **Cardiopulmonary bypass management and neurologic outcomes: an evidence-based appraisal of current practices.** Anesth Analg. 2006 Jul;103(1):21-3.

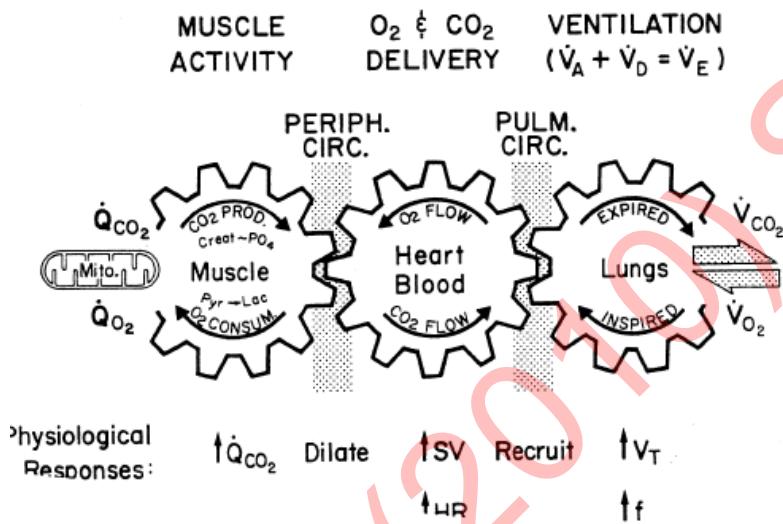


Last Year's (2010) Syllabus

Exercise Physiology

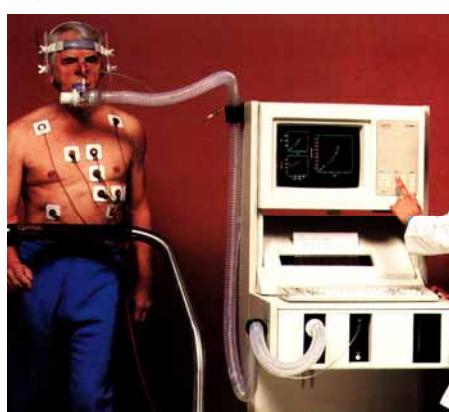
I. HEART AND LUNGS DURING EXERCISE: GOALS

- A. Principal goals of the circulatory and respiratory systems during exercise:
 1. Adequate O₂ delivery to exercising muscle
 2. Adequate ventilation (CO₂ removal)
- B. Integrated responses of lungs, heart, muscle

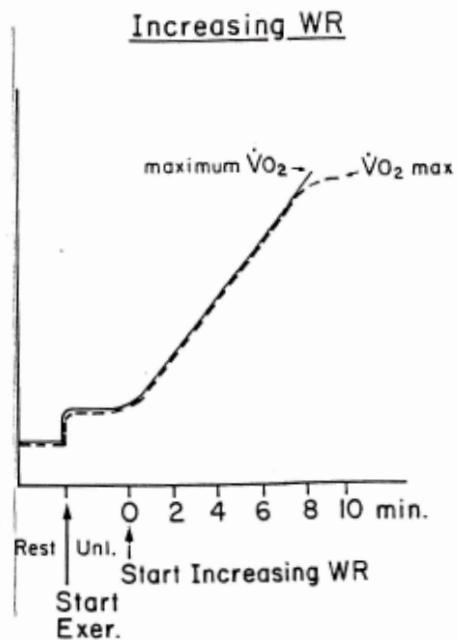


II. MEASURING EXERCISE PERFORMANCE

- A. Best measure of performance:
 1. O₂ consumption (VO₂)
 2. Calculated from minute ventilation and inspired and expired O₂ concentrations
- B. Cardiopulmonary Exercise Testing



C. Ramp Protocol: VO₂max



D. Dr. Fick (again)

1. How does VO₂ rise?

2. By Fick principle:

$$\dot{V}O_2 = CO(CaO_2 - CvO_2)$$

$$= CO \times CaO_2 - CO \times CvO_2$$

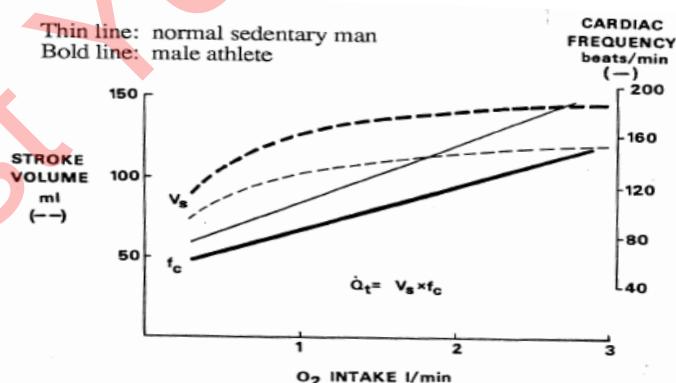
(units are: L/min·mL/L)

= O₂ to periphery – O₂ from periphery

3. So, if VO₂ ↑, CO and/or CaO₂ – CvO₂ must ↑.

4. They both do: $\dot{V}O_2 = HR \cdot SV (CaO_2 - CvO_2)$

E. HR and SV Responses



F. CO, VO₂ and a-vO₂Δ all ↑

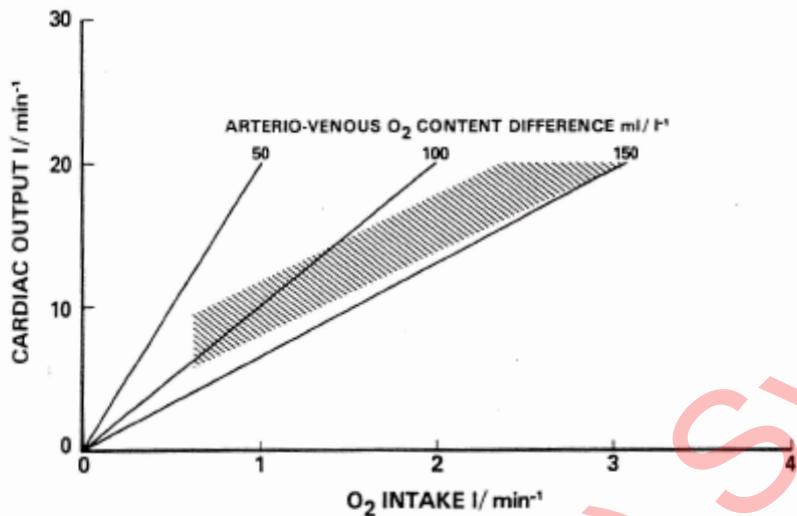
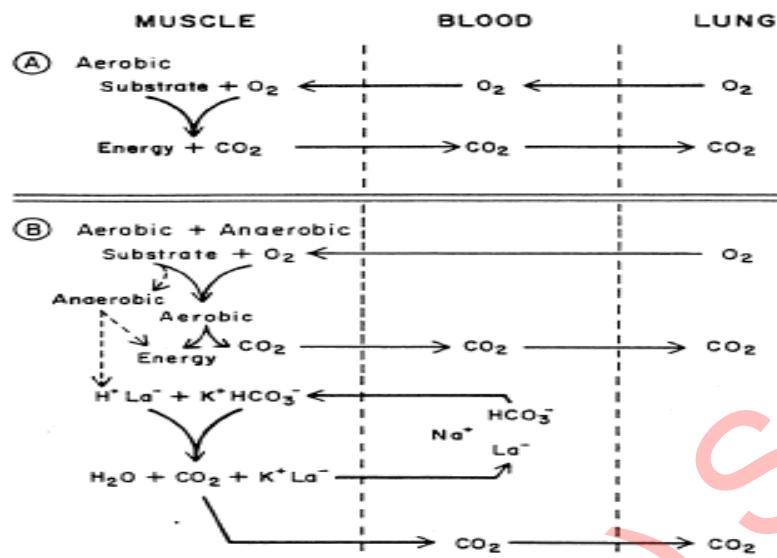


Figure 2–11. Normal range (± 1 SD) of cardiac output in exercise.

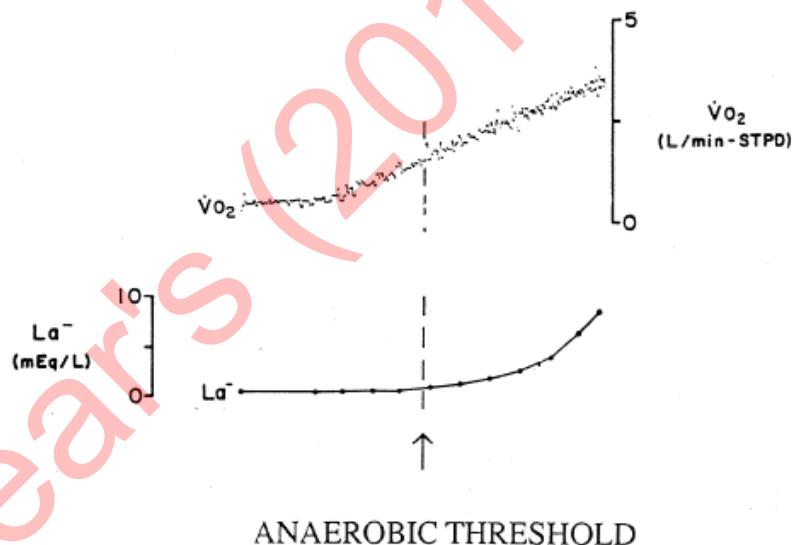
- G. What limits VO_{2max} and exercise capacity
1. Normally, the exhaustion of circulatory reserve
 2. HR, SV, Ca-vO₂Δ responses all at maximum levels.
 3. Exercising muscle can no longer sustain aerobic metabolism
- H. What defines a circulatory limitation to exercise?
1. Classically: Anaerobic threshold
 2. Shift from principally aerobic to principally anaerobic metabolism



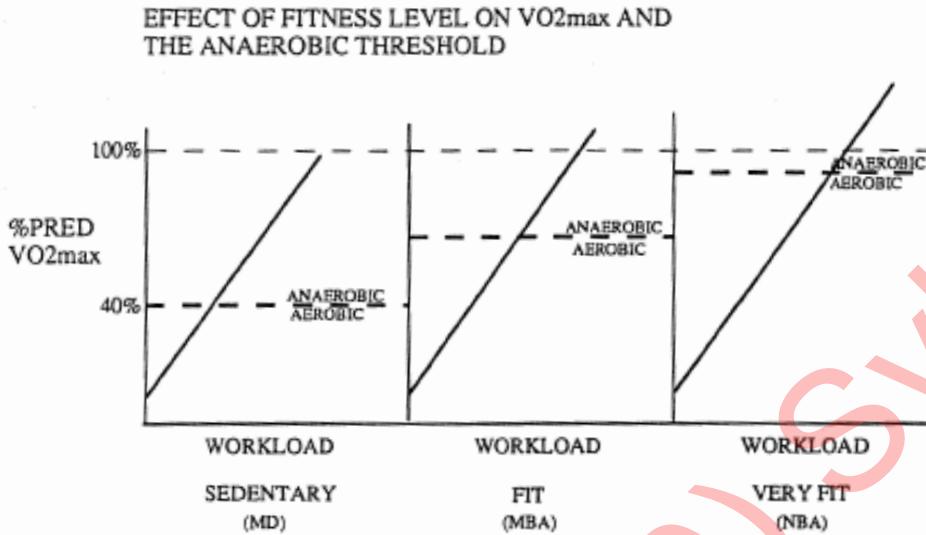
III. CO₂ PRODUCTION: AEROBIC VS. ANAEROBIC METABOLISM



A. Anaerobic Threshold (AT): Lactate Levels



B. Effects of Fitness Level



C. Abnormal Circulatory Limitation

1. Low VO₂max and early AT
2. Causes: Any lesion, from alveolus to mitochondrion, that blocks O₂ delivery and utilization
 - a. Hypoxemia
 - b. Pulmonary vascular disease and right heart failure
 - c. Left heart failure
 - d. Peripheral vascular disease
 - e. Anemia or abnormal Hgb
 - f. Myopathy

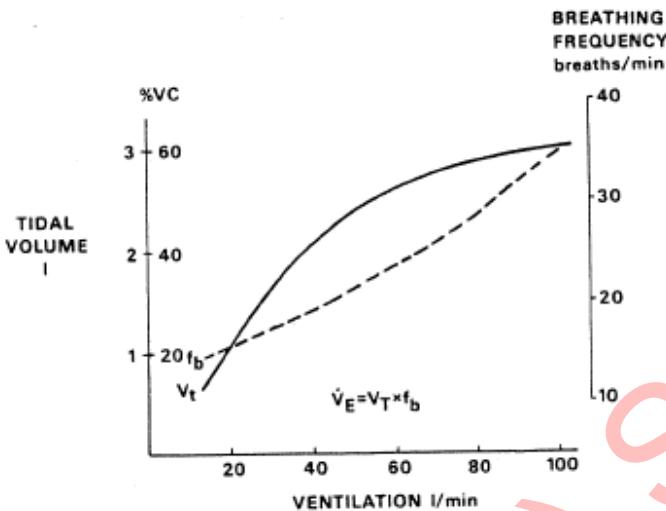
D. Ventilatory Response to Exercise

	V _E (L/min)	Tidal volume (L)	Respiratory rate (breaths / min)
Rest	6	0.5	12
Maximal Exercise	192	4	48
Relative ↑	32x	8x	4x

Ventilation at rest and at maximal exercise in a large, healthy, fit male

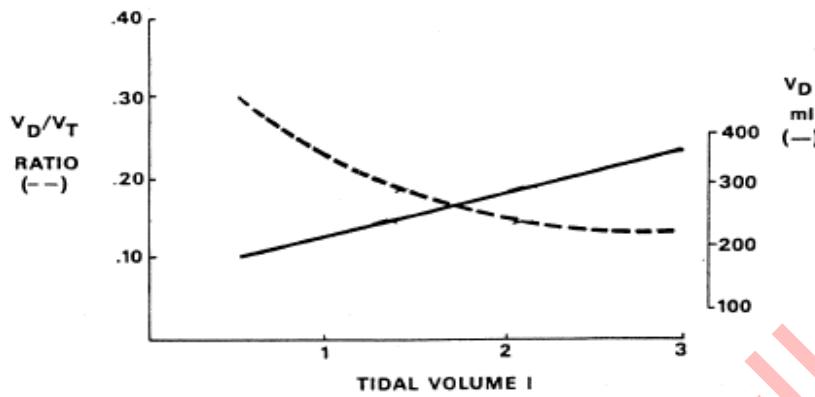


E. Tidal Volume and Respiratory Rate Responses



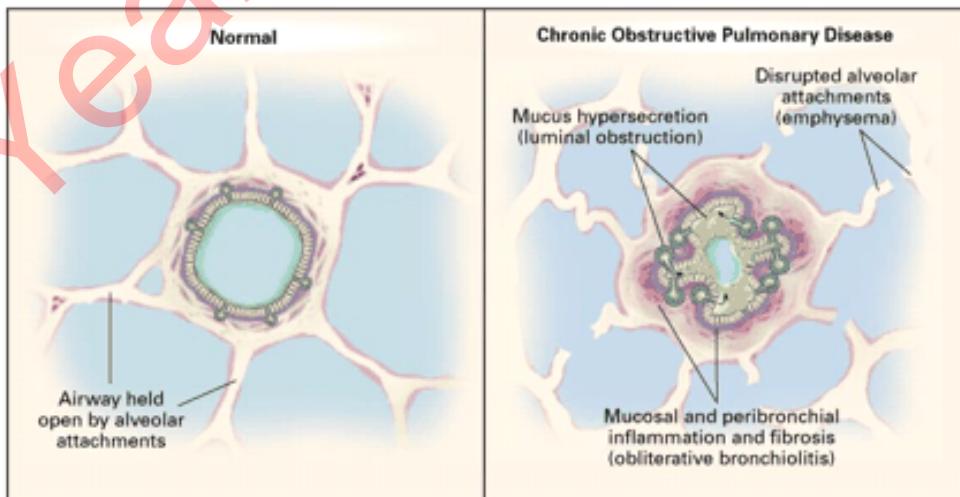
1. The most useful formula in the ICU
$$\text{VCO}_2 = \frac{\text{VE} \times \text{PaCO}_2}{(1 - \text{Vd}/\text{Vt})}$$
2. Dead Space
 - a. $\text{Vd}/\text{Vt} = \text{dead space:tidal volume ratio}$
 - b. During exercise:
 - 1) Anatomic dead space $\uparrow\uparrow$ (tethering effect of high lung volumes on the conducting airways)
 - 2) Alveolar dead space \downarrow
 - i. V/Q improved
 - ii. \uparrow 'd bloodflow to lung apices (where V/Q is high at rest)
 - c. Net effect: Total (physiologic) dead space (Vd) \uparrow
 - d. However, $\text{Vd} \uparrow/\text{Vt} \uparrow\uparrow$ means $\text{Vd}/\text{Vt} \downarrow$
 - e. Take home: ventilation is MORE efficient during exercise
 3. $\text{Vd} \uparrow$ but $\text{Vd}/\text{Vt} \downarrow$



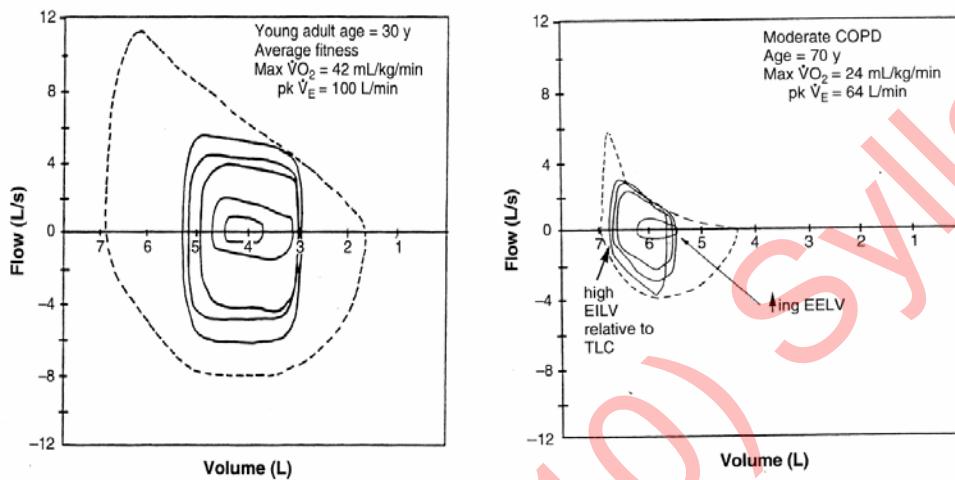


IV. VENTILATORY LIMITATION

- A. When is ventilation a limiting factor?
 1. MVV = maximal voluntary ventilation: Measured directly, or as FEV1 x 35.
 2. VEmax / MVV serves as a “dyspnea index”: Measures ventilatory reserve
- B. VEmax / MVV \geq 70% signals a ventilatory limitation to exercise
 1. Usually not reached by normal subjects except at peak exercise
 2. Can result from high VE or low MVV
 3. Patients with ventilatory limitation
 - a. Moderate to severe COPD
 - b. Severe restrictive lung disease
- C. Chronic Bronchitis



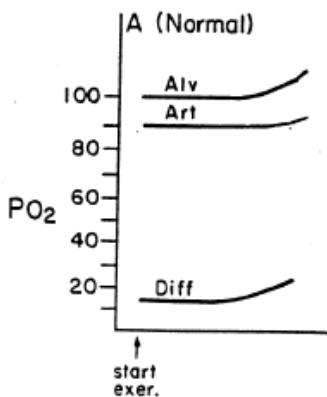
- D. Flow-Volume Loops During Exercise
1. Normal subjects at rest have substantial flow and volume reserve to call upon during exercise
 2. Patients with moderate to severe COPD have little extra capacity to breath at higher flows and tidal volumes



V. PULMONARY VASCULAR FUNCTION DURING EXERCISE

- A. Central vascular pressures all ↑ with incremental exercise
- B. PA – PCW = CO·PVR
↑ ↑↑ ↓
- C. ↓ PVR is due to pulmonary vascular recruitment and distension
 1. Improves overall V/Q matching
 2. Allows V_d/V_t to ↓
 3. Critically important for adequate oxygenation during exercise
- D. Oxygenation during exercise
 1. Despite greater extraction of O₂ in the periphery, blood is reoxygenated due to:
 - a. Hyperventilation at heavy workloads
 - b. Improved V/Q matching
 - c. Increased diffusion surface area
 2. Oxygenation During Exercise (PO₂ Levels)





SUMMARY

- A. Exercise is normally limited by exhaustion of circulatory reserve, but patients with reduced lung function (eg, COPD patients) can reach a ventilatory limitation (eg, COPD)
- B. Heart rate, stroke volume, and peripheral O₂ extraction all increase to allow VO₂ to rise during exercise
- C. The pulmonary response to exercise includes increases in tidal volume and respiratory rate, a fall in Vd/Vt (more efficient ventilation) and recruitment/distension of the pulmonary vasculature to accommodate the rise in CO (plus better matching of V&Q at the lung apices).
- D. The ventilatory response to exercise (VE) is predictable from the relation of VE to CO₂ production, PaCO₂, and 1-Vd/Vt (efficiency factor). Ventilatory responses during critical illness follow the same rules!!
- E. On a "ramp" protocol, as the subject moves from light exercise (below AT) to heavy exercise (above AT) to "full-out" exercise, the slope of VE vs. workload increases, while VO₂ rises linearly. This relates, in part (there are local factors at work as well!) to the appearance of lactic acid above the AT, and the need to compensate for the metabolic acidosis at the highest levels of exercise.



Last Year's (2010) Syllabus

Ischemic Heart Disease

Reading assignment: Katzung (10th ed), Ch. 35 (statins),
Ch. 36 (aspirin), Ch. 19 (nitric oxide)

LEARNING OBJECTIVES:

- A. Understand the roles that nitric oxide plays in the function of vascular endothelial cells and in the development of atherosclerosis.
- B. Understand the contributions of LDL cholesterol and inflammation to the development of atherosclerosis. Learn the pharmacology of HMG-CoA reductase inhibitors. Understand the rationale for their use in the prevention of atherosclerotic cardiovascular disease.
- C. Understand the role of thrombosis in the patho-physiology of coronary artery disease (CAD). Learn the pharmacology of low-dose aspirin and understand the rationale for its use in CAD.

TOPICS

- A. Atherosclerosis
- B. Inhibitors of HMG CoA reductase
- C. Aspirin



Last Year's (2010) Syllabus

CONGESTIVE HEART FAILURE

OBJECTIVES

1. Review the indices of cardiac performance.
2. Introduce commonly used devices for gauging cardiac function in patients.
3. Discuss the incidence of congestive heart failure (CHF) and its financial impact.
4. Consider the prognosis of patients with CHF.
5. Describe the clinical manifestations of CHF and introduce two classification systems for describing severity of cardiac dysfunction.
6. Identify the etiologies of CHF.
7. Describe the pathophysiology of CHF:
 - a. Compensatory Mechanisms
 - b. CHF at the Cellular and Sub-cellular Levels
 - c. Myocardial Remodeling
 - d. The Neurohormonal Component of CHF
8. List Current Therapies for CHF.
9. Preview Experimental Therapies for CHF.

I. DEFINITION

- A. Congestive heart failure (CHF) is a condition in which the heart fails to pump enough blood to support metabolizing tissues. It is characterized by impediment to left ventricular emptying and/or left ventricular filling. CHF is a disorder caused by low cardiac output. However, it is also a disorder in which overly active compensatory mechanisms play an important role in disease progression.¹

II. CARDIAC PERFORMANCE

- A. Depends upon:
 1. “Preload”
 2. Inotropic State of Cardiac Muscle (Starling Curve)
 3. “Afterload”



III. OPTIMAL SARCOMERE LENGTH AND THE CONCEPT OF “PRELOAD”

- A. Recall that at longer muscle lengths the force developed by cardiac muscle fibers increases progressively until the L_{max} point. At a sarcomere length of 2.2 μm , there is optimal overlap of thin and thick filaments, maximizing the formation of cross-bridges. There also appears to be a relationship between sarcomere length and myofilament sensitivity to Ca^{+2} , with 2.2 μm representing the optimal sarcomere length for Ca^{+2} activation.
- B. When force generated and muscle length are plotted for cardiac muscle, one observes that greater force occurs as muscle length increases until the L_{max} is exceeded (see Figure 1). The muscle length is considered the “preload.”

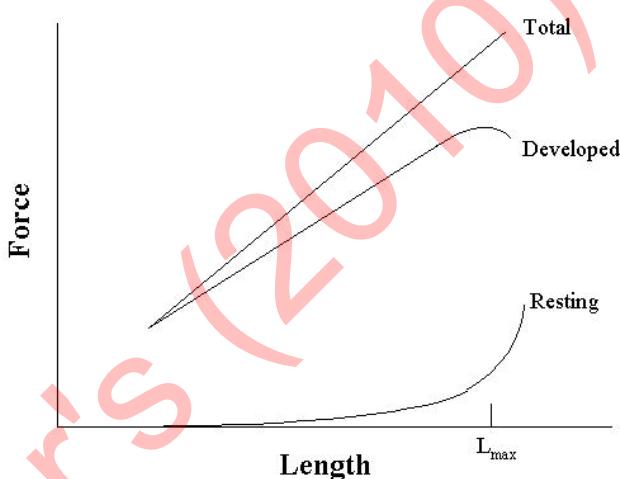


Figure 1. Force-Length Curve. The resting force of cardiac muscle gradually increases until the L_{max} is reached, at which point it rises abruptly. The developed force rises to a peak at the L_{max} and declines after this point.

IV. THE CHALLENGE OF DETERMINING “PRELOAD” AT THE ORGAN LEVEL

- A. At the organ level the relationship between force generated and muscle length still holds. The force of ventricular contraction increases (within certain limits) as a function of end-diastolic ventricular muscle length. End-diastolic ventricular muscle length is proportional to end-diastolic ventricular volume. Therefore,



- ventricular end-diastolic volume can serve as a surrogate for “preload” at the organ level.
- B. Although end-diastolic ventricular volume is a reasonable measure of “preload,” end-diastolic ventricular pressure is often more expedient to determine in patients. Therefore, ventricular end-diastolic pressure is commonly used clinically to gauge “preload” rather than end-diastolic volume.
 - C. Importantly, the relationship between ventricular end-diastolic pressure and end-diastolic volume in the heart is dynamic. The compliance of cardiac muscle can change rapidly. As a result, the relationship between end-diastolic pressure and end-diastolic volume can also change. For example, ischemia can cause the compliance of cardiac muscle to decrease significantly in a patient with coronary artery disease. In this instance, the same volume of blood might generate a higher intra-ventricular pressure after the onset of ischemia than before the ischemic event. Pressure data, therefore, must be interpreted within the context of the clinical status of the patient in order to provide useful information regarding “preload.”
 - D. Excessive “Preload” Can Compromise Perfusion to the Myocardium
 - 1. The volume of blood inside the ventricle does more than simply stretch the cardiac muscle fibers to enhance contractility. If the intra-ventricular volume rises too much, it will cause significant pressure on the adjacent ventricular wall. This pressure can lead to a reduction in the driving force for perfusion of the myocardium by the coronary arteries (i.e., it can diminish the pressure gradient between the aortic root and the distal aspects of the coronary vessels within the myocardium). In this situation, coronary perfusion may be reduced and myocardial function may become impaired.

V. MEASURING “PRELOAD,” CARDIAC OUTPUT, AND “AFTERLOAD” IN PATIENTS

- A. Fluid-filled catheters can be advanced into the right side of the heart after being introduced percutaneously into the internal jugular, external jugular, subclavian, or femoral veins. A central venous (CVP) catheter allows measurement of pressure at the junction of the superior vena cava and the right atrium. A pulmonary artery (Swan-Ganz) catheter is used to determine right atrial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure (which reflects left ventricular end diastolic pressure), and cardiac output. It also facilitates determination of systemic vascular resistance (“afterload”).



- B. Perhaps the most interesting aspect of a Swan-Ganz catheter is that it is inserted into the right side of the heart, but it allows the evaluation of left ventricular “preload”, output, and “afterload” (see Figures 2 and 3).

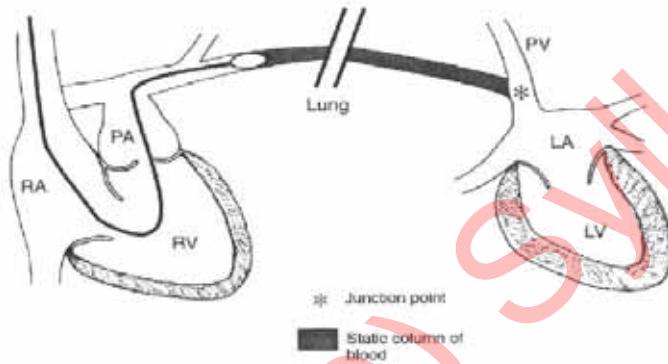


Figure 2. Swan-Ganz Catheter. The Swan-Ganz Catheter is a balloon-tipped flow guided catheter that is inserted percutaneously. The catheter tip is advanced into a pulmonary artery branch. In the absence of significant pulmonary disease or high alveolar pressures, a static column of blood is generated from the left atrium to the Swan-Ganz catheter tip when the balloon is inflated. During opening of the mitral valve, the pressure measured at the tip of the Swan-Ganz catheter (with the balloon inflated) reflects left ventricular end diastolic pressure. The Swan-Ganz catheter can also be used to determine cardiac output by injection of saline into the right atrium. A thermistor on the Swan-Ganz catheter tip allows thermodilution analysis and calculation of blood flow through the heart. Because all blood that passes through the pulmonary artery is soon ejected from the heart by the left ventricle, this technique is used to approximate left ventricular output. Schematic from Mark JB. Atlas of Cardiovascular Monitoring. Churchill Livingstone. New York. 1998.



$$\text{Systemic Vascular Resistance} = \frac{(\text{Mean Arterial Pressure} - \text{Central Venous Pressure}) \times 80}{\text{Cardiac output}}$$

Normal = 800 to 1200 dyne/second/cm⁵

$$\text{Cardiac Output} = \text{Heart Rate} \times \text{Stroke Volume}$$

Normal = 4.5 to 9.0 liters/minute

$$\text{Cardiac Index} = \frac{\text{Cardiac Output}}{\text{Body Surface Area}}$$

Normal = 2.5 to 4.0 liters/minute/m²

Figure 3. Values and Formulas used to characterize Cardiovascular Status.

- C. Techniques for measuring cardiac chamber volume are also available, including transthoracic and transesophageal echocardiography (see Figures 4-6). A certain degree of expertise is required to perform these procedures, and the studies can be technically difficult in certain patients. Also, they cannot be used continuously.
- D. Echocardiography is advantageous in that it allows the simultaneous evaluation of cardiac chamber volume, wall motion, and valvular function. Echocardiography can also be used to estimate cardiac performance. It can be used to approximate ejection fraction (EF) and cardiac output (CO).

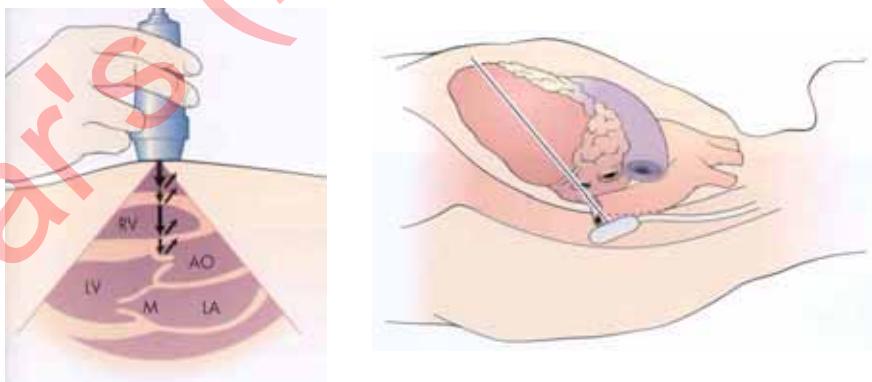


Figure 4. Transthoracic (left) and Transesophageal (right) Echocardiography. Transthoracic and transesophageal echocardiography can be used to evaluate cardiac function and structure. The transthoracic approach is more expedient and can be performed on awake, non-sedated patients. However, the quality of the images may be inferior to those obtained using the transesophageal approach. In addition, transthoracic echocardiography requires that appropriate acoustic windows be identified. In certain patients (patients with chest wall deformities, trauma patients



with immobilization devices, or morbidly obese patients), these imaging windows may be difficult to obtain. Images acquired by the transesophageal approach are usually of higher quality. However, the transesophageal approach requires placement of the echo probe into the esophagus and/or the stomach. Transesophageal echocardiography, therefore, requires that the patient be sedated or undergo general anesthesia. Images from Miller RD and Reves JG, Atlas of Anesthesia, Volume VIII. Churchill Livingstone, Philadelphia.1999.

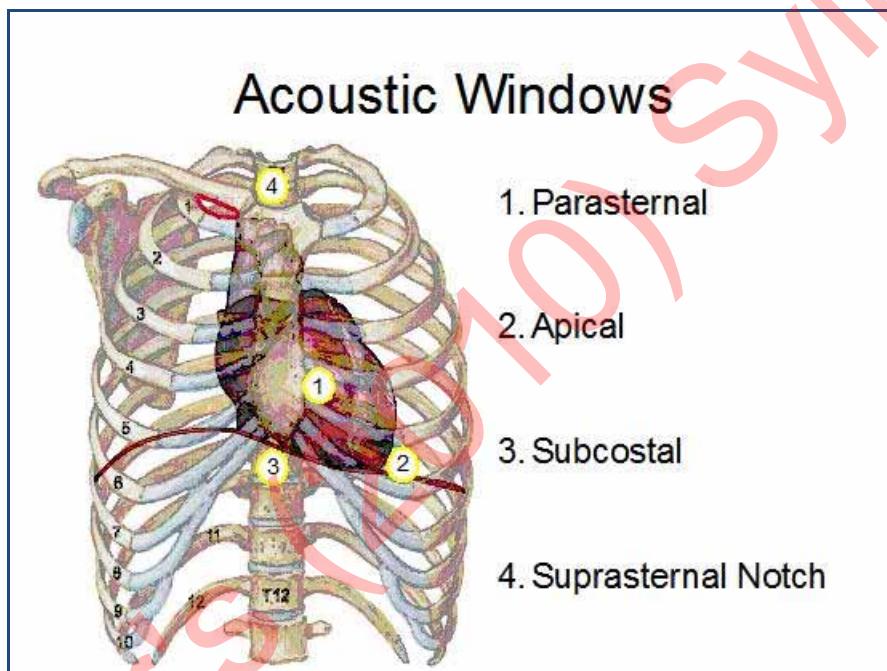


Figure 5. Transthoracic Echocardiography. Four views are used in transthoracic echocardiography: parasternal, apical, subcostal, and suprasternal. To obtain an appropriate image, an acoustic window must be identified that avoids the sternum, the ribs, or other organs. The apical approach affords a four-chamber view that can be used to estimate ventricular volume. Image from University of Minnesota, 2006.



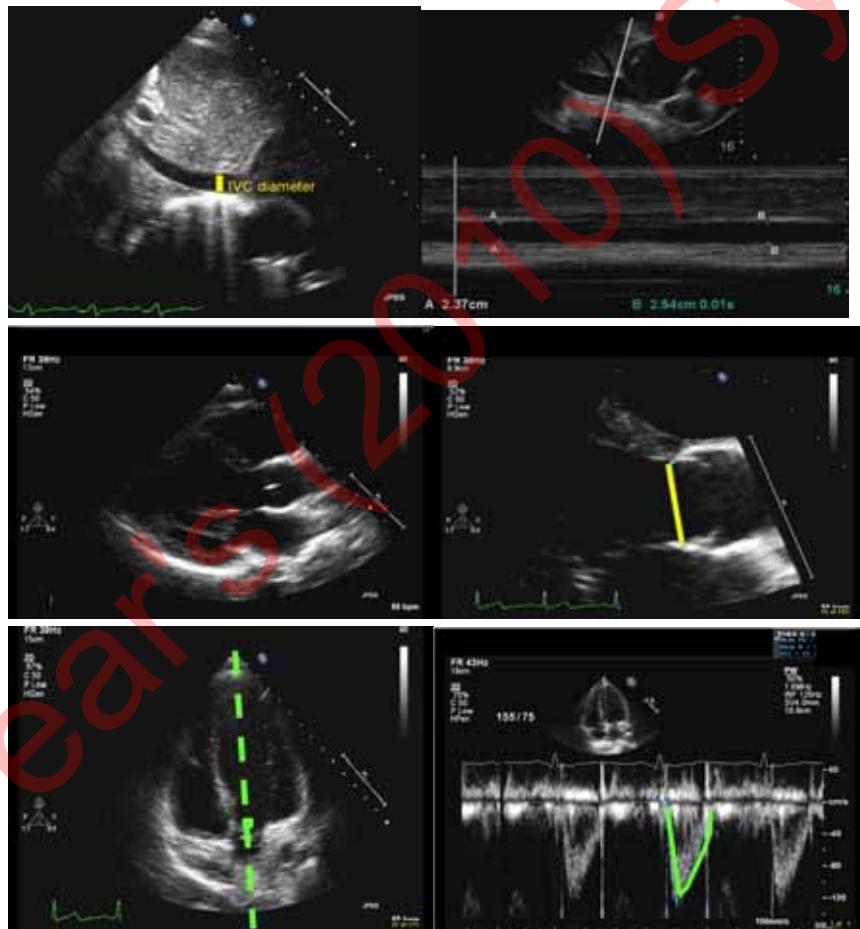
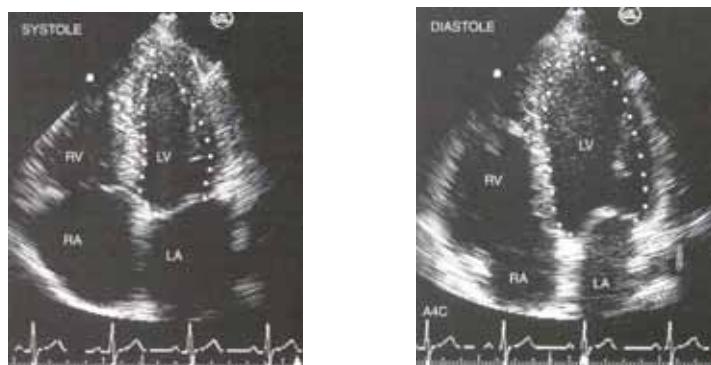


Figure 6. Transthoracic Echocardiography can be used to determine Preload and Stroke Volume/Cardiac Output. Preload can be evaluated in two ways: By estimating the left ventricle end diastolic volume and by evaluating the inferior vena cava diameter. Stroke volume/cardiac output can also be evaluated in two ways: By using the Simpson Method and by measure how much blood flows through the left ventricle outflow tract during each heart beat.

Figure 6 (continued). The Simpson Method involves tracing the endocardial border of the left ventricle at end systole (top left) and at end diastole (top right). The calculated end systolic volume is then subtracted from the end diastolic volume to determine the stroke volume. The cardiac output can then be estimated by multiplying the stroke volume by the heart rate. Note that echocardiography provides two-dimensional images of a three dimensional structure. Therefore, certain assumptions must be made to calculate chamber volumes. One assumption is that the left ventricle is shaped like a cone. That assumption is usually valid. However, certain disease states can alter the ventricular geometry. The top two images are from Otto CM. Textbook of Clinical Echocardiography, 2nd Ed. W.B. Saunders Co. Philadelphia. 2000. In the second row of images, a subcostal view of the inferior vena cava is shown. On the left side is a 2 Dimensional image. On the right side, an M-mode beam is shown being directed across the inferior vena cava as it enters the right atrium. To evaluate left ventricle preload, the diameter of the inferior vena cava is measured at inspiration and at expiration. The objective is to assess whether respiratory variation in the inferior vena cava diameter is present. If the inferior vena cava is less than 2 cm or if respiratory variation exists, the patient's intravascular volume may be depleted and cardiac output might be improved by increasing the intravascular volume (i.e., the left ventricle is still on steep part of the Starling Curve). In the third row of images, a parasternal long axis view is shown. On the left, the left ventricular outflow tract is identified. On the right, its diameter is measured after zooming in on the structure during mid-systole. Using the diameter measurement, a Cross Sectional Area of the left ventricle outflow tract can be calculated. This is part of the calculation to determine how much blood is flowing through the left ventricle outflow tract with each heart beat. The other part of the calculation involves determination of the Velocity Time Integral using the apical five chamber view. In the fourth row of images, an apical five chamber view is



shown. The apical five chamber view can be used to calculate the Velocity Time Integral using pulse doppler imaging. On the left, the pulse doppler beam is directed in the line of the left ventricular outflow tract. On the right, a pulse doppler measurement is taken just proximal to the aortic valve and the Velocity Time Integral is calculated by determining the area under the curve. The left ventricle stroke volume can be calculated by multiplying the Cross Sectional Area of the left ventricle outflow tract and the Velocity Time Integral. The details of the measurements described in this figure legend are beyond the scope of this course. However, the idea that left ventricle preload and stroke volume/cardiac output can be easily determined using echocardiography should be appreciated (i.e., you will not be tested on these details!).

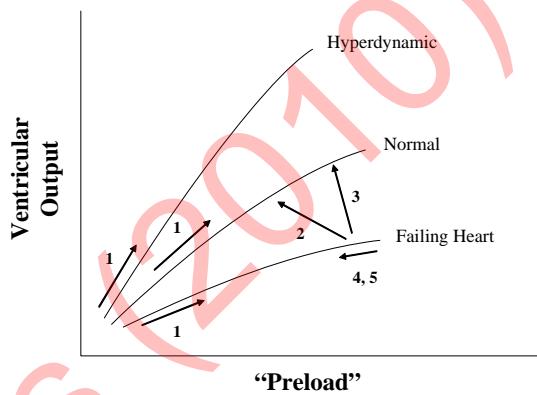


Figure 7. Starling Curves for the Normal, Hyperdynamic, and Failing Heart. Increasing “preload” (1) will improve ventricular output in normal, hyperdynamic, and failing hearts within certain limits. Clinically, greater “preload” can be achieved by increasing intravascular volume. Pharmaceutical agents can elicit a shift from one Starling Curve to another. Arterial vasodilators (2) decrease “afterload” and improve ventricular output. They also elicit a small decrease in “preload.” Inotropic agents (3), such as dopamine, epinephrine, and norepinephrine, improve ventricular output by changing the inotropic state of cardiac muscle. Venodilators (4) and diuretics (5) can decrease ventricular volume by causing “pooling” of blood outside the central venous system and by reducing intravascular volume, respectively.



VI. INOTROPIC STATE OF CARDIAC MUSCLE AND “AFTERLOAD”: DEFINING STARLING’S CURVES

- A. Clinically, it is useful to plot “preload” versus ventricular output (the Starling relationship). By doing so, one can easily identify normal, hypodynamic, and hyperdynamic ventricular function. The inotropic state of the cardiac muscle as well as the “afterload” determines the Starling Curve on which the heart “moves.” The “preload” determines where along the Starling Curve the heart “resides.” It is important to understand how different therapeutic agents and interventions affect the Starling Curves (see Figure 7).

VII. CLINICAL SCENARIO

A 35 year old woman (Mrs. Thompson) presents to your clinic with shortness of breath that has become progressively more severe during the past month.

Six weeks prior to presentation Mrs. Thompson gave birth to a healthy baby boy (her third child). The pregnancy was uncomplicated. The delivery was a normal spontaneous vaginal delivery.

Mrs. Thompson reports that during the past month she developed an intolerance to lying flat and now requires four pillows to prop her head up when sleeping. She also describes fatigue that has worsened over the course of the past six weeks. Most recently (for the past week) she has experienced a non-productive cough. She denies fevers or use of any medications. She has no known drug allergies.

She had been breastfeeding, but her fatigue and shortness of breath have forced her to transition the baby to formula feeds. The baby is healthy and has achieved age-appropriate milestones. Her husband and two other children are also healthy.

Physical examination reveals a pale woman in mild distress. Her heart rate is 120 beats per minute. Her respiratory rate is 35 breaths per minute. Her oxygen saturation by pulse oximetry is 89% while breathing room air. She is 5 feet 6 inches tall and weighs 155 lbs. (70 kg). Her blood pressure is 155/85 mm Hg. Jugular venous distension is apparent. Hepatomegaly is noted, as is moderate lower extremity edema. Auscultation of the chest reveals bilateral crackles, a third heart sound, and a pansystolic murmur best heard at the apex consistent with mitral regurgitation.

Electrocardiogram (ECG) demonstrates sinus tachycardia at 120 beats per minute. Chest radiograph (CXR) demonstrates cardiac enlargement, increased pulmonary vascularity, and moderate-severe pulmonary edema. Echocardiography reveals elevated left ventricular end diastolic (7.0 cm) and end systolic (5.8 cm) dimensions and an abnormally low ejection



fraction (25%). Atrial dilatation (5.2 cm X 5.6 cm) and moderate mitral regurgitation are also observed, and a small pericardial effusion is present.

Questions:

1. Which Starling Curve do you think best characterizes Mrs. Thompson's heart?
2. Where do you think her heart "resides" on this Starling Curve?
3. You decide to administer 20 mg of IV furosemide (lasix), which is a loop diuretic. How might this intervention affect the position of Mrs. Thompson's heart on the Starling Curve?
4. Two hours later, Mrs. Thompson remains short of breath. However, now her blood pressure has fallen to 105/60 mm Hg. If you were to repeat the transthoracic echocardiogram, would you expect to see a difference in the wall motion or dimensions of the left ventricle compared to the prior examination?
5. You decide to begin an infusion of dobutamine (an inotropic and afterload reducing agent). How might this intervention affect the Starling Curve on which Mrs. Thompson's heart resides? If you were to repeat the transthoracic echocardiogram once again, would you expect the wall motion of the left ventricle to change after institution of the dobutamine infusion?

VIII. THE PRESSURE-VOLUME RELATIONSHIP

- A. The pressure volume-loop (see Figure 8) diagrams the relationship between intraventricular pressure and volume throughout the cardiac cycle.

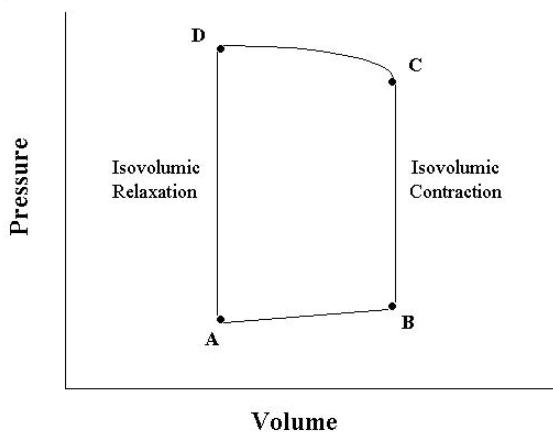


Figure 8. Pressure-Volume Loop. As time proceeds, the PV



points go around the loop in a counter clockwise direction. The point of maximum volume and minimal pressure is located at the bottom right part of the loop (B). This point marks the onset of systole. During the first part of the loop, pressure rises but volume remains constant (isovolumic contraction). When left ventricle pressure exceeds aortic root pressure, the aortic valve opens. At this point (C), ejection of blood from the ventricle begins and volume within the ventricle diminishes. When the ventricle reaches its maximum activated state (D), the aortic valve closes and isovolumic relaxation begins. Eventually, filling of the ventricle begins with mitral valve opening (A).

- B. Pressure-volume loops can be used to describe “preload,” compliance, “afterload,” and contractility (see Figure 9). Further, if one is bored and has a great deal of free time, one can diagram the changes in the pressure-volume loops expected during states of cardiac dysfunction, such as CHF (see Figure 10).

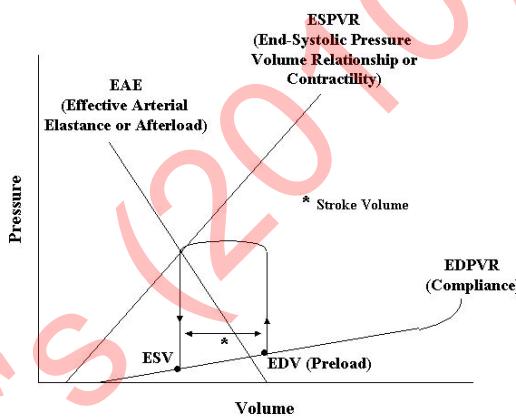


Figure 9. Pressure-Volume Loop Depicting Clinically Relevant Information. Pressure-volume loops can be used to accurately depict clinically relevant information, such as stroke volume, “preload”, compliance, contractility, and “afterload.”



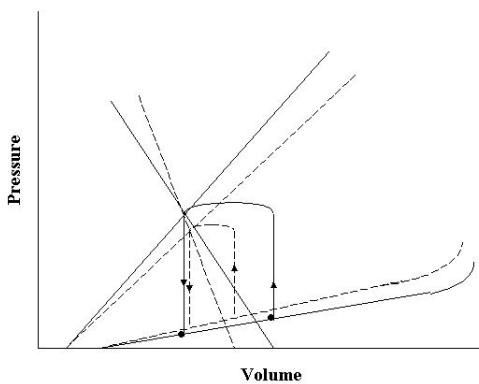


Figure 10. Changes in the Pressure-Volume Relationship. Changes in the pressure-volume loop that one might expect for a “volume-overloaded” heart failure patient are depicted.

IX. ANOTHER CLINICAL SCENARIO

A 79 year old male (Mr. Jones) is going to be admitted to the Intensive Care Unit post-operatively after undergoing revision of a left total hip replacement. The initial hip replacement was performed due to degenerative joint disease. The prior prosthesis became infected and was surgically removed three weeks ago. Subsequently, Mr. Jones was treated with intravenous antibiotics.

He has a history of coronary artery disease and is status post two myocardial infarctions during the past five years. He has renal insufficiency due to poorly controlled essential hypertension.

His intraoperative course has been complicated by an acute 1500 mL blood loss and an episode of hypotension (80/40 mm Hg). Immediately after the onset of hypotension he developed ischemic changes on his ECG. The Anesthesiologist immediately administered two units of packed red blood cells, one unit of fresh frozen plasma, and 1.5 liters of normal saline.

However, before these fluids could be administered the patient's pulmonary artery pressures increased from 20/12 to 47/30 mm Hg. His pulmonary capillary wedge pressure increased from 10 to 27 mm Hg. His cardiac output dropped from 5.4 to 2.8 liters per minute.

As the fluid was administered, the patient's blood pressure initially increased to 120/70, and the ischemic changes resolved. His central venous pressure increased from 4 to 14 mm Hg. His pulmonary artery pressures decreased to 35/24 mm Hg. His pulmonary capillary wedge



pressure decreased to 21 mm Hg. His cardiac output increased to 4.9 liters per minute.

Unfortunately, with the administration of two additional units of packed red blood cells and one unit of fresh frozen plasma, his blood pressure decreased again to 100/50. His central venous pressure rose to 25 mm Hg, and his cardiac output dropped to 3.2. There was again evidence of ischemia by ECG. His pulmonary capillary wedge pressure increased to 26 mm Hg.

Questions:

1. On which Starling Curve did Mr. Jones' heart reside at the beginning of the surgery/anesthesia?
2. If you had performed a transesophageal echocardiogram at the beginning of the surgery, would you have expected to observe wall motion abnormalities in the areas affected by his previous myocardial infarctions?
3. How do you think the position on the Starling Curve changed at the time of the acute blood loss episode?
4. How might cardiac ischemia affect which Starling Curve Mr. Jones' heart resides upon?
5. What might you expect to see by transesophageal echocardiography in terms of ventricular wall motion during cardiac ischemia?
6. During the episode of cardiac ischemia, what information might an echocardiogram provide that a pulmonary artery catheter could not?
7. With the administration of the first two units of packed red blood cells Mr. Jones' hematocrit increased, his oxygen carrying capacity improved, and the cardiac ischemia resolved. Why did the additional packed red blood cells and fresh frozen plasma cause him to deteriorate again? Where did his heart lie on the Starling Curve after this additional fluid administration?
8. You are debating whether to start a nitroglycerin infusion (venodilator and coronary artery dilator) versus an inotropic agent to improve his ventricular output after the second episode of hypotension. Would you expect these agents to change the Starling Curve on which Mr. Jones' heart sits? Would you expect them to keep his heart on the same Starling Curve but change its position on that curve?



9. After the administration of a venodilator like nitroglycerin, what might you observe by transesophageal echocardiography in terms of intra-ventricular chamber volume?

X. INCIDENCE OF CHF AND IT'S FINANCIAL IMPACT

- A. CHF affects approximately 5 million Americans and more than 6.5 million Europeans. It is the most common reason for hospitalization in the elderly. 20% of hospital admissions in patients over age 65 are due to CHF. Approximately 1% of the U.S. population over age 65 suffers from CHF.²
- B. Each year about 550,000 new cases of CHF are diagnosed in the United States (more than 1,000,000 cases worldwide). Further, CHF results in approximately 1,000,000 hospitalizations per year in the United States. Over the past 20 years, hospitalizations due to CHF have risen 155%.³ In 2006, the estimated direct and indirect cost of treating CHF in the United States was \$29.6 billion. More Medicare dollars are spent for the diagnosis and treatment of CHF than for any other diagnosis. In the United States, about \$500 million annually is spent on drugs for the treatment of CHF.^{4,5,6,7,8}
- C. Coronary artery disease is present in 50% to 60% of patients with CHF. Hypertension is present in 72% of patients with CHF. CHF patients commonly have several other comorbidities, including renal disease (30%), diabetes mellitus (43%), and chronic obstructive pulmonary disease (30%).^{9, 10, 11}

XI. PROGNOSIS OF PATIENTS WITH CHF

- A. Five year survival in patients with CHF is only 50%.¹²
- B. Patients hospitalized for treatment of acute decompensated CHF have a 4% to 8% in-hospital mortality.¹³ They have a 9% mortality rate at 60 to 90 days and a 29% mortality rate at 1 year.^{9, 14} They have a re-hospitalization rate of 30% at 90 days.¹⁵
- C. Co-existence of kidney disease and CHF significantly worsens prognosis of patients with CHF.¹⁶
- D. In patients with acute CHF or chronic CHF with acute decompensation, several factors have been associated with worse prognosis: reduced left ventricle ejection fraction, low blood pressure on admission to the hospital (systolic blood pressure < 115 mm Hg), elevated pulmonary capillary wedge pressure, blood urea nitrogen (BUN) greater than 43 mg/dL, creatinine greater than 2.75 mg/dL, elevated serum troponin, hyponatremia (low serum sodium concentration), and significant elevation of serum b-type natriuretic peptide level.^{9, 13, 15, 17}



XII. TYPES OF HEART FAILURE:

- A. Acute Heart Failure versus Chronic Heart Failure versus Acute Decompensation of Chronic Heart Failure
- B. Left-sided versus Right-sided Heart Failure
- C. Systolic versus Diastolic Heart Failure – 40% to 55% of CHF patients will have normal or relatively normal left ventricular systolic function.... more commonly females than males.^{9, 10, 11}
- D. Diastolic Heart Failure – During the past ten years, it has been recognized that a significant number of patients hospitalized with acute CHF demonstrate primarily diastolic left ventricular dysfunction while having normal or relatively normal left ventricular systolic function.¹⁸

The prevalence of diastolic heart failure depends upon the definition used. However, recent data suggest that between 3.1% and 5.5% of patients over age 65 suffer from the disorder,¹⁸ and the number of individuals affected may be increasing.¹⁹ Up to 50% of hospital admissions for CHF are now patients with primarily diastolic heart failure.²⁰ Compared to patients with systolic heart failure, patients with diastolic heart failure tend to be older, are more commonly female, have a higher prevalence of hypertension (64% to 78%), and have a lower incidence of coronary artery disease.^{19, 21, 22, 23}

Mortality is not as great for patients with diastolic heart failure as it is for patients with systolic left ventricular dysfunction and heart failure.¹⁵ However, morbidity and re-hospitalization rates are similar.²⁴

XIII. SYMPTOMS AND SIGNS OF CHF:

- A. Weakness*
- B. Fatigue*
- C. Reduced Exercise Tolerance*
- D. Dyspnea (shortness of breath)
- E. Lower Extremity Edema
- F. Sacral Edema
- G. Orthopnea
- H. Paroxysmal (Nocturnal) Dyspnea
- I. Cheyne-Stokes Respirations during Sleep
- J. Increased Incidence of Arrhythmias
- K. Tachycardia



- L. Heart Murmurs
 - M. Diminished Pulse Pressure
 - N. Distended Neck Veins
 - O. Pulsus Alternans
 - P. Pulmonary Rales
 - Q. Hydrothorax
 - R. Hepatomegaly
 - S. Liver Failure
 - T. Ascites
 - U. Decreased Urine Output
- * Earliest Symptoms

XIV. CHEST X-RAY FINDINGS CONSISTENT WITH CHF:

- A. Enlarged Heart
- B. Distention of the Pulmonary Veins
- C. Pleural Effusions

IV. DIAGNOSTIC ADJUNCTS – RAPID MEASUREMENT OF B-TYPE NATIURETIC PEPTIDE

- A. Recent data suggest that serum assay of b-type natriuretic peptide is helpful for improving the accuracy of diagnosing CHF.¹⁵ One study of 1,530 patients presenting to the emergency room with dyspnea demonstrated that b-type natriuretic peptide serum level improved the accuracy of CHF diagnosis from 65% - 75% up to 81%.²⁵ BNP levels above 100 pg/mL have been shown to have a sensitivity of 90% and a specificity of 76% for the diagnosis of CHF. They have also been shown to be very useful for discriminating patients with dyspnea caused by uncomplicated lung disease (who had BNP values below 100 mg/dL).²⁶
- B. Evaluating BNP levels in CHF patients in the emergency room has been shown to decrease the need for hospitalization and decrease the need for intensive care unit admissions. It has been shown to decrease total hospital stay by 3 days, to decrease the cost of treatment, and to decrease time to initiation of definitive therapy in the emergency room by 30 minutes.^{15, 27}
- C. BNP levels have also been shown to correlate with the severity of CHF. Higher levels have been correlated with worse left ventricular systolic function, a poorer prognosis, and a higher likelihood of functional deterioration and mortality.²⁸ In a study of 114 patients admitted to the hospital with NYHA class IV CHF, predischarge



BNP level was most strongly associated with death or readmission within 6 months.^{15,29}

- D. It should be pointed out that like all tests; measurement of BNP level has its shortcomings. For example, BNP levels are elevated not only in patients with CHF but also in patients with massive pulmonary embolism, severe pulmonary hypertension, and renal failure. Conversely, BNP levels may not be elevated in patients with “flash” pulmonary edema due to acute CHF.¹⁵
- E. Many institutions (including Stanford Hospital) use N-terminal (NT) proBNP measurements rather than BMP measurements. After synthesis, biologically active BNP is generated by peptide cleavage. The inactive aminoterminal fragment (NT-proBNP) is released during the cleavage process. Levels of NT-proBNP and BMP correlate with each other, but they are not interchangeable. When using NT-proBNP, a cut off of less than 300 pg/mL is used to rule out congestive heart failure. Age dependent cut offs are used to rule in congestive heart failure (>450 pg/mL for patients less than 50 years old; >900 pg/mL for patients 50 to 75 years old; >1800 pg/mL for patients older than 75 years).⁷⁰

New York Heart Association Functional Classification System

- used to quantify the degree of functional limitation imposed by CHF⁶

Class I (Mild) – No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, or shortness of breath

Class II (Mild) – Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitations, or shortness of breath

Class III (Moderate) – Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitations, or shortness of breath

Class IV (Severe) – Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

ACC/AHA Classification System

- recognizes established risk factors and structural prerequisites for the development of CHF⁷

Stage A - Patients at high risk for developing CHF due to condition(s) strongly associated with CHF. No identified structural or functional abnormalities of the pericardium, myocardium, or cardiac valves. No current signs or symptoms of CHF. (Example: Patients with hypertension; Patients with coronary artery disease; Patients with diabetes mellitus; Patients with alcohol abuse; Patients with history of rheumatic fever.)



ACC/AHA Classification System (continued)

Stage B – Patients who have developed structural heart disease that is strongly associated with the development of CHF but who have not demonstrated signs or symptoms of CHF. (Example: Patients with left ventricular hypertrophy or fibrosis; Patients with left ventricular dilatation or hypocontractility.)

Stage C – Patients with current or prior symptoms of CHF associated with underlying structural heart disease. (Example: Patients with dyspnea or fatigue due to left ventricular dysfunction; Asymptomatic patients undergoing treatment for prior symptoms of CHF.)

Stage D – Patients with advanced structural heart disease and marked symptoms of CHF at rest despite maximal medical therapy who require specialized interventions. (Example: Patients who are frequently hospitalized for CHF; Patients in the hospital awaiting heart transplantation; Patients at home receiving continuous intravenous support for symptom relief or who are being supported with a mechanical circulatory assist device.)

XVI. ETIOLOGIES OF CHF

- A. Impaired Myocyte Function
 - 1. Diffuse (Myocarditis, Cardiomyopathies, Global Cardiac Ischemia)
 - 2. Focal (Regional Cardiac Ischemia)
- B. Increased Pressure Load
 - 1. Intracardiac Obstruction (Valvular Disease Stenosis, Hypertrophic Cardiomyopathy with Aortic Outflow Obstruction, Tumor)
 - 2. Extracardiac Obstruction (Systemic Hypertension, Pulmonary Hypertension)
- C. Increased Volume Load
 - 1. Intracardiac (Valvular Insufficiency and Regurgitation, Left to Right Shunt... Atrial Septal Defect or Ventricular Septal Defect)
 - 2. Extracardiac (Anatomic Shunts... Patent Ductus Arteriosus, metabolic derangement... Beriberi, Thyrotoxicosis)
- D. Decreased Compliance
 - 1. Constrictive Pericarditis (Tuberculosis, Radiation)
 - 2. Hypertropy (Cardiomyopathies, Hypertension, Aortic Stenosis)
 - 3. Acute Cardiac Ischemia



XVII. PATHOPHYSIOLOGY OF CHF

- A. CHF may progress rapidly or slowly. In both instances, the endpoint is deterioration of cardiac output and hypoperfusion of vital organs
 - 1. Compensatory Mechanisms: To compensate for the reduced cardiac output in CHF, an elevation of ventricular filling pressure (“preload”) occurs. This results in rightward movement along the Starling Curve. Elevated filling pressures may be brought about by enhanced re-absorption of water in the kidney. If intra-ventricular volume increases too much, elevated filling pressures can compromise subendocardial blood flow, causing or worsening cardiac ischemia. For this reason, increasing “preload” may initially be compensatory and beneficial but may eventually become detrimental. With continued low cardiac output, sympathetic nervous system stimulation occurs. In addition, the renin-angiotensin-aldosterone axis is activated and vasopressin is released from the pituitary gland. These processes lead to additional sodium and water retention as well as vasoconstriction (increasing both “preload” and “afterload”). Activation of the sympathetic nervous system will also result in cardiac β adrenergic receptor activation. Initially, this will improve inotropic performance of cardiac muscle. Together, the compensatory processes of CHF may transiently increase cardiac output and systemic blood pressure. However, over time compensatory processes such as cardiac $\beta 1$ adrenergic receptor activation will cause myocardial injury. When this occurs, the left ventricle will begin to fail and the increased volume retention and “afterload” will lead to pulmonary congestion. Cardiogenic shock may eventually occur.⁷
 - 2. CHF at the Cellular and Sub-cellular Levels: Prolonged stimulation by the sympathetic nervous system leads to desensitization and down-regulation of cardiac β adrenergic receptors.⁸ In CHF patients a decrease in β adrenergic receptor density, uncoupling of β adrenergic receptors from their signaling cascades as a consequence of increased β adrenergic receptor kinase (β ARK1) activity, and increased Gai protein levels are all observed.³⁰ Clinically, the hearts of CHF patients become refractory to catecholamine stimulation.
 - a. Whether cardiac β adrenergic receptor desensitization and down-regulation are maladaptive or represent a protective response at the level of the myocyte is a matter of debate. It has been hypothesized that



desensitization and down-regulation reflect each cells' attempt to protect itself from the toxic effects of prolonged β adrenergic receptor activation. However, desensitization can have a detrimental impact upon cardiac function (reduced inotropic state of the cardiac muscle).^{30, 31}

- b. Administration of β adrenergic receptor blocking agents restores responsiveness to catecholamine stimulation in the hearts of CHF patients. These agents lead to a reversal of desensitization and down-regulation (normalization of β ARK1 activity and Gai levels). Although the idea of administering β blocker therapy to CHF patients may seem somewhat counter-intuitive, β blockers appear to allow the intracellular signaling system to return toward a normal state despite on-going elevation of catecholamine levels in CHF patients. In contrast, administration of β adrenergic receptor agonists and phosphodiesterase inhibitors has been shown to decrease survival of patients with CHF if administered for prolonged periods of time, even though they improve cardiac function acutely.
- c. Catecholamine stimulation of the myocardium appears to involve a delicate balance. Acute activation improves the inotropic state of the cardiac muscle and provides benefit to the organism as a whole in many circumstances. However, prolonged activation (as occurs in CHF) leads to compensatory and sometimes detrimental changes on the cellular and molecular levels.

3. Myocardial Remodeling:

Myocardial remodeling is a common feature of CHF, regardless of the etiology. Several factors have been associated with myocardial remodeling, including continuous exposure to elevated catecholamine levels, mechanical stress, and angiotensin. Myocardial remodeling consists of several molecular and cellular events that lead to changes in heart structure and function.

These events include hypertrophy, myocyte apoptosis, reactivation of fetal gene programs, and alterations in the quantity and composition of the extra-cellular matrix. Several pharmaceutical agents (including β adrenergic receptor blockers, angiotensin converting enzyme [ACE] inhibitors, and certain vasodilators) have been shown to



diminish myocardial remodeling and to slow progression of CHF.

Myocardial remodeling on the cellular and subcellular levels often leads to changes in left ventricle geometry and progressive deterioration of left ventricle contractile force. These changes in left ventricle geometry can lead to mitral valve regurgitation due to an increase in the size of the mitral annulus and altered physical relationships of the mitral valve structures. Increasing mitral regurgitation, in turn, can contribute to further deterioration of left ventricular function and worsening of CHF symptoms.¹⁵

4. The Neurohormonal Component of CHF: Sympathetic nervous system activation occurs as blood flow to vital organs (such as the brain and the kidney) diminishes. Release of norepinephrine from sympathetic nerve terminals innervating the heart leads to the cellular and sub-cellular effects described above. Release of epinephrine from the adrenal glands contributes to further vasoconstriction mediated by α_1 adrenergic receptors. Activation of the rennin-angiotensin-aldosterone axis also occurs during CHF, particularly during acute development of CHF. This process leads to enhanced retention of salt and water. CHF is, therefore, not only a disease of the heart. The neurohormonal component of CHF plays an important role in disease progression.

XVIII. GENETIC PREDISPOSITION TO CHF ONSET AND PROGRESSION:

- A. The genetic factors that lead to the development and progression of CHF are not well defined. Substantial inter-individual variability in terms of disease progression and the response to therapeutic agents is observed. Some polymorphisms, such as the β_2 adrenergic receptor Ile164 polymorphism, have been shown to confer significant risk for rapid progression of CHF.³² Other polymorphisms, such as the β_1 adrenergic receptor Arg389 polymorphism, predisposes to CHF by instigating hyperactive signaling, which eventually leads to depressed receptor-stimulatory G protein (Gs) coupling and ventricular dysfunction. The Arg389 variant demonstrates a more robust therapeutic response to β adrenergic receptor blocking agents.³³
- B. Polymorphic variations in the genes encoding several other myocyte signaling and structural elements may also be important in determining susceptibility to CHF onset and progression as well as response to therapeutic agents. Widespread use of genetic analysis and prognostication is still not available but promises to be an important clinical tool in the near future.³⁴



XIX. CURRENT THERAPIES FOR CHF:

- A. Clinical treatment of CHF depends upon the etiology and chronicity. Correction of the precipitating process, whenever possible, is the first step in effective therapy. Dietary sodium restriction (2-3 grams/day), fluid and free water restriction, discontinuation of medications that depress cardiac function, exercise, and administration of oxygen are second step interventions for chronic CHF.
- B. Individuals with ischemic cardiac disease may benefit from angioplasty or coronary artery bypass surgery. Patients with valvular disease causing CHF may have conditions amenable to surgical correction. Heart transplantation is an option that may be available when life expectancy is extremely limited and resource utilization is warranted.⁸
- C. The short term goals for treating a patient with acute CHF or decompensation of chronic CHF focus on relieving symptoms (such as shortness of breath), optimizing blood pressure, improving cardiac output and perfusion of vital organs, stabilization of other comorbidities (including renal dysfunction and pulmonary dysfunction), and preventing arrhythmias. Treatment or prevention of myocardial injury is also essential.¹⁵ For patients with chronic CHF, improving functional capacity and quality of life are important short term goals. It should be emphasized, however, that improvement in symptoms and quality of life does not necessarily correlate with improved survival for patients with acute or chronic CHF.¹⁷
- D. The long term goals of treating a patient with CHF include decreasing mortality and slowing the cardiac structural abnormalities.
- E. Therapeutic Options Currently Available.
 - 1. Diuretics – act directly on the kidney to inhibit sodium, potassium, and water re-absorption. Diuretics decrease “preload” and may improve peripheral and pulmonary edema. Thiazide diuretics are commonly used in mild CHF. Loop diuretics (act at different sites in the renal tubule) may be added to enhance the diuretic effect in severe CHF. There are no randomized clinical trials that demonstrate the efficacy of diuretic therapy for the treatment of patients with acute CHF. However, the use of loop diuretics is supported by a long history of clinical success.¹⁵
 - a. Examples: hydrochlorothiazide (thiazide), furosemide (loop)



2. Potassium Sparing Diuretics – antagonize aldosterone. Aldosterone levels are elevated in CHF. Aldosterone promotes sodium retention, magnesium and potassium loss, sympathetic nervous system activation, parasympathetic nervous system inhibition, myocardial and vascular fibrosis, and baroreceptor dysfunction.³⁵ In patients with moderate or severe CHF who were receiving an ACE inhibitor and a loop diuretic (with or without Digoxin) spironolactone therapy was shown to reduce symptoms, hospitalizations, and mortality.³⁶
- a. Examples: spironolactone
3. Venous Vasodilators – decrease symptoms of CHF by causing “pooling” of blood in the peripheral vasculature. This peripheral “pooling” of blood reduces the volume of blood in the ventricles and reduces cardiac filling pressures. The African-American Heart Failure Trial (A-Heft) study demonstrated a 40% relative risk reduction in mortality at 10 months and a 33% relative risk reduction in first hospitalization for African-Americans with NYHA class II-IV CHF who received a combination of hydralazine and isosorbide dinitrate. A combination tablet is now commercially available and is approved for treatment of CHF in African Americans with CHF and left ventricular systolic dysfunction.^{15, 38} Intravenous nitroglycerins is also useful for the treatment of acute CHF caused by coronary ischemia because it improves coronary blood flow. A major limitation to the use of nitroglycerin is the rapid development of tolerance to the drug’s effect.¹⁵
- a. Example: nitroglycerin, isosorbide dinitrate
4. Arterial Vasodilators – decrease symptoms of CHF by reducing “afterload” which can improve cardiac output. These agents are most beneficial for the treatment of hypertension-related CHF with pulmonary edema as well as severe CHF caused by acute mitral regurgitation.¹⁵
- a. Examples: hydralazine, nitroprusside, angiotensin converting enzyme (ACE) inhibitors, Angiotensin Receptor Blockers (ARBs)



5. Dobutamine – is a β_1 adrenergic receptor (AR) and β_2 AR agonist whose primary effect is to increase cardiac contractility. However, it also has vasodilator properties which can reduce afterload. It is used for treatment of acute CHF and for stabilizing patients with decompensation of chronic CHF. Limitations of Dobutamine include enhanced atrioventricular node conduction that may lead to rapid ventricular response in patients with atrial fibrillation cardiac rhythm. In addition, Dobutamine increases myocardial oxygen demand and oxygen consumption. Continuous Dobutamine infusion has been shown to increase mortality in patients with chronic CHF.^{39, 40, 41}
6. Digoxin – works by inhibiting myocyte sodium/potassium pumps, which leads to increased intracellular calcium levels and better inotropic performance of the heart. Digoxin can prevent CHF due to mildly impaired systolic function. Digoxin also reduces conduction through the atrioventricular node and, therefore, is useful for treating heart failure patients in atrial fibrillation cardiac rhythm with rapid ventricular response. At least one study has demonstrated that Digoxin does not improve overall mortality in patients with CHF.⁴² The drug also has a narrow therapeutic window and significant toxicities when blood levels are excessive. Digoxin should be avoided in patients with hypokalemia, bradycardia, and heart block.¹⁵
7. β Adrenergic Receptor Blockers – ameliorate the progression of CHF by reducing detrimental remodeling of the myocardium. The combined α and β adrenergic receptor blocker, Carvedilol, has been shown to reduce the risk of all-cause mortality by 35% or more in patients with stable heart failure who are already receiving ACE inhibitors and diuretics.³⁵ The selective β_1 adrenergic receptor blockers, Bisoprolol and Metoprolol, have been shown to decrease mortality by 34%.^{43, 44} β blockers counter the deleterious effects of enhanced sympathetic nervous system activity on the heart. They are not useful in the setting of acute cardiac dysfunction because they impede the action of endogenous and exogenous inotropic agents. Their role is in the long-term management of patients with CHF.
- a. Examples: Metoprolol (β_1 blocker), Atenolol (β_1 blocker), Bisoprolol (β_1 blocker), Carvedilol (α , β_1 , β_2 blocker), Esmolol (β_1 blocker), Propranolol (β_1 and β_2 blocker)



8. Angiotensin Converting Enzyme (ACE) Inhibitors – have been shown to reduce mortality and improve symptoms in patients with left ventricular dysfunction.⁴⁵ ACE Inhibitors have also been shown to prevent detrimental cardiac remodeling and progression of CHF.⁴⁶ Several large randomized trials have shown that ACE inhibitors also decrease mortality after myocardial infarction.^{47, 48}
- a. Examples: Enalapril, Lisinopril, Ramipril
9. Angiotensin II (Type I) Receptor (AT1) Blocking Agents (ARBs) – inhibit the biologic effects of angiotensin II by blocking the type I receptor. Adverse effects due to angiotensin II receptor blockers are less frequent than with ACE inhibitors. Although AT1 blockers have been shown to reduce morbidity and mortality,⁴⁹ the ELITE II trial suggested that in heart failure patients mortality was not improved by an angiotensin II receptor blocker compared to an ACE inhibitor.⁴⁵ Angiotensin II receptor blockers should be considered in patients who cannot tolerate ACE inhibitors due to adverse effects.⁵⁰
- a. Examples: Losartan, Valsartan
10. b-type Natriuretic Peptide – is a recombinant human peptide that is identical to the endogenous 32 amino acid hormone produced by the ventricle in response to increased wall stress, hypertrophy, and volume overload. b-type natriuretic peptide has venous dilation, arterial dilation, coronary artery dilation, natriuretic, and diuretic properties. It can reduce “preload” and “afterload.”^{51, 52} It inhibits the effects of activating the renin-angiotensin system. A recent meta-analysis of 3 randomized trials using recombinant human BNP suggested a slight increase in mortality for recombinant human BNP when compared to placebo. One hypothesis is that the adverse effects were caused by impairment of renal function. In June 2003, a special advisory panel convened to review the safety of recombinant human BNP recommended that it be used only in patients admitted to the hospital with acute decompensated heart failure. Further studies are expected.^{15, 53, 54}
- a. Examples: Nesiritide
11. Antiarrhythmic Agents – Patients with CHF and atrial fibrillation cardiac rhythm are at high risk for thromboembolism. Amiodarone is the safest antiarrhythmic drug in heart failure and can help to maintain sinus rhythm.⁵⁵ Unfortunately, no antiarrhythmic agent has been shown to have favorable effects on survival in moderate to severe heart failure patients.⁵⁶



- a. Examples: Amiodarone
- 12. Implantable Cardioverter-Defibrillators (ICDs) –
Approximately one half of patients with CHF die suddenly, primarily due to ventricular arrhythmias. Although antiarrhythmic drugs do not improve survival in these patients,⁵⁵ single-lead, shock-only ICDs reduce mortality by 23%.⁵⁶ The approved use of ICD therapy for prevention of sudden cardiac death has now been extended to prophylactic primary prevention therapy in patients with symptomatic CHF NYHA classes II – IV and left ventricular ejection fraction less than 35%.¹⁵
- a. Examples: Medtronic ICD
- 13. Cardiac Resynchronization Devices –
About 25% of CHF patients have abnormal cardiac electrical conduction that causes dys-synchronous contraction within and between the walls of the left and right ventricles. This phenomenon can reduce the efficiency of ventricular emptying. Mitral regurgitation may also occur, and atrioventricular coupling may be disturbed. Atriobiventricular pacemakers have been shown to resynchronize cardiac contraction, improve pump function, reduce symptoms, and increase exercise tolerance and quality of life in patients with severe CHF.^{57,58,59,60, 61,62,63} These devices have also been shown to reduce the incidence of death or hospital admission in patients with severe CHF.^{64,65}

XX. TEMPORARY ASSIST, BRIDGE TO TRANSPLANT, AND EXPERIMENTAL THERAPIES

- A. Vasopressin Inhibitors – are currently being evaluated in clinical trials for patients with acute CHF. Vasopressin is a hormone synthesized by the hypothalamus that controls free water clearance. It also acts on V1a receptors in vascular smooth muscle and the myocardium to cause peripheral and coronary vasoconstriction and myocyte hypertrophy. Levels of vasopressin are increased in patients with CHF. Higher vasopressin levels correlate with greater CHF severity, and inhibiting vasopressin would theoretically be beneficial. Three vasopressin antagonists are currently being studied, Conivaptan, Tolvaptan, and Lixivaptan.^{11, 66, 67} Each of these agents increases urine volume and free water excretion. Long term results with regard to mortality and impact upon ventricular remodeling and renal function are pending.¹⁵



- B. Istaroxime – inhibits the sodium-potassium ATPase pump and increases sarcoplasmic reticulum calcium ATPase 2a (SERCA 2a) activity. Istaroxime has been studied for treatment of acute decompensated heart failure in the HORIZON-HF trial, a randomized placebo controlled trial of 120 normotensive patients at three European centers. Istaroxime was found to lower pulmonary capillary wedge pressure, increase cardiac index, and decrease left ventricle end diastolic volume at the highest dose studied. It also increased systolic blood pressure, lowered heart rate, and induced a lusitropic effect. Istaroxime has not been studied over long time periods or in patients with hypotension associated with acute decompensated heart failure.⁷¹
- C. Intra-Aortic Balloon Pump - a temporary assist device. The device is inserted into the femoral artery. The tip of the device is advanced into the descending aorta distal to the take-off of the left subclavian artery. During systole a balloon on the tip of the device deflates, facilitating blood flow through the aorta. During diastole, the balloon inflates and augments aortic root pressure. The higher pressure enhances coronary artery blood flow.⁴⁸
- D. Ventricular Assist Device (VAD) - is a partially or fully implantable device that assists the pumping of blood through the circulatory system. The device is frequently used as bridge-to-transplant. It can also be used as a temporizing measure while the heart recovers from a surgical procedure. Recent evidence suggests that ventricular assist support is associated with an increase in $\beta 1$ adrenergic receptor density, a reduction in β ARK1 expression, and restoration of the myocardial response to catecholamine stimulation in addition to several biochemical changes indicative of “reverse remodeling.”⁶⁸ World Heart Corporation, Thoratec, Abiomed, Arrow International, CardiacAssist Inc., and MicroMed Technology all market VADs.⁵⁷
- E. ABIOMED AbioCorTM Implantable Replacement Heart- intended to serve as an alternative to heart transplantation. The AbioCorTM device has no external elements. Power is supplied to the device by an internal battery pack that can last 30 minutes. An external battery pack worn on a belt can power the device and recharge the internal battery using a coil that transmits energy through the skin. The device contains an activity sensor that can automatically increase the rate of pumping during exertion.
- F. Jarvik 2000® – a valveless, electrically powered axial flow pump that is inserted into the left ventricle and continuously pushes oxygen-rich blood from the ventricle into the descending aorta. The Jarvik 2000 is approved by the FDA as a bridge to transplantation.



- G. Cell-based Therapies – Stem cells are multipotent, undifferentiated cells capable of multiplication and differentiation. There is great interest in stem cell therapy for the treatment of CHF. Several investigators at Stanford (including Dr. Robert Robbins and Dr. Phil Tsao) are evaluating whether cell based therapies might benefit patients with heart disease.⁶⁹
- H. Ventricular Remodeling (Batista Procedure) – is a surgical technique that involves removing a section of the heart muscle from the left ventricle of a dilated heart. The ventricle is then re-shaped by the surgeon to a smaller, more normal size. The procedure is investigational. Procedure failure necessitates immediate heart transplantation. The Cleveland Clinic discontinued this procedure due to disappointing results.

XXII. STUDY QUESTIONS

- 1. Congestive heart failure is a condition in which the heart fails to pump enough blood to support metabolizing tissues. True or False?
- 2. Cardiac performance depends upon which of the following?
 - A. Preload, Age, and Height.
 - B. Preload, Inotropic State of the Cardiac Muscle, and Temperature.
 - C. Preload, Inotropic State of the Cardiac Muscle, and Afterload.
 - D. Inotropic State of the Cardiac Muscle, Time of Day.
 - E. Age, Height, and Time of Day.
- 3. In cardiac muscle, developed force increases continuously until the tissue ruptures. True or False?
- 4. On the organ level, the relationship between force generated and cardiac muscle length is the inverse of that found in cardiac muscle strip preparations. True or False?
- 5. Which of the following pressure measurements is used clinically to approximate left ventricular preload?
 - A. Central venous pressure.
 - B. Pulmonary artery pressure.
 - C. Systemic vascular resistance.
 - D. Pulmonary capillary wedge pressure.
 - E. Pupil Diameter.
- 6. By plotting left ventricular preload versus ventricular output, one can identify normal, hyperdynamic, and failing hearts. True or False?



7. Pressure-volume loops can be used to describe which of the following properties of the left ventricle?
- Preload, Afterload, Physical Size.
 - Preload, Afterload, Contractility.
 - Preload, Infarction Area, Stroke Volume.
 - Stroke Volume, Compliance, Temperature.
 - Afterload, Stroke Volume, Physical Size.
8. Diastolic dysfunction is most common in young males with coronary artery disease. True or False?
9. More Medicare dollars are spent for the diagnosis and treatment of CHF than for any other diagnosis. True or False?
10. Patients hospitalized for treatment of acutely decompensated CHF have an in-hospital mortality rate of:
- 0.25% - 0.5%
 - 1% - 2%
 - 4% - 8%
 - 10% - 12%
 - 40% - 50%
11. Serum assay of b-type natriuretic peptide:
- Distinguishes infectious versus non-infectious causes of CHF.
 - Improves the accuracy of CHF diagnosis from 65% to 99%.
 - Is not effective if the patient has chronic obstructive pulmonary disease (COPD).
 - Has been shown to decrease the need for hospitalization.
 - Can also be used to gauge alcohol intoxication.
12. Which of the following are known etiologies of CHF?
- Global cardiac ischemia.
 - Really long lectures.
 - Nitroglycerin.
 - Amiodarone.
 - Vasopressin Inhibitors.
13. For proper evaluation of cardiac function using transesophageal echocardiography the patient must not be sedated. Sedatives will render the evaluation inaccurate. True or False?
14. Echocardiography may identify regional or global ventricular wall motion abnormalities. True or False?



15. Which of the following commonly occur in CHF patients receiving β blocker therapy?
- A. Normalization of β ARK1 activity and G α i levels.
 - B. Worsening myocardial ischemia.
 - C. More frequent arrhythmias.
 - D. Activation of fetal gene programs in myocytes.
 - E. Paranoid schizophrenia.

Last Year's (2010) Syllabus



Last Year's (2010) Syllabus

Drugs Used in Angina Pectoris

Reading assignment: Katzung, Ch. 12 (angina) and 19 (nitric oxide)

LEARNING OBJECTIVES:

- A. Understand the factors that influence cardiac oxygen supply and demand and the patho-physiology of angina pectoris.
- B. Learn the pharmacology of the organic nitrates and understand the rationale for their use in angina pectoris.
- C. Do the same for the calcium channel blockers.
- D. Do the same for the beta adrenergic receptor blockers.
- E. Understand the rationale for using certain anti-anginal drugs in combination.

TOPICS

- A. Organic nitrates
- B. Calcium channel blockers
- C. Beta adrenergic receptor blockers



Last Year's (2010) Syllabus

CARDIAC ANATOMY: RELATIONSHIP TO TOMOGRAPHIC ANATOMY

LEARNING OBJECTIVES:

- A. To provide the student with an introduction to cardiac anatomy, the relations of the heart in the thorax and to define the sub-systems of coronary anatomy and cardiac innervations.
- B. Appreciation of Basic and Tomographic anatomy
- C. Application of morphology to clinical medical situations
- D. Direction or further study through reference material cited below.

LECTURE OVERVIEW:

- A. General description of cardiac anatomy and relations
- B. Morphology of the various heart chambers and valves
- C. Coronary artery morphology
- D. Tomographic anatomy of the heart and great vessels
- E. The Visual Human Dissector: A tomographic trip
- F. Relations to tomographic techniques
- G. References material

The unique opportunity of this introduction lecture is to define the tomographic anatomy of the heart in the planes used with modern tomographic techniques such as magnetic resonance, computerized tomography and ultrasound. These will be related to computerized human dissection. Further study of these features is available through Stanford University's computer learning on course work and from the references quoted below.

There are 3 reference planes in the body (slide 3): The sagittal and coronal planes (named after the sutures in the skull) and the horizontal plane. The heart has its own planes whose long axis lies about 45° off the body plane axes. There are two long axis planes from the cardiac apex to the base, i.e. the four and two chamber planes. Its short axis is orthogonal to these planes.

The heart lies in the mid thorax in the middle mediastinum. Its relations are the lungs laterally, the trachea and esophagus and vertebral bodies posteriorly, the thymus and great vessels superiorly. Inferiorly the heart lies on the central tendon of the diaphragm. (slides 4-6) The liver is their relation immediately below the diaphragm. Anteriorly, the heart lies behind the sternum and the costochondral junction. A small part lies immediately behind the ribs where the



lung does not intercede over the left lower sternal area to the apex. This can be palpated clinically in the 4th left intercostal space in the mid-clavicular line just below the left nipple.

The heart is surrounded by the pericardial sac, part of the primitive coelomic cavity into which it invaginates during embryogenesis. Thus the heart lies in a space (the pericardium), which has visceral and parietal layers, the visceral layer being the epicardium and the parietal layer the fibrous pericardium. On the outside of the heart on the pericardial surface lie the two phrenic nerves (left & right) which lie anterior to the hilum of the lung and transmit the vascular and bronchial elements to it. The Vagus nerves run posterior to the hilum of the lung on the esophageal surface.

The innervation of the heart is complex and variable. There are plexuses of nerves behind the great veins. Sympathetic innervation is via the lower cervical and superior thoracic ganglia, and the parasympathetic innervation via the Vagus nerves. The fibers course over the connective tissue to the vascular and muscular sites along the cardiac vessels.

The surfaces of the heart are as follows:

The heart has two margins. The acute margin is on the inferior and anterior surfaces of the right ventricle. The obtuse margin is over the lateral surface of the left ventricle. The anterior surface is made up of the right atrium and the great systemic veins on the right. The right atrial appendage (right auricle) and the right ventricle form the major anterior surface. The anterior descending coronary artery is a delimiting artery between the two ventricles and, with its accompanying vein, lies on the junction of the ventricular septum with the left and right ventricles. A small part of the left ventricle and atrium make up the rest of the anterior surface. On X-ray, the right heart is made up, from top to bottom, of the superior vena cava, the right atrium, and the inferior vena cava. The left heart border, from top to bottom, is made up of the aortic knuckle, the main pulmonary artery, the left atrial appendage and the left ventricle.

Posteriorly the heart is largely comprised of the left ventricle and left atrium on the left, with lesser portions of the right-sided chambers making up the posterior surface. The posterior descending coronary artery and its accompanying vein is the vascular bundle delimiting the attachment of the ventricular septum to the myocardium of the left and right ventricles. The fatty tissue around the heart lies largely in association with the vascular bundles. When the heart is removed from the pericardial sac, the anchoring vessels are seen as the support of the heart within the pericardium. These spaces between the vessels form the transverse and oblique pericardial sinuses.

The coronary veins arise from the oblique vein lying over the left atrium (the vein of Marshall - a remnant of the anterior left-sided cardinal vein from embryogenesis) and the vena comitantes (accompanying vein) of the left anterior coronary artery called the great cardiac vein. This vein then forms the coronary sinus, which runs in the posterior coronary groove toward the right atrium picking up the lesser and least cardiac veins and other tributaries as it courses toward its termination in the coronary sinus which leads into the right atrium. The term



coronary means crown, depicting (as it were) the heart with a crown over its division between the atria and ventricles.

The heart is a muscular pump. Muscle has only one attribute - it can shorten and lengthen. The muscle of the heart is structured in a complex manner to act as a squeezing structure, and the cardiac valves act as one-way directional valves in a pump, (slide 7-8). There are four valves: the two between the atria and ventricles are termed the atrioventricular valves, and the two between the ventricles and great arteries are termed the aortic and pulmonic valves. The atrioventricular valves prevent reflux of blood into the atria during ventricular Systole and allow atrioventricular filling in Diastole.

The mitral (bicuspid) valve lies on the left and the tricuspid valve on the right. The mitral valve is so called because of its resemblance to a bishop's Mitre (Latin). The tricuspid valve has 3 cusps.

The mitral valve has a large anterior (aortic) leaflet, which extends deeply into the ventricle. Its circumferential diameter is 1/2 of the posterior cusp that has 3 small divisions. Effective closure is achieved by the anterior leaflet coapting along the zone of commissural apposition. At their free edges the atrioventricular valves are supported by chordae tendineae (tendinous cords) which are like tree branches. They divide from their origin at the papillary muscles, form primary, secondary and tertiary chordae, which then attach to the commissures (spaces of apposition between the valves) rather than to individual valvar leaflets. During cardiac contraction the papillary muscle contracts first, tensing the valvar apparatus so that the force of contraction does not rupture the valves. It is this snap which, on auscultation, gives rise to the first heart sound. The tricuspid valve has a similar purpose but is a less effective valve than the mitral because of its more complex structure. Fortunately, it performs under about 1/3 – 1/4 of the pressure demands of the left side of the heart.

There are two groups of papillary muscles lying within the left ventricle - termed the anterolateral (AL) and posteromedial (PM) groups. The papillary muscle within the right ventricle varies in size from the large anterior single papillary muscle which supports the commissure between the anterior and posterior leaflets, to the posterior papillary group having 2 – 3 beats and supporting the commissure between the posterior and anterior leaflet. A separate muscle within the outlet of the right ventricle (Muscle of Lancisi) supports the anterior septal cusps of the tricuspid valve. Additional small supports of the septal leaflet arise from direct septal chordae tendineae. These will be referred to again in connection to the architecture of the right ventricle.

The aortic and pulmonary valves are similar in structure, having 3 leaflets or cusps. When seen side-on they look like half moons and are therefore termed semilunar valves. The cusps are roughly equal in size with some variation. They are attached to the underlying ventricular muscle at the base, and to the aortic root above. In their midline each aortic cusp has a central little nodule (Nodule of Aranantius). The aortic valve is a little thicker than the pulmonary valve and coronary arterial ostia arise from it. The aortic cusps facing the pulmonary artery each give rise within the sinuses of Valsalva to a coronary artery. The left



coronary artery arises from the left cusp and the right coronary artery arises from the right cusp. There is no coronary artery arising from the posterior cusp, which is in continuity with the anterior leaflet of the mitral valve.

The conventional manner for defining the structures is by examining the heart morphologically along the lines of flow. This assures completeness during examination. The surface of the right atrium, (slide 9-11), shows a large appendage with a broad base connected to the rest of the atrium. This section of the atrium receives the superior and inferior vena cava. When the atrium is opened several important structures are identified. First the muscular bundles called the pectinate muscles (comb-like) are seen to come from the right atrial appendage and spread themselves over the vestibule of the right atrium (the portion proximal to the tricuspid valve). The smooth part of the atrium lying between the veins is called the sinus intervenarum (lake between the veins). As one looks at the atrial septum medially (remember, we are opening this atrium from the right side of the body) one identifies an oval depression - the fossa ovalis. This area is the place where fetal communication between the atria existed, allowing oxygen-rich umbilical venous blood to be shunted away from the right ventricle and across into the left atrium. From there the blood flows to the important fetal structures, the brain and heart. As this is a thin membranous rather than muscular structure, it is often possible to illuminate it by shining a light from the left atrium to define its extent. It is notable that the true area of communication of the atrial septum is only a little larger than this structure, and that other structures which appear on the medial aspect lie outside the confines of the septum. The upper orifice in the sinus intervenarum is the entrance of the superior vena cava and the lower orifice is the inferior vena cava. There is another orifice in the medial aspect of the atrium adjacent to the tricuspid valve, situated below and marking the exit point of the atrium. This structure is the coronary sinus that we saw from the outside of the heart. A valve-like structure or semilunar membrane is seen in the right atrium. These structures form the valve of the inferior vena cava. The Eustachian valve and the valve of the coronary sinus (Thebesian valve), join to form the tendon of Todaro. This, together with the tricuspid septal leaflet, makes up a triangular area (the triangle of Koch) an area that contains the atrioventricular node so important for cardiac conduction.

At the upper end of the atrium between the superior vena cava and the atrial appendage lies a thick ridge of muscle called the Crista Terminalis (Terminal Crest). It is the muscular ridge between the sinus intervenarum and the true atrium. At the upper end of this ridge is the area of the sinus node which drives automatic cardiac electrical activity through specialized Purkinje cells. This area is on the right valve of the sinus venosus and its extension the Eustachian valve. The left valve of the sinus venosus forms the thick ridge or limbus of the fossa ovalis.

The right ventricle shows a clear division. The ventricle is heavily trabeculated (muscle bundles). The papillary muscles support the commissures of the tricuspid valve. There is a large muscle running in the anterior groove between the inlet and outlet sections of the ventricles. It arises under the pulmonary valve superiorly and travels between the junctions of the anterior wall with the ventricle



to the apex of the right ventricle. This muscle is termed the septomarginal trabeculation or the septal band. In some texts those who believe that it moderated over expansion of the right ventricle refer it to as the moderator band. Running over the top of the ventricle, between the pulmonary valve and at right angles to the septal band, is a structure termed the ventricular infundibular fold (because it runs between the outlet of the right ventricle termed the infundibulum) or the parietal band of the Crista, (crest above the ventricle). Thus, for some morphologists, there is a Crista supraventricularis (crest above the ventricle) with a septal or a parietal band. I prefer that these be called the septomarginal trabeculation and the ventricular infundibular fold.

The septomarginal trabeculation is also an anatomic and embryologic landmark between the inlet and the outlet of the ventricle. It gives direct rise from the right ventricle to all the papillary muscles of the right ventricle, including the chordae tendineae. As the ventriculoinfundibular fold is muscular, there is no connection between the tricuspid and pulmonary valve. The ventricles are tripartite, all containing sections defined most clearly from the ventricular septum discussed below. These are the inlet, muscular (or trabecular) and outlet positions of both ventricles. The papillary muscles define the inlet. The outlet is above the terminal crest. The trabecular septum is the rest, and is the muscular portion of the ventricle.

With regard to the left side of the heart, when viewed from the left side, the small finger-like left atrial appendage is seen anteriorly, and the entrance of the left pulmonary veins posteriorly. The lower border of the appendage is crenulated and its attachment to the body of the left atrium is narrow. The pectinate muscles of this atrium are much finer than its fellow on the right side, and do not extend out of the atrial appendage as its fellow on the right side does. The left atrial aspect of the atrial septum can be illuminated to demonstrate the thin septum primum which has a horseshoe curve. The left ventricle has two papillary muscles attached to the inferior and lateral walls and the septum is free of attachment of papillary muscles. The anterior leaflet of the mitral valve is in fibrous attachment with the non-coronary cusp of the aortic valve. The lack of septal attachment of the mitral valve and the fibrous continuity of the anterior mitral valve leaflet to the non-coronary cusp are two distinctive differences between the left and right ventricle. The septal surface of the left ventricle and its right-sided fellow form the smooth upper septal surface and fine apical trabeculations. Because of pressure differences the left ventricle is also thicker walled than the right ventricle. As noted previously, the ventricle can be divided into inlet, trabecular and outlet portions. There is a fourth component - the membranous septum - a little fibrous tissue lying under the aortic valve between the right and non-coronary cusps when seen on the left side, and just under the septal leaflet of the tricuspid valve when viewed from the right side.

In slide 12, the conduction system of the heart contains cellular and fibrous elements. The automatic firing comes from the cellular elements within the sinoatrial and atrioventricular nodes, and also within the upper cells lying within the His-Purkinje system. A hierarchical firing is present where the faster rates lie within the highest (sinoatrial) area and the periodicity decreases as the



conduction system progresses distally. The sinoatrial node is a small cigar-shaped structure lying between the atrial appendage and the superior cava almost on the surface of the heart. It has a rich arterial supply from both coronary arteries. There are no actual connections between the two nodes, although the fibers tend to run in the areas between the appendages and vascular entry.

The atrioventricular node lies within the triangle of Koch and then penetrates above the muscular and below the membranous septum, where it runs on the left ventricular septal surface for a small distance. As the bundle divides the right bundle runs back toward the right ventricle, perforating near the muscle of Lancisi within the right ventricle and then running toward the right ventricular apex under the septomarginal trabeculation. The left bundle divides into an anterior and posterior bundle (hemi bundle). These bundles are also apically directed and enter in the papillary muscles from the apical route to terminate within these muscles.

Slides 13-17 demonstrate the origins and course of the coronary artery. The left main coronary artery has a short course and divides into a left anterior descending coronary artery and a circumflex. Short branches usually arising from the circumflex artery and termed diagonal branches also arise fairly proximally. The proximal left coronary and its branches lie in the left portion of the coronary groove, and the left coronary and circumflex runs posterior to the pulmonary artery. The left anterior descending artery arises laterally to the pulmonary trunk on the surface to the heart. The proximal circumflex lies in the coronary groove under the left atrial appendage. The more distal branches of the circumflex are called the obtuse marginal branches. Posteriorly, in a minority of hearts, the posterior descending coronary artery terminates from the circumflex coronary artery, while in the majority of hearts the posterior descending usually arises from the terminal right coronary artery. The former circumstance is referred to as left-dominant, whereas the latter is referred to as a right dominant system.

The left anterior coronary artery gives rise predominantly to several septal perforators and surface branches of the left ventricle, and some smaller branches to the right ventricle.

The right coronary artery runs in the right coronary groove. Its first branches are to the sinoatrial node and the right ventricular outflow (conus). It supplies the right ventricle with branches as it circles the groove inferiorly and posteriorly. On the posterior surface of the heart it supplies the area of the atrioventricular node and branches to both ventricles. The posterior descending, arising from either vessel, gives arterial supply to both sinoatrial and atrioventricular nodes. The coronary arteries are terminal vessels, which means they do not have collateral branches under normal circumstances.

Tomography is a slice technique. (slides 18 –27) This and subsequent slides will define the tomographic anatomy obtained by various modalities. The first slide shows dynamic real-time ultrasound images recorded in a child at 30 frames per second. The ultrasound now passes from the cardiac apex and permits accurate



information as well as the ability to observe the actual beating and motion of the heart. The subsequent slides show tomograms, which are the interactive data, showing the power of tomographic techniques in a real anatomic case. The use of computerized tomography and magnetic resonance imaging and dynamic 3 dimensional spatial reconstruction techniques are the tools of modern medicine.

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TAKE HOME POINTS:

- A. In order to study the heart the student must have an intimate knowledge of basic cardiac anatomy, with this introduction and references provide.
- B. As much of cardiac study uses tomographic methods, this course provides an opportunity through on-line methods for study of tomographic anatomy and its clinical applications



Last Year's (2010) Syllabus

Positive Inotropic Agents

Reading assignment: Katzung (10th ed), Ch. 13

LEARNING OBJECTIVES:

- A. Understand the autonomic and hormonal compensatory changes that heart failure evokes.
- B. Learn the pharmacology of digoxin. Pay special attention to the mechanisms of its beneficial and adverse effects, its effects on cardiac rhythm, and the effects of potassium ion and calcium ion on digoxin action.
- C. Learn the pharmacology of (1) beta adrenergic receptor agonists and (2) inhibitors of phosphodiesterase-3.

TOPICS

- A. Digitalis
- B. Bipyridines
- C. Beta adrenergic receptor agonists



Last Year's (2010) Syllabus

Congestive Heart Failure

Reading assignment: Katzung (10th ed), Ch. 13

LEARNING OBJECTIVES:

- A. Understand the autonomic and hormonal compensatory changes that occur when the heart fails. Understand the vicious cycles in cardiovascular function that accompany the changes and that make heart failure worse.
- B. Understand the rationale for using various drug groups to alter preload, afterload, and contractility in patients with heart failure.
- C. Understand the rationale for using blockers of the SANS and RAAS in treating chronic heart failure.

TOPICS

- A. Congestive heart failure
 - 1. Acute
 - 2. Chronic



Last Year's (2010) Syllabus

CONGENITAL MALFORMATIONS OF THE HEART AND BLOOD VESSELS

(Based in part on lecture notes originally written by Paul Pitlick, M.D.)

I. THE FETAL AND TRANSITIONAL CIRCULATION

A. Introduction

1. Congenital heart defects occur in 0.8% of newborns, making heart disease one of the most common congenital defects and the leading cause of death due to all congenital malformations. Approximately 30,000 babies with heart defects are born each year in the United States. In severity, congenital defects span a spectrum from those which are potentially lethal in the first few days of life to those with minor hemodynamic significance and which are often found incidentally in adult autopsies. With current diagnostic procedures and recent advances in medical and surgical therapy, many of the complications of these defects can be treated and/or prevented, thus markedly increasing survival and adding to the quality of life for the majority of patients.
2. Even with the most severe cardiac defects (e.g. the hypoplastic left heart syndrome, in which the left ventricle and ascending aorta are diminutive), most babies with congenital heart disease do quite well in utero and rarely manifest symptoms of heart failure or growth retardation before birth. To better understand the pathophysiology of these congenital cardiac lesions, one must first understand the special features of the fetal circulation and the multitude of hemodynamic, hormonal and biochemical changes which occur during and after birth.

II. FETAL CARDIOVASCULAR SYSTEM

A.

The fetus exists within the fetal membranes (chorion and amnion) and uterus, bathed in amniotic fluid. While it has been shown that the fetus does have respiratory movements, gas exchange does not occur via the lungs. Similarly, nutrient and waste exchange do not occur via the alimentary tract. The placenta performs these important functions in the fetus, however, since the placenta is removed from the circulation at birth, there are several important transitions which must occur between the fetal, newborn and adult cardiovascular systems. Most of our current knowledge about the fetal circulation has been obtained from animal studies, with pioneering studies in the fetal lamb performed by Dr. Abraham Rudolph and his colleagues. However, more recently the



development of improved techniques of in utero cardiac ultrasound, has allowed investigators to obtain similar information in the human fetus. There are several important differences between the fetal cardiovascular system and that of the infant or adult:

1. Sympathetic Innervation. The fetal myocardium has a lower density of sympathetic nerve endings and lower density of β -adrenergic receptors than does the adult myocardium and these receptors are less effectively coupled to downstream effectors such as adenylyl cyclase. Although the fetus does have the ability to increase heart rate and stroke volume in response to sympathetic stimulation, this capacity is blunted when compared to the adult.
2. Myocardium. Both in vivo and in vitro studies demonstrate that the fetal myocardium has different contractile properties than that of the adult, although the significance of this is still the subject of some debate. Morphologically, the fetal myocardium has a higher ratio of interstitial space to myocytes, and myocytes are more randomly oriented as opposed to the parallel arrangement of the adult heart. The fetal myocardium also has a less well-developed T-tubule system than the adult, so that extension of the sarcoplasmic reticulum in proximity to muscle fibers is not as extensive. Additionally, the fetal heart relies on extracellular calcium entering via sarcolemmal calcium channels for triggering contraction as opposed to the adult heart where most of the calcium for activation comes from calcium-induced calcium release from the sarcoplasmic reticulum. Length-tension (or pressure-volume) curves in fetal sheep myocardium demonstrate higher resting tension and lower active tension than adult curves (Figure 1), indicating less compliance than the adult heart.

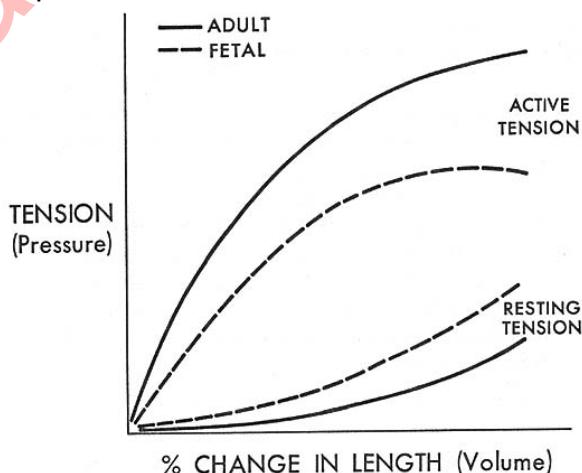


Figure 1: Differences between the resting length-tension relationship of adult and fetal myocardium.

These early studies suggested to investigators that the ability of the fetal heart to utilize the Frank-Starling mechanism to increase stroke volume is significantly diminished compared with the adult heart. When saline was infused, the fetal cardiac output increased only about 30% compared with a 200% increase seen in the adult. However, these studies failed to account for the fact that by changing preload with large volume infusions, the investigators were also increasing afterload. The fetal heart is very sensitive to changes in afterload, and these increases were part of the reason why fetal cardiac output appeared to be blunted in response to volume. Subsequent studies, controlling for changes in afterload, have shown that the fetal heart does respond to changes in preload, although perhaps still less well than the adult heart. The clinical significance of this finding is that lesions which result in volume loading of the fetal heart (e.g. tricuspid valve regurgitation due to Ebstein's anomaly) are usually very poorly tolerated.

- C. Pulmonary vasculature. There are major histological differences between the fetal, newborn and adult pulmonary vascular beds. The extent of smooth muscle lining intra-acinar pulmonary arteries changes with advancing age. In the fetus, the small arteries have a thick medial smooth-muscle layer. Since the placenta supplies oxygen to the fetus, there is no reason for a large amount of blood flow through the pulmonary circulation; it is the chronic constriction of the pulmonary vessels that maintains a high resistance in the fetal pulmonary circulation. This constriction is maintained by the low fetal PO₂, although whether this is due to lack of vasodilator pathways or chronic release of vasoconstrictors has not been fully determined. The leukotrienes LTC₄ and LTD₄, vasoconstrictors derived from arachidonic acid, are thought to play a role since inhibition of leukotriene production results in a dramatic reduction in pulmonary vascular resistance in the sheep fetus. Endothelin may also play a role, as blockade of endothelin A receptors also decreases pulmonary resistance in the fetus. Thus, with a very vasoconstricted pulmonary bed, only 7-8 percent of total fetal cardiac output flows to the lungs. With advancing gestational age, an increase in the number of pulmonary vessels associated with lung growth gradually increases the pulmonary vascular cross-sectional area and gradually decreases pulmonary vascular resistance, although pulmonary resistance remains quite high until the time of birth (Figure 3-1).



- D. Hemoglobin. In the early embryo, metabolic exchange occurs by diffusion, but as the fetus grows diffusion becomes inadequate to meet cellular metabolic needs, and thus the circulatory system develops during the first trimester. With the development of the fetal circulation, oxygen transport by hemoglobin becomes progressively more important. Since hemoglobin is the major carrier of oxygen in blood, alterations in hemoglobin concentration and/or oxygen affinity will have a large effect on oxygen delivery to the tissues.
1. Concentration. In the fetus, hemoglobin concentration increases with age (Figure 2a), and at term is actually higher than in the adult; this high level of hemoglobin is important to the fetus in that it allows more oxygen to be carried to the tissues.

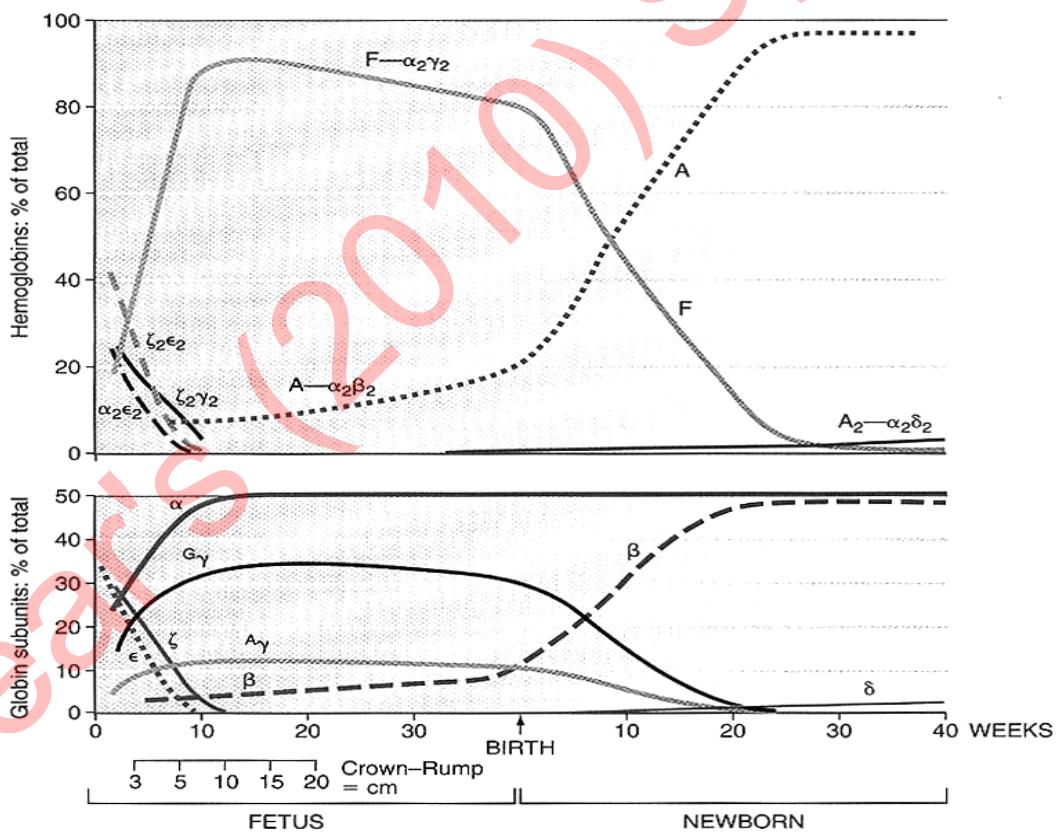


Figure 2: Changes in hemoglobin composition from embryo to fetus to newborn. The top figure shows changes in hemoglobin tetramers, the bottom changes in the individual globin subunits.



2. Hemoglobin-oxygen affinity. In addition to a change in total hemoglobin concentration, hemoglobin in the fetus also undergoes an evolution in oxygen affinity (Figure 2). As seen in Figure 2b, early in gestation several minor hemoglobin constituents appear, but by the second month the major hemoglobin is Hgb F. Hemoglobin F consists of two alpha and two gamma chains, while Hgb A, the major constituent of adult hemoglobin, consists of two alpha and two beta chains.

The oxygen-hemoglobin dissociation curves for adult (curve a) and fetal (curve b) hemoglobins are shown in Figure 4-13. Fetal hemoglobin has a higher affinity for oxygen so that the curve for fetal hemoglobin is shifted to the left. At any given oxygen tension (pO_2) fetal hemoglobin is more highly saturated with oxygen, and thus can carry a greater volume of oxygen than can adult hemoglobin. In this figure, fetal hemoglobin would carry 18 ml O₂/100 ml at a pO_2 of 40 torr, whereas adult hemoglobin would only carry 14 ml O₂/100 ml at the same pO_2 . In humans, this difference between fetal and adult hemoglobin is related to their different affinities for binding 2,3-DPG. The higher affinity of fetal hemoglobin for oxygen is important in the fetal environment, because oxygen exchange occurs in the placenta at a lower pO_2 than it does in the adult lung, so that having a "stickier" hemoglobin aids in oxygen exchange. This advantage only exists at the low pO_2 s associated with the fetal environment, however. At a normal post-natal pO_2 of 100 (Figure 4-13), adult and fetal hemoglobin are both 100% saturated and carry the same amount of oxygen per ml. This is the pO_2 range at which the lungs operate post-nasally, thus, there is no advantage to fetal hemoglobin after birth. In fact, this can be deleterious to the sick newborn, since fetal hemoglobin binds oxygen more avidly and thus oxygen is less readily dissociated from fetal hemoglobin to peripheral tissues.



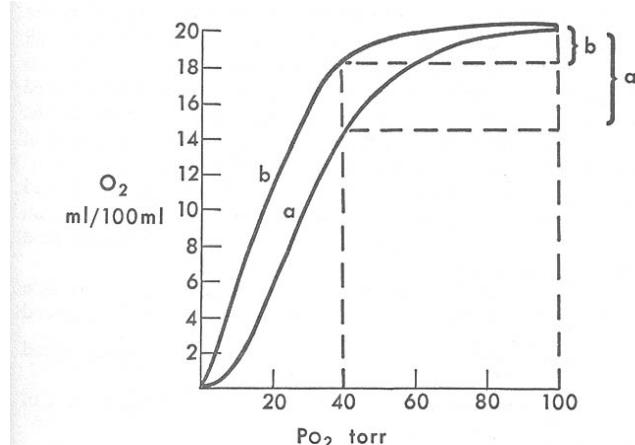


Fig. 4-13.—The effect of shifting the oxygen dissociation curve to the left or to the right on the amount of oxygen that is delivered at the tissue site is demonstrated. Although at high PO_2 the amount of oxygen attached to hemoglobin is similar for both curves, at the venous PO_2 level of about 40 torr, the amount of oxygen that would be extracted in the case of curve *b* (shift to the left) is considerably less than for curve *a*.

In Figure 4-13, the amount of oxygen delivered to the tissues when blood passes from the post-natal arterial circulation ($\text{pO}_2=95$) to the venous circulation ($\text{pO}_2=40$) would be only 2 ml for fetal hemoglobin (bracket *b*) whereas it would be almost 6 ml for adult hemoglobin (bracket *a*). It is controversial whether this disadvantage of fetal hemoglobin in the post-natal state is of clinical importance. It is likely not significant to the normal newborn but could hinder tissue oxygen delivery to the tissues in the newborn with severe respiratory or cardiac disease.

- E. The atmosphere contains about 21% oxygen, so the pO_2 of air at sea level is: 0.21×760 torr (Barometric pressure at sea level), or about 160 torr. Because some of this oxygen is contained in water vapor, when breathing room air, the alveolar pO_2 is normally about 105 torr. Since pulmonary venous blood does not completely equilibrate with alveolar pO_2 when passing through the lungs, pulmonary venous pO_2 (and thus also systemic arterial pO_2) is about 95 torr, corresponding to a hemoglobin saturation of 95-97%. In the body tissues, oxygen is extracted, and systemic venous pO_2 decreases to approximately 40 torr (hemoglobin saturation of approximately 70%).
1. Dissolved oxygen. There are two components of oxygen in the blood: dissolved oxygen and hemoglobin-bound oxygen. Dissolved oxygen is a linear function of the partial pressure of oxygen (pO_2) whereas hemoglobin-bound oxygen is determined by the oxygen-hemoglobin dissociation curve (see above). Dissolved oxygen is a very small component of total blood oxygen content (0.03 ml oxygen per liter of blood for each 100 torr) and thus can usually be neglected in calculations.



- F. Fetal Circulation. The course of the fetal circulation is schematically illustrated in Figures 1-1, 1-2 and 1-5. We will examine the anatomy and physiology of the fetal circulation, and review the incredible changes which occur in the perinatal transitional period (Figure 2-1) eventually leading to the adult circulation (Figure 2-2).
1. Anatomy. Several structures which play an important role in the fetal circulation, including the placenta, umbilical cord (including the umbilical arteries and umbilical vein), ductus venosus, foremen ovale, and ductus arteriosus.
 - a. Placenta. The only means of communication between the fetus and the outside world is the placenta. The placenta is embryologically derived from both maternal and fetal tissue, and the blood supply of the two components normally remains separate. Gases (O_2 from the mother and CO_2 from the fetus), nutrients from the mother, and fetal waste products are exchanged in the placenta. However, the placenta is not as efficient an oxygen delivery organ as are the lungs, so that the maximum volume of oxygen that can be exchanged is limited by the venous pO_2 of placental blood.



Fig. 1-1.—The mammalian fetal circulation. The general course of the circulation is shown. DA—ductus arteriosus, Ao—aorta, PA—pulmonary artery, RV—right ventricle, LV—left ventricle, RA—right atrium, LA—left atrium, DV—ductus venosus.

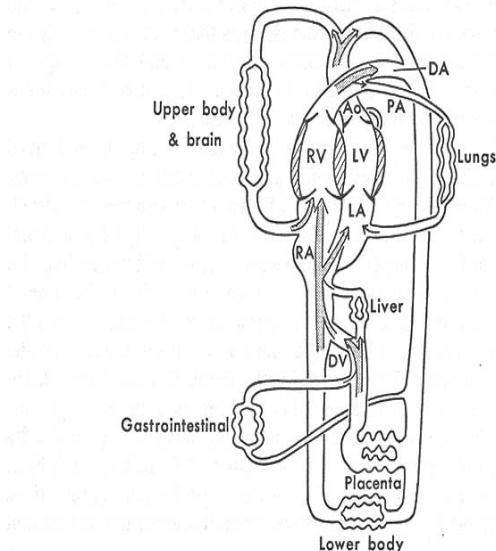


Fig. 1-5.—This shows the percentages of the combined ventricular output that return to the fetal heart, that are ejected by each ventricle and that flow through the main vascular channels. Figures are those obtained from late-gestation lambs.

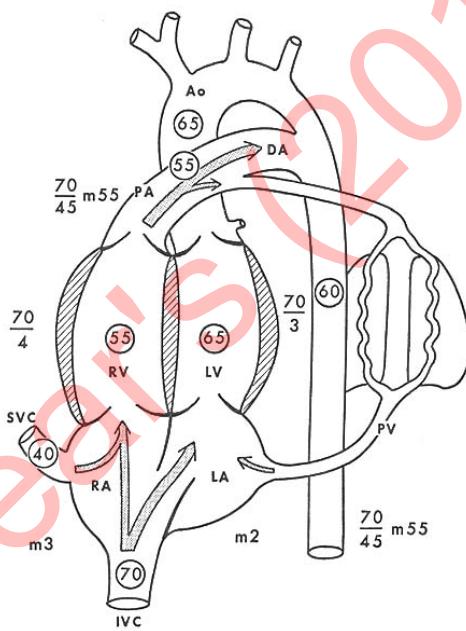
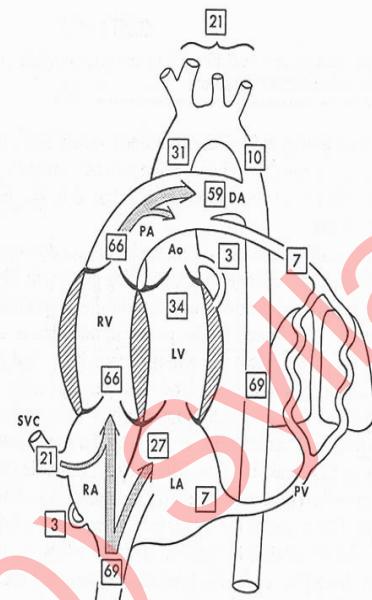


Fig. 1-2.—The course of the circulation in the heart and great vessels in the late-gestation fetus. The figures in circles within the chambers and vessels represent per cent oxygen saturation levels. The figures alongside the chambers and vessels are pressures in mm Hg related to amniotic pressure level as zero. m—mean pressure.

- b. Umbilical cord. The umbilical cord, which connects the placenta and fetus, is about 1.5 cm in diameter. It contains the two umbilical arteries and single umbilical vein, and the rest is composed of a gelatinous substance called Wharton's jelly. The umbilical arteries are branches from the fetal iliac

- arteries, and carry blood from the fetal descending aorta to the placenta (Figure 1-1). The umbilical vein carries oxygenated blood from the placenta back to the fetus.
- c. Ductus Venosus. When the umbilical vein enters the abdomen, it courses in a cephalad direction on the underside of the anterior abdominal wall. In the region of the liver it dips dorsally, and enters the fetal inferior vena cava by means of a structure called the ductus venosus (DV in Fig 1-1). Where the inferior vena cava enters the right atrium there is a flap of tissue known as the Eustachian valve. This valve helps direct inferior vena caval blood flow preferentially across the foramen ovale.
 - d. Foramen Ovale. The foramen ovale is a flap valve (shaped somewhat like a windsock) in the interatrial septum. As we shall see later, pressure is slightly higher in the fetal right atrium (RA) than in the left atrium (LA), which forces the flap open, allowing blood to shunt from the right atrium to the left atrium.
 - e. Ductus Arteriosus. In the fetus, the pulmonary artery is connected to the thoracic descending aorta by means of the ductus arteriosus (DA in Fig. 1-1). In effect, the main pulmonary artery-ductus arteriosus-descending aorta connection forms a large vessel bringing blood from the fetal right ventricle (RV) to the descending aorta. Because the pulmonary circulation is vasoconstricted during fetal life, the lungs receive only a small percentage of fetal right ventricular output, which preferentially flows through the ductus arteriosus to the lower resistance lower body circulation and to the placenta (because of its high vascular cross-sectional area, the placenta is a very low resistance vascular bed). As we shall see later, the fetal left ventricle ejects mainly into the ascending aorta and the fetal right ventricle into the descending aorta, essentially as two separate or parallel circulations. The area of the aortic arch between the head and neck vessels and the ductus arteriosus (called the aortic isthmus) carries only approximately 10% of fetal cardiac output. Experiments in fetal lambs show that division of this part of the aortic arch does not significantly affect the “parallel” fetal circulation.



Fig. 2-1.—The course of the circulation within the first day after birth. A small left-to-right shunt through the ductus arteriosus and through the foramen ovale may be present. The figures in circles are oxygen saturation percentages in the various chambers and vessels, and the figures alongside are pressure levels in mm Hg. DA—ductus arteriosus, Ao—aorta, PA—pulmonary artery, RV—right ventricle, LV—left ventricle, RA—right atrium, LA—left atrium, SVC—superior vena cava, IVC—inferior vena cava, PV—pulmonary vein, m—mean pressure.

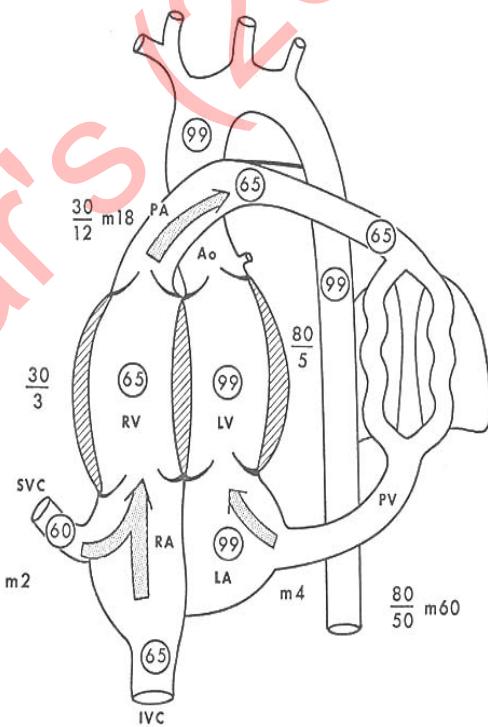
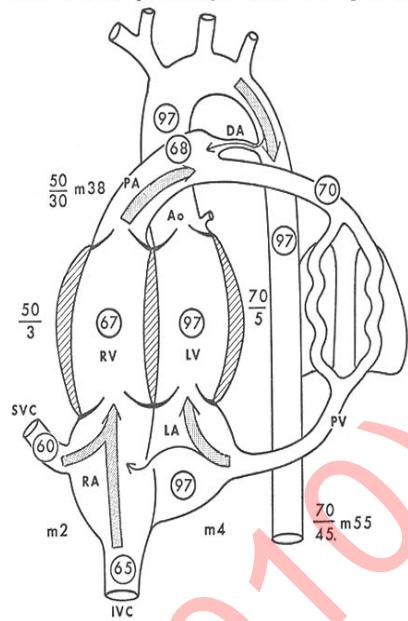


Fig. 2-2.—The course of the circulation is similar to that of the adult within a few days after birth. A pulmonary arterial pressure somewhat higher than that in the adult persists for several months.



2. Physiology. In the adult, although there may be beat-to-beat differences between the output of the right ventricle (RV) and that of the left ventricle (LV), essentially all blood entering the right side of the heart also travels through the left side, so that pulmonary blood flow (Q_p) is equal to systemic blood flow (Q_s). In the fetus, because there are communications between the pulmonary and systemic circulations at several levels (great arteries via the ductus, atria via the foramen ovale) the fetal pulmonary and systemic blood flows are not exactly equal, with the right ventricle transiting slightly higher volumes of blood flow. There are also important differences in fetal intracardiac pressures, oxygen saturations and vascular resistances in comparison to the newborn or to the adult.
- a. Pressures. Figure 1-2 shows the intracardiac and intravascular pressures in the late-gestation fetus. The mean pressure in the right atrium (RA) is slightly higher than the pressure in the left atrium (LA), because the volume of blood flow from the inferior and superior vena cavae is much greater than that returning from the fetal lungs, thus blood shunts right-to-left through the foramen ovale. The ductus arteriosus is a large communication between the pulmonary artery and the descending aorta, thus pressure in the pulmonary artery and aorta are approximately equal although resistance in the pulmonary circulation is much higher than in the fetal descending aorta, resulting in blood flowing right to left across the ductus arteriosus. Fetal right and left ventricular pressures are also equal because they are both coupled to the systemic circulation. Systemic arterial pressures in the fetus are lower than adult values, whereas fetal pulmonary arterial pressures are higher than those in the adult.
- b. Oxygen contents. Although the maternal systemic arterial pO_2 is about 95 torr, the pO_2 of the maternal venous side of the placenta is only about 40 torr. Furthermore, the pO_2 of fetal blood does not equilibrate totally with the pO_2 of maternal blood during passage through the vasculature of the placenta. Thus, the pO_2 of fetal umbilical venous blood is only about 30 torr. Due to the higher oxygen binding affinity of fetal hemoglobin, this low pO_2 corresponds to an oxygen saturation of about 70%, which is still quite low compared with the normal postnatal systemic oxygen saturation (Figure 1-2. Oxygen



saturations are the figures in the circles). Thus, the fetus lives (and thrives) in a low oxygen environment.

Umbilical venous blood has the highest oxygen saturation in the fetus (70%), having just returned from the placenta (Figure 1-2). Umbilical venous blood mixes with blood from the inferior vena cava (IVC) (which has a lower saturation, returning from the fetal lower body), and the resulting oxygen saturation is about 65%. Between one-third to one-half of this blood is preferentially shunted across the foramen ovale into the left atrium (LA) where it mixes with pulmonary venous blood (remember that in the fetus pulmonary venous blood has not been exposed to a high concentration of oxygen in the lungs, as in the adult). There is (at least in the fetal sheep) a partial division of the blood flows from the lower body and the ductus venosus within the IVC, so that the more highly oxygenated blood from the ductus venosus flows along the medial aspect of the IVC and is kept partially separated from the lower oxygenated lower body blood. This stream of oxygenated blood is then preferentially shunted across the foramen ovale, further increasing the oxygen saturation of the blood entering the left atrium.

Blood from the left atrium enters the left ventricle, and from there is delivered mostly to the upper body, brain and (via the coronary arteries) to the myocardium itself. The remainder of the blood from the IVC and ductus venosus mixes with blood from the superior vena cava (SVC), which has a saturation of 40%, and passes through the tricuspid valve into the right ventricle (RV) where the combined saturation is about 55%. From the right ventricle, blood is pumped via the pulmonary artery across the ductus arteriosus to the descending aorta and primarily supplies the lower body and placenta. A small portion of right ventricular blood (approximately 7%) flows from the pulmonary arteries directly into the lungs.

- c. Fetal blood flows. The fetal circulation is essentially a parallel rather than a series one: the right ventricle pumps blood predominantly to the lower body; the left ventricle predominantly to the upper body. Thus, fetal cardiac output is usually described by the term combined ventricular output (CVO) since it is actually the sum of the outputs of both the right and left ventricles. Figure 2-3 shows the actual volumes of



blood passing through the late-gestation fetal sheep heart and Figure 1-5 shows these blood flows as percentages of the fetal combined ventricular output.

As seen in Figure 2-3, fetal right ventricular plus left ventricular output totals about 450 ml/min/kg ($RV=300 + LV=150$), about half of which is distributed to the placenta for gas and nutrient exchange, while the rest goes to the fetal body. Compare these volumes with the volumes of blood passing through the heart postnatally (Figure 2-4). As seen in Figure 1-5, the RV in the fetal sheep is the dominant cardiac chamber, providing nearly 2/3 of the total cardiac output, whereas the LV provides only 1/3. This degree of right ventricular dominance is less pronounced in the human, mainly because of the much large brain size in the human requiring larger volumes of ascending aortic (and thus left ventricular blood flow).

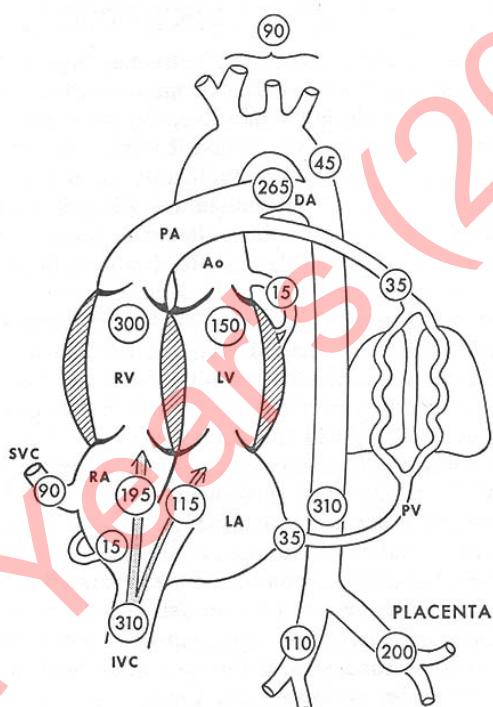


Fig. 2-3. The volumes of blood in ml/min/kg that flow through various chambers and vessels in the late-gestation fetus. Compare with Figure 2-4.

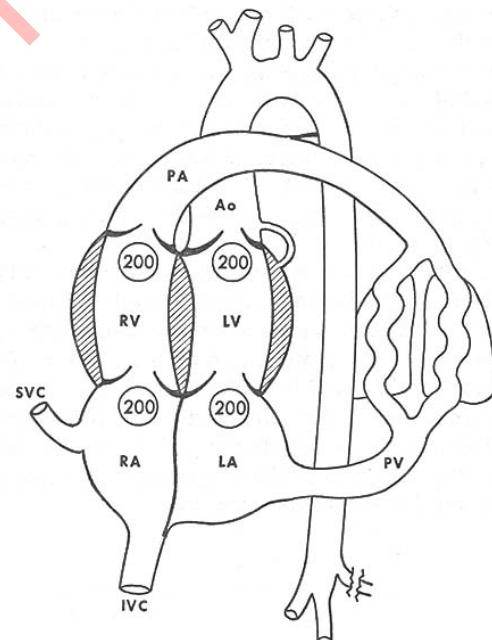


Fig. 2-4. The volumes of blood ejected by each ventricle and returning to each atria are similar postnatally. Compare with Figure 2-3.



To illustrate the distribution of fetal cardiac output, let's follow the circulatory pattern in the fetus, using blood return from the placenta as an arbitrary starting point (Figure 1-5). Placental return via the umbilical vein and ductus venosus mixes with blood from the lower body via the IVC and enters the RA. This represents 69% of blood return to the heart. The foramen ovale is positioned in such a fashion that 1/3 of the blood from the IVC/placenta (27% of total venous return) is shunted across the atrial septum into the LA where it mixes with the small amount of blood returning from the lungs (7%). Left atrial blood then enters the LV, representing 34% of the combined ventricular output (CVO). Most of this blood (31% of CVO) goes to the brain and upper body, 3% of CVO goes to the heart, and about 10% of CVO goes via the aortic isthmus to the descending aorta. Blood from the upper body returns to the heart via the superior vena cava (SVC), representing 21% of total venous return. In the RA this blood mixes with the remainder of IVC/umbilical venous blood that did not shunt across the foramen ovale. The remaining 3% of venous return to the fetal heart is accounted by venous return from the heart itself, entering into the RA via coronary sinus. Right atrial blood enters the RV and represents 66% of CVO. Blood from the RV is then pumped into the main pulmonary artery, from which only about 7% of CVO goes into the right and left pulmonary arteries; the remainder (59% of CVO) traverses the ductus arteriosus into the descending aorta where it mixes with the small amount of blood (10% of CVO) which has gone around the aortic isthmus from the LV. About 2/3 of the descending aorta flow goes to the placenta, whereas the rest goes to the fetal lower body.

Because combined ventricular output (CVO) in the fetus is the product of heart rate and stroke volume of each ventricle, alteration of any of these parameters may change CVO. Certainly, heart rate does vary in the fetus, but there is controversy about how important are changes in stroke volume.

Experimental interventions in the sheep fetus, seeking to duplicate conditions of stress in the human fetus, have been able to clearly influence ventricular filling, changing stroke volumes of the RV and LV, and altering the above distribution of fetal cardiac output.



It is not known what exact changes occur in the presence of intrauterine stress or of congenital cardiac disease, although serial studies using fetal echocardiography have shed considerable light onto the evolution and progression of congenital heart lesions. A lesion which results in even a modest perturbation in the patterns of fetal blood flows, can markedly influence cardiac development. For example, a fetus with a moderate degree of aortic stenosis (valve narrowing) at mid-gestation will have increased resistance to filling of the left ventricle. This will result in less blood flowing across the foramen ovale less blood flowing through the left ventricle during fetal development. It has long been hypothesized that normal cardiac chamber development in the fetus is dependent on normal blood flows. We can now prove this hypothesis by following such a fetus serially (from mid-gestation to term) using echocardiography. In many (but not all) cases, the left ventricle will fail to grow proportionately with the rest of the heart, resulting in severe hypoplasia of the left ventricle (hypoplastic left heart syndrome) in the newborn.

- d. Pulmonary vascular resistance. Vascular resistance is the ratio of blood pressure to blood flow. As we have seen above, fetal pulmonary pressure is high while flow is low, thus fetal pulmonary vascular resistance is high compared to the adult circulation. In the next section we will see how the dramatic changes in pulmonary blood flow occurring in the perinatal period are responsible for many of the changes of the transitional circulation.

3. Summary. The fetal circulation is a parallel circuit with the RV supplying blood to the fetal lower body and the LV supplying blood to the fetal upper body. Three fetal structures are critical for the maintenance of this parallel circulation: the ductus venosus, the foramen ovale, and the ductus arteriosus. The net result of the fetal flow pattern is that the more highly oxygenated and nutrient enriched (umbilical venous) blood tends to be preferentially distributed to the fetal organs which have the greatest metabolic demands: the brain and the heart. The blood which has passed through the fetal body and which has the lowest oxygen and nutrient content passes through the RV to the placenta, where gas exchange and excretion of waste products occurs. Subtle alterations in this pattern of fetal



blood flow can result in more substantial alterations in cardiac development over the course of fetal life.

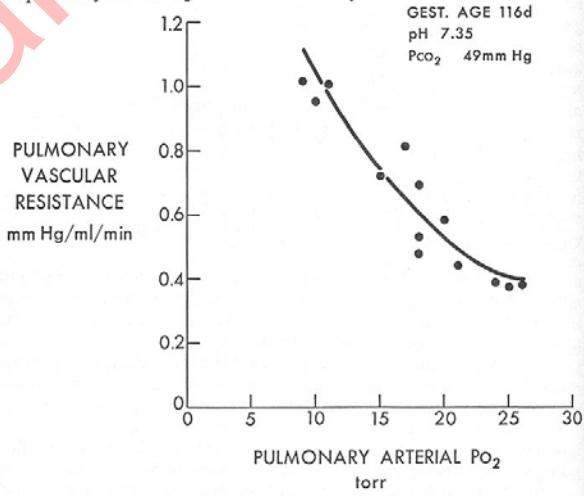
III. EARLY POSTNATAL CHANGES

At the time of delivery, the fetus, placenta, and fetal membranes are expelled from the uterus. Respiratory efforts by the newborn will now cause room air (pO_2 approximately 100 torr) to be inhaled while alveolar gases are expelled. Several major changes in the cardiovascular system must therefore occur in order for the transition from the placental to the pulmonary circulation to proceed. These changes are both anatomic and physiologic (Figure 2-1 (see above)).

A. Anatomical

1. Pulmonary vasculature. With the first breath of life and expansion of the lungs, the alveoli expand. Changes also occur in the pulmonary arterial tree such that the lumina enlarge while the walls thin, although this process takes several weeks before it is fully complete. It has been shown that many factors influence pulmonary vascular tone, physical as well as hormonal. For example, expansion of the lungs alone (without altering fetal pO_2) decreases pulmonary vascular resistance compared to the unventilated lung. There is then a further decrease in resistance when lung expansion is followed by ventilation of the lungs with oxygen (Fig. 3-2). Since an increase in fetal alveolar pO_2 (which should increase pulmonary venous pO_2) can cause pulmonary vasodilation independent of increases in arterial pO_2 , it has been shown that diffusion of alveolar oxygen into precapillary vessels mediates

Fig. 3-2.—The pulmonary vascular resistance is very sensitive to small changes in pulmonary arterial pO_2 , as shown in this study in a fetal lamb.



the vasodilatory response. Of interest, when investigators increased fetal arterial pO_2 without expansion of the lungs or



change in alveolar pO₂, there was also a marked decrease in pulmonary resistance, indicating the importance of both expansion and oxygenation in reducing pulmonary vascular resistance after birth. There are a number of vasoactive agents which have been shown to affect the fetal pulmonary vascular bed. Vasodilators such as acetylcholine, tolazoline, bradykinin, adenosine and histamine all produce vasodilation, although repeated infusion of drugs like acetylcholine results in a diminution of the response (tachyphylaxis). This vasodilation is endothelium-dependent and mediated by the release of nitric oxide (NO) and stimulation of cGMP in vascular smooth muscle cells. Adrenomedullin, released by the adrenal gland, has also been shown to be a prominent pulmonary vasodilator in some species. Other small molecules (CO₂, H⁺, and Ca⁺⁺) also influence pulmonary vascular tone, e.g. acidosis and hypercarbia promote pulmonary vasoconstriction.

2. Fetal cardiovascular structures. The most obvious anatomic change at birth is the separation of the fetus from the placenta, however, major internal changes also occur.
 - a. Umbilical cord. The umbilical cord is divided and clamped at birth. The umbilical vessels are sensitive to many vasoactive hormones (see below) and go into spasm, preventing blood loss; these vessels may be cannulated for approximately 7-10 days after birth, and this is often performed for resuscitating sick newborns. The umbilical stump dries out quickly, and falls off in about 10 days.
 - b. Ductus arteriosus. The vascular tone of the ductus arteriosus is also sensitive to many of the same vasoactive hormones and small molecules which alter pulmonary vascular tone, although some molecules exert opposite effects upon the pulmonary vasculature and the ductus arteriosus. For example, both bradykinin and oxygen promote ductal constriction, whereas they are pulmonary vasodilators. Prostaglandins (PGE) play a major role in ductal patency. Prostaglandins are produced in the wall of the ductus from arachidonic acid by the enzyme cyclo-oxygenase (COX). Both COX-1 and COX-2 have been shown to be involved. The ductus synthesizes both PGE₂ and PGI₂ (prostacyclins), which relax ductal muscle, although PGE₂ is far more potent. Immediately after birth, circulating levels of PGE₂ fall rapidly. Normally the ductus arteriosus closes within the first few days of life. Modulation of



ductal prostaglandin levels can be utilized therapeutically. Prostaglandin E1 is used routinely to maintain ductal patency in infants with certain types of congenital cardiac defects (see Clinical Correlation). In premature infants, the COX inhibitor indomethacin has been used to constrict a persistently patent ductus.

- c. Ductus venosus, like the ductus arteriosus, is a vascular structure, and as soon as the placenta is removed from the circuit, it carries no flow; functional closure therefore occurs quite rapidly.
- d. Functional closure of the foramen ovale also occurs within the first few days of life, related to changes in the pressure relationships in the right and left atria, as we shall see below. However, probe patency of the foramen may continue for many years, and in up to 15% of adults.

B. Physiology

- 1. Pulmonary vascular resistance. The most important physiological change at the time of birth is the abrupt fall in pulmonary vascular resistance which is associated with dilation of the pulmonary vascular bed (Figure 3-1). This is partially due to a rapid vasodilation of pulmonary vessels, however, a second component of this decrease in resistance is related to a remodeling that occurs over the first few weeks and months of life. This includes the anatomic recruitment of new vessels plus a thinning of the medial smooth muscle layer of pulmonary arterioles. The rapidity of this decrease in resistance is species dependent. In the lamb and puppy it occurs quite rapidly, over 5-7 days, however, in the human it is slower, occurring over 6-8 weeks. The timing of this decrease in resistance affects the time of clinical presentation of many congenital cardiac defects. Lesions, such as left-to-right shunts (e.g. ventricular septal defects), that are influenced by the balance between the systemic and pulmonary resistances, may not present with symptoms until the pulmonary vascular resistance has fallen to "adult" levels.



2. Pressures. With the drop in pulmonary vascular resistance, pulmonary pressure also falls, even though pulmonary flow rises dramatically (Figure 3-1). This marked increase in blood flow through the pulmonary circulation can lead to soft systolic murmurs over the right and left lung fields in the first few weeks of life, known as physiological peripheral pulmonic stenosis. These murmurs will disappear as the pulmonary circulation fully remodels, usually by 6-8 weeks of age.

When pulmonary flow (and therefore blood return to the left atrium) increases, LA pressure exceeds RA pressure (Figure 2-1 (see above)) and the flap covering the foremen ovale physiologically closes. A small left-to-right shunt can be visualized across the foramen ovale by echocardiography during the first few days or weeks of life, however, as the pressure difference between the two atria is low and the volume of flow is small, this does not result in an audible heart murmur.

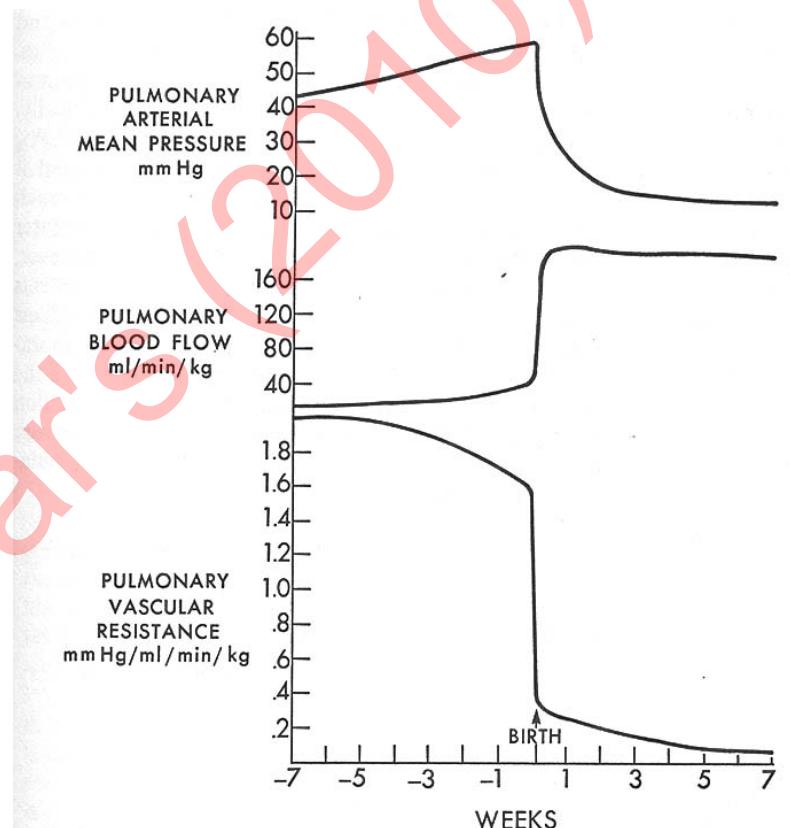


Fig. 3-1.—The changes in pulmonary arterial pressure, pulmonary blood flow and calculated pulmonary vascular resistance during the 7 weeks preceding birth, at birth and in the 7 weeks postnatally. The prenatal data were derived from lambs and the postnatal data from other species.



3. Oxygen saturation. With the increase in pulmonary blood flow, oxygenation of pulmonary venous blood, and reversal of the interatrial shunt from right-to-left to left-to-right, systemic oxygenation rapidly increases to near adult levels.
4. Distribution of blood flow. As pulmonary vascular resistance and pressure begin to fall, and systemic resistance increases slightly (due to the removal of the low resistance placental circulation) the direction of shunting through the ductus arteriosus reverses, with flow now going left-to-right from the aorta to pulmonary artery (Figure 2-1 (see above)). Frequently, the ductus arteriosus remains patent for a brief period after birth, and in many newborns results in a soft systolic murmur which can be heard beneath the left clavicle during the first few days of life. When the ductus finally closes, left ventricular output will be equal to right ventricular output and the circulation has made a complete transition from a parallel to a series circuit.

IV. LONGER-TERM POSTNATAL CHANGES

While the most dramatic alterations in the cardiovascular system occur at birth, it is appropriate to consider the changes at birth to be a phase in the evolution of the adult cardiovascular system, some components of which take several years to complete.

- A. Pulmonary vascular bed. During the first year of life the muscular layer lining the pulmonary arterioles extends to the level of the respiratory bronchiole, and then during the next 5-10 years to the level of the alveolar ducts. Medial smooth muscle reaches the alveolar level by the early teenage years, and alveolar arterioles finally acquire a smooth muscle lining in the late teens. Abnormal muscularization of the pulmonary vascular bed can lead to severe physiologic derangements (persistent pulmonary hypertension of the newborn) and persistence of the fetal pattern of blood flow in the newborn, resulting in low arterial oxygen saturations.
- B. Hemoglobin. Hemoglobin concentration falls after birth, reaches a nadir at about three to six months of age (Figure 19-2), and rises again to adult levels over the next decade. At the time of delivery, the concentration of adult hemoglobin (hemoglobin A) is already rising, and this change accelerates after birth, until after about six months of age there is normally very little fetal hemoglobin (Figure 2).



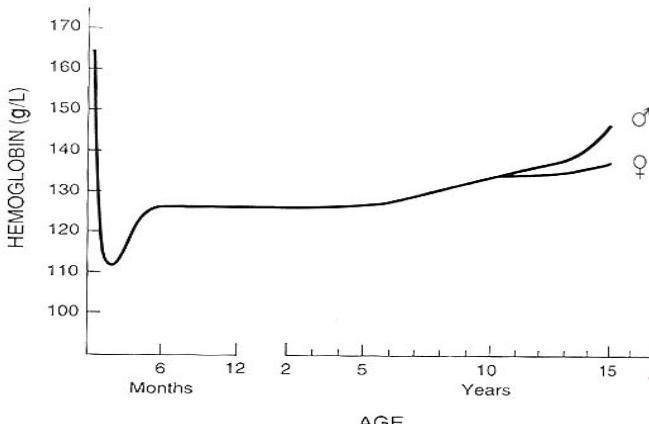


FIGURE 19-2 Developmental changes in mean hemoglobin levels 0–15 years.

C. Circulation

1. Anatomy. The rates of closure of major fetal pathways are illustrated in the Figure on the following page.
 - a. After rapid functional closure, the ductus venosus scars closed within a few weeks, becoming the ligamentum venosus.
 - b. The ductus arteriosus usually achieves functional closure within the first days of life, although total anatomical closure may not occur for many months. The adult structure is called the ligamentum arteriosus. If the ductus remains patent for many years, there is an increased incidence of pulmonary vascular disease (see Clinical Correlation) and/or risk of infection, called endocarditis.
 - c. The foramen ovale functionally closes when pulmonary flow rises, and the flap covering the foremen ovale is held closed by the higher LA pressure. Complete anatomic closure may take much longer, however, and in about 15% of adults it is still possible to pass a catheter through this structure, although shunting of blood does not occur under normal circumstances. However, patency of the foramen ovale has been implicated in some adults with stroke due to a paradoxical thromboembolism traveling from the systemic venous circulation, across the foramen, and out the LV to the carotid arteries.
 - d. The remaining fetal vascular structures become the following:
 - 1) umbilical stump → umbilicus
 - 2) umbilical vein → ligamentum teres



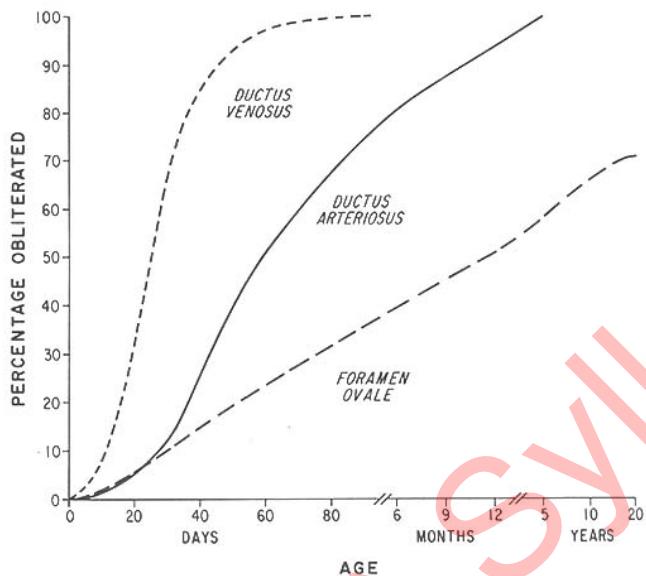


Fig. 2.3 Average percentages of obliterated fetal blood passages according to age. (Modified from R. E. Scammon and E. H. Norris.⁶²) (Reproduced with permission from F. H. Adams: *Heart and Circulation in the Newborn and Infants*, edited by D. E. Cassels. Grune & Stratton, New York, 1966.

- 3) umbilical arteries -> medial umbilical folds
2. Physiology
- Pulmonary pressures fall dramatically immediately after birth, and then continue to fall more slowly over the next several weeks (Figure 3-1 (see above)). Thereafter, pulmonary arterial pressures remain low throughout life in the absence of external stimuli such as high altitude, chronic lung disease such as emphysema, primary pulmonary hypertension, or congenital heart disease. Systemic arterial pressure rises with age, and continues to rise during adulthood.
 - Oxygen saturations rapidly rise after birth. Normally, there is no significant further change in these values with advancing age after birth.
 - Within a few hours after birth, after functional closure of the foremen ovale and ductus arteriosus, pulmonary blood flow in the newborn becomes equal to systemic blood flow. With growth, cardiac output increases in order to provide adequate metabolic needs to the individual, and increase as an approximate linear function of body surface area (Figure 1-19). Cardiac index (cardiac output/body surface area), however, is actually higher at birth and decreases throughout childhood, and thereafter



remains relatively constant throughout life (Figure 1-20).

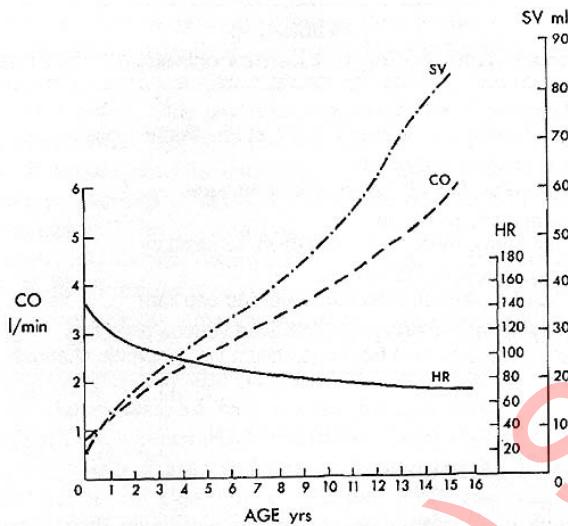


Figure 1-19. Diagram depicting the changes in cardiac output (CO), heart rate (HR), and stroke volume (SV) during infancy, childhood, and adolescence.

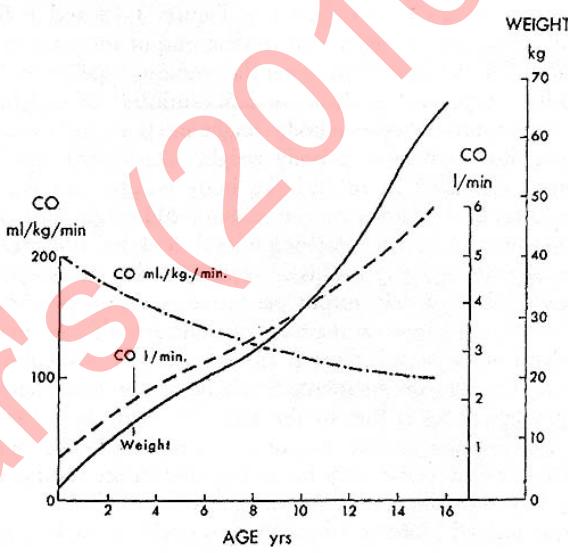


Figure 1-20. The relationships between changes after birth in body weight, actual cardiac output, and cardiac output in mL/min/kg body weight.



V. CLINICAL CORRELATIONS

Case I Pulmonary atresia/ventricular septal defect. The beneficial effect of patency of the ductus arteriosus in certain forms of congenital heart disease.

- A. Introduction. A baby is born with pulmonary atresia (i.e. the pulmonary valve and/or main pulmonary artery is not patent) and a ventricular septal defect (a hole in the ventricular septum). In the fetus with this combination of defects, blood cannot go directly from the right ventricle into the pulmonary artery, but instead goes from the right ventricle into the left ventricle via the ventricular septal defect. All of the output from the heart therefore goes through the aortic valve, and is distributed to the body of the fetus and to the placenta. Since there is no forward flow through the pulmonary valve, the LV supplies all of the systemic blood flow. Blood flow through the ductus arteriosus is reversed from the normal fetal pattern (left-to-right instead of right-to-left) with the ductus providing the small amount of blood flow (approximately 7% of CVO) into the lungs during fetal life. After delivery, as long as the ductus arteriosus remains patent, blood continues to flow from the aorta into the pulmonary artery, allowing some blood to reach the lungs and oxygenation to occur. However, under the influence of the higher level of oxygen in the newborn, the ductus may begin to close. When it begins to narrow, flow to the lungs is reduced, leading to severe systemic desaturation (cyanosis) and, if untreated, to rapid demise. This usually occurs within the first few days of life absent medical intervention.
- B. Exercises
1. Trace out the fetal and neonatal circulatory pathways to visualize the effect on fetal blood flow patterns and the postnatal ductal dependence in a patient with pulmonary atresia/ventricular septal defect.
 2. Let us examine several conditions to which the baby may be subjected, referring to the data in Table II. Remember that since blood flowing into the lungs comes from the aorta, the values for pO₂, O₂ saturation, and oxygen content for pulmonary arterial blood will be the same as the respective values for systemic arterial blood. In clinical pediatric cardiology, this is known as a total mixing lesion, since systemic venous and pulmonary venous blood flows are totally mixed in the heart.



TABLE II

Location	Room Air	100% O ₂	PGE ₁ +Room Air
Mixed venous O ₂ sat	45	45	60
Systemic arterial O ₂ sat	60	??	??
Pulmonary venous O ₂ sat	90	100 (pO ₂ = 500)	90
Q _p :Q _s	??	0.6	2.0

- a. Breathing room air. Given the values in the first column of Table II we can see that the baby is cyanotic with a systemic saturation of 60%, which corresponds to a pO₂ of about 25 torr. What is the ratio of pulmonary flow to systemic flow (Q_p/Q_s)? To solve this, you must use the Fick equation, but first you must calculate the oxygen contents for both pulmonary and systemic circulations. To do this you will need to know two important pieces of information: first, a term newborn has a hemoglobin of about 18 mg/dL; a term newborn normally consumes about 160 ml O₂/min/M² (body surface area of about 0.22 M²). Also, remember that in a total mixing lesion, the systemic and pulmonary arterial oxygen saturations are the same.

$$\begin{aligned} \text{O}_2 \text{ content (ml/dL)} &= \text{O}_2 \text{ sat (\%)} \times \text{Hgb (mg/dL)} \\ &\times 1.36 \text{ (ml O}_2/\text{mg Hgb)} \end{aligned}$$

Fick equations:

$$Q_s = \text{VO}_2 / (\text{CAO}_2 - \text{CMV}_2)$$

$$Q_p = \text{VO}_2 / (\text{CPV}_2 - \text{CPAO}_2)$$

Once you have calculated each of the flows, divide them for the ratio of Q_p:Q_s. What do you think of the physiologic significance of the value you have gotten? What does it say about the status of this infant's ductus arteriosus?

There is actually a much easier way of calculating the Q_p:Q_s using oxygen saturations alone. Using the formula for the Fick equation and a little simple algebra, see if you can figure out this pediatric cardiologist's "trick" for rapidly determining the ratio of pulmonary to systemic blood flow in a cyanotic child.



- b. Breathing 100% O₂. Since the baby is cyanotic, it is usual clinical practice to first give O₂ (either by head box or via an endotracheal tube). How helpful will this be in this case? Oxygen exerts a variety of physiological effects (including potentially a stimulus to further close the ductus arteriosus!), but let us assume that the pulmonary/systemic blood flow ratio (Qp/Qs) is 0.6 as shown in the second column of Table II. What happens to the systemic O₂ saturation with oxygen administration? To solve this, you need the baby's hemoglobin (18.0 gm/dl), and you again need to refer to the fetal hemoglobin-oxygen dissociation curve to calculate oxygen contents. (in this case, because of the high inspired oxygen tension of 500 torr, dissolved O₂ in pulmonary venous blood is not negligible and must be included in the calculation).
- c. Prostaglandin E1. A life-saving effective therapeutic maneuver would be to pharmacologically dilate the ductus arteriosus, increasing pulmonary blood flow. This can usually be accomplished by administration of Prostaglandin E1 (PGE1), which is a potent ductal vasodilator. You start the drug, which will increase pulmonary blood flow, let's say to the ratio shown in column 3 of Table II. What will happen to the systemic arterial O₂ saturation now (assume that the infant is again breathing room air)?
- d. Answers
- 1) Qp:Qs = 0.5
 - 2) systemic arterial saturation = 68%. Note the relatively small rise in saturation with oxygen administration, as compared to the large rise which one would expect in the absence of a right to left shunt. If the full cardiac output can't enter the lungs, then no matter how much oxygen is given, the arterial oxygen level will still be low. This is, in fact, a commonly used maneuver to differentiate cyanotic congenital heart disease from pulmonary disease in the newborn, and is called the hyperoxia test. If after the administration of 100's oxygen, the arterial PO₂ does not rise above about 150 torr, the infant most likely has a right-to-left shunt.
 - 3) systemic arterial saturation 80%



Case 2 Patent Ductus Arteriosus with Eisenmenger Physiology

1. Persistence of a fetal pathway leads to elevated pulmonary vascular resistance and the Eisenmenger reaction.
2. In the fetus, pulmonary arterial pressure is high, while pulmonary flow is low; thus pulmonary resistance is high. After delivery, pulmonary arterial pressure falls while pulmonary flow rises, and pulmonary resistance therefore falls. If the ductus arteriosus remains widely open after birth, a condition called patent ductus arteriosus, pulmonary arterial pressure will remain as high as systemic pressure since there is a free communication between the two circuits. Combined with this elevation of pulmonary arterial pressure, the normal postpartum fall in pulmonary vascular resistance also occurs (although to a lesser extent due to the stimulus of the high pressure) and thus pulmonary flow increases. This total pulmonary blood flow will be composed of:
 - a. poorly oxygenated blood returning from the body via the vena cavae, which enters the right ventricle and is then pumped into the pulmonary artery.
 - b. highly oxygenated blood which enters the pulmonary artery from the aorta via the patent ductus. Thus, the Qp:Qs will be greater than 1.0 and is often as high as 4-5:1, indicating multiple times normal blood flow into the lungs as into the systemic circulation.
3. When this high-flow state persists for a long time (usually many years), a response called the Eisenmenger reaction occurs in which the walls of the pulmonary arterioles become thicker and the lumina become smaller. As this happens, pulmonary vascular resistance begins to rise and eventually pulmonary blood flow falls, the fall initially coming at the expense of blood shunting across the ductus (i.e. a smaller left to right shunt across the ductus). As the reaction progresses and pulmonary vascular scarring and fibrosis occurs, resistance becomes very high and the ductal shunt may actually reverse, in which case poorly oxygenated venous blood shunts from the pulmonary artery to the aorta, thus reducing blood flow to the lungs and producing cyanosis. In the extreme, so little flow gets into the pulmonary vascular bed that the patient cannot survive. In the early stages of the Eisenmenger reaction, the pulmonary vascular changes are related to smooth muscle hypertrophy and vasoconstriction and are reversible if the extra flow is removed by surgical ligation of the ductus, which is usually an easy procedure. However, if the condition is allowed to progress to the point where ductal right-to-left shunting



occurs, the pulmonary vascular changes are not reversible, and simple closure of the ductus may prove lethal (these patients are then candidates only for heart-lung transplantation).

4. While it may take years for irreversible pulmonary vascular resistance changes to occur with a patent ductus arteriosus, this phenomenon can occur in many other congenital cardiac defects, and can progress at a fast rate, sometimes within the first year of life. Thus it is very important that children with cardiac defects be evaluated early in life, in order to prevent this complication.
5. Exercises: Shown in Table III are serial catheterization information for a patient with a large patent ductus arteriosus at several ages in his life. Calculate pulmonary and systemic blood flows and flow indices, and pulmonary vascular resistance for each age. You may assume that the VO₂ is 150 ml/min/M², and that the left atrial (pulmonary venous) oxygen saturation is 95% at all ages.

Table III

	<u>Newborn</u>	<u>3 mos</u>	<u>1 yr</u>	<u>5 yr</u>	<u>10 yr</u>	<u>20 yr</u>
Body Surface Area (M ²)	0.22	0.29	0.44	0.81	1.1	1.8
Hgb (gm/dl)	18.0	13.0	13.0	15.0	15.0	16.5
Mixed Venous Sat	70	70	70	70	68	63
Pulmonary Arterial Sat	75	88	86	77	72	63
Ascending Aorta Sat	95	95	95	95	95	93
Descending Aorta Sat	95	95	95	95	90	70
Pressures (mm Hg) Pulm. Artery(s/d,m)	60/45,50	85/25,50	95/30,55	100/55,70	110/60,75	110/70,82
Aorta (s/d,m)	60/45,50	85/40,55	95/40,60	100/65,70	110/70,80	110/70,82
Left Atrium(mean)	5	15	12	8	7	5
Right Atrium(mean)	3	7	7	5	4	5



V. SUMMARY/GOALS

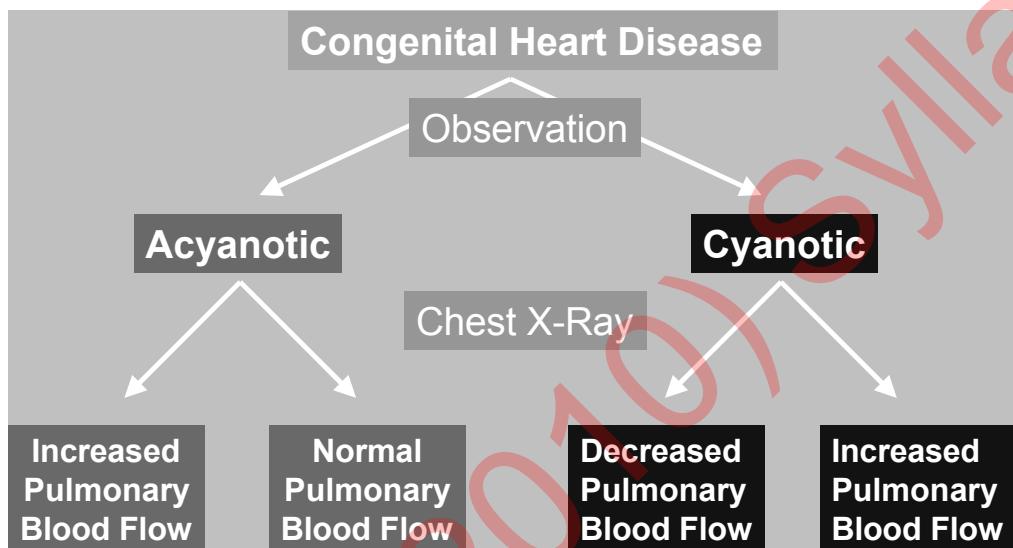
- A. As we have seen, there are several important anatomic and physiologic differences between the fetal circulatory pathways, the newborn, and the adult circulation. The fetus lives in a low oxygen environment, yet grows and develops normally. The fetus adapts to this environment with specialized hemodynamic, metabolic, and hematologic adaptations. For example, increased levels of hemoglobin, increased affinity of fetal hemoglobin for oxygen, and a preferential distribution of blood to different parts of the body: the fetal organs with the highest metabolic demands (brain and heart) receive blood which has a higher concentration of oxygen and other nutrients than the blood which flows to the fetal lower body, placenta and abdominal viscera.
- B. The anatomic structures which are unique to the fetus (ductus arteriosus, ductus venosus, foremen ovale) normally close or are lost at the time of birth. Physiologically, pulmonary blood flow is low in the fetus, while pulmonary pressure is at systemic levels; at birth, pulmonary blood flow increases as pulmonary resistance and pressure falls. Ventilation of the lungs (both physical expansion and increased alveolar PO₂) is associated with much of the fall in pulmonary resistance.
- C. It is hoped that the student will be able to discuss the locations and functions of the various fetal structures, the composition of venous return to the heart, the distribution of venous return between the right and left ventricles, and the distribution of ventricular output from the heart. Examples are also provided to illustrate 1) one situation in which persistence of a fetal pathway may actually be beneficial (pulmonary atresia), and 2) what can happen if complete transition from the fetal circulation does not occur (patent ductus arteriosus).



VI. A PHYSIOLOGIC APPROACH TO THE EVALUATION OF THE PATIENT WITH CONGENITAL HEART DISEASE

(Note: This section has now been published in Bernstein D. Cardiology in Pediatrics for Medical Students 2nd Ed. Lippincott Williams and Wilkins, Philadelphia, 2003.)

- A. Congenital cardiac defects can be classified into two major groups based on the presence or absence of cyanosis (Figure 1).



1. Figure 1. Physiologic classification of congenital heart disease based on presence or absence of cyanosis and pattern of pulmonary blood flow.
- B. The chest X-ray can then be used to further refine the diagnosis based on whether the pulmonary vascular markings show evidence of increased, normal or decreased pulmonary circulation (Figure 2).



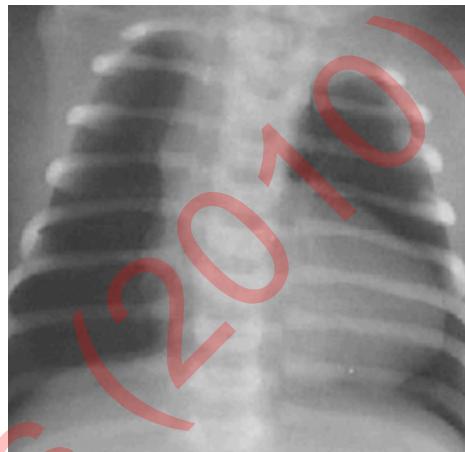
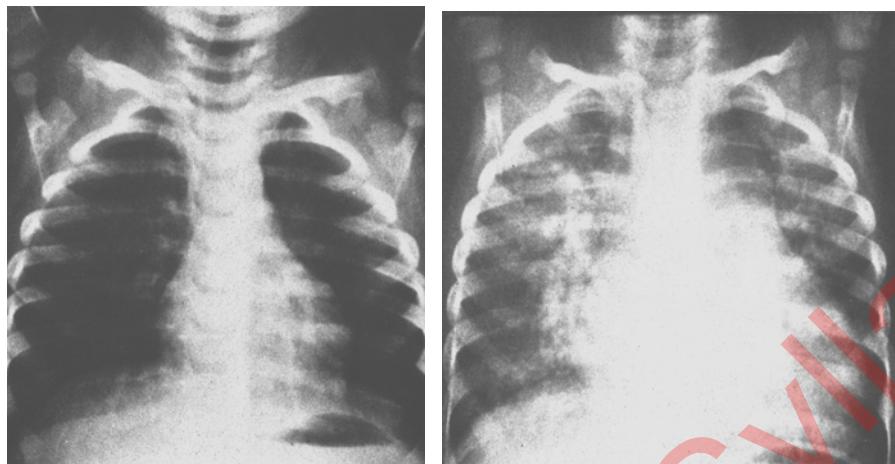


Figure 2. Top Left: Normal heart size and pulmonary vascular markings in a patient without congenital heart disease. Top Right: Increased heart size and increased pulmonary vascular markings in an acyanotic patient with a ventricular septal defect. Bottom: "Boot" shaped heart and decreased pulmonary vascular markings in a cyanotic patient with tetralogy of Fallot.



- C. Acyanotic Congenital Heart Lesions (Figure 3). This group of congenital lesions can be divided by physiological principles into those that induce a volume load on the heart (most commonly due to a left-to-right shunt but also due to atrioventricular valve regurgitation or to abnormalities of the myocardium itself-the cardiomyopathies) and those that induce a pressure load on the heart (subvalvar, valvar or great vessel stenoses). The chest X-ray is a useful tool for differentiating between these two major categories, since heart size and pulmonary vascular markings will usually both be increased in the left-to-right shunt lesions.

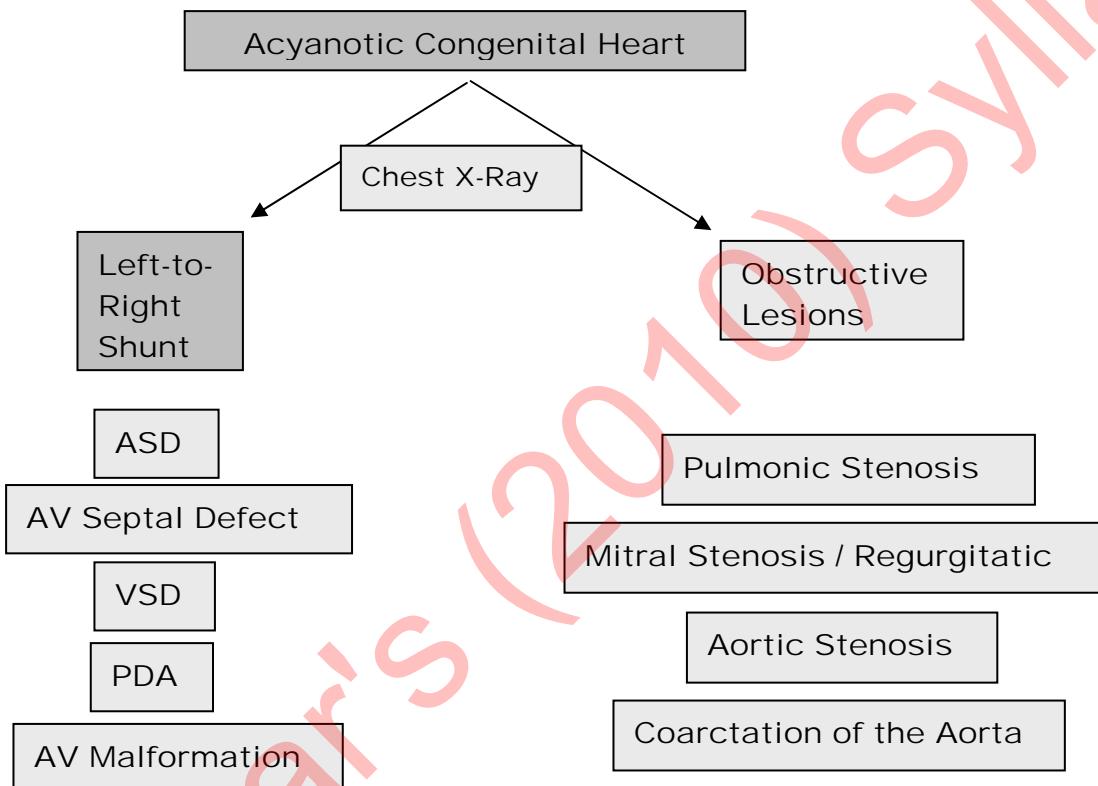


Figure 3. Classification of acyanotic congenital heart defects based on physiologic perturbation.

1. Volume lesions. The most common lesions in this group are the left-to-right shunts: atrial septal defect (ASD), ventricular septal defect (VSD), atrioventricular septal defect (AV canal or endocardium cushion defect), and patent ductus arteriosus (PDA). The common pathophysiologic denominator in this group of lesions is a communication between the left and right sides of the circulation and the shunting of fully oxygenated blood back into the lungs. The direction and magnitude of a shunt across a defect such as a large VSD depends on the relative pulmonary and systemic pressures and vascular resistances. Although pulmonary



vascular resistance falls dramatically at birth, it remains moderately elevated for several weeks before declining to normal adult levels. Thus, in a lesion such as a large VSD, there may be little shunting or symptoms in the first week of life, and it is not unusual that a murmur is not heard in the newborn nursery. As pulmonary resistance drops over the first month of life, the left-to-right shunt increases, and so does the intensity of the murmur and the symptoms. This is true for other left-to-right shunt lesions such as AV septal defect and PDA as well.

The increased volume of blood in the lungs is quantitated by pediatric cardiologists as the pulmonary to systemic blood flow ratio or Qp:Qs. Thus, a 2:1 shunt implies two times the normal pulmonary blood flow (Figure 4). This increase in pulmonary blood flow decreases pulmonary compliance and increases the work of breathing. Fluid leaks into the interstitium or alveoli causing pulmonary edema and the common symptoms: tachypnea, chest retractions, nasal flaring, poor feeding and wheezing (Table 1). In order to maintain a left ventricular output which is now several times normal (although most of this output is ineffective, since it returns to the lungs) heart rate and stroke volume must increase, mediated by an increase in sympathetic stimulation. The increased work of breathing and the increase in circulating catecholamines lead to an elevation in total body oxygen requirements, taxing the oxygen delivery capability of the circulation. Thus, the common symptoms of tachycardia, sweating, irritability and failure to thrive. While isolated valvular regurgitant lesions are less common, atrioventricular valve regurgitation is often a feature of complete AV septal (AV canal) defects. The combination of left-to-right shunt and valve regurgitation increases the volume load on the heart and usually leads to earlier presentation and more severe symptomatology. As opposed to the left-to-right shunts, the cardiomyopathies (see below) cause heart failure directly due to diminished cardiac muscle function, leading to increased atrial and ventricular filling pressures, and to pulmonary edema secondary to increased capillary pressure.



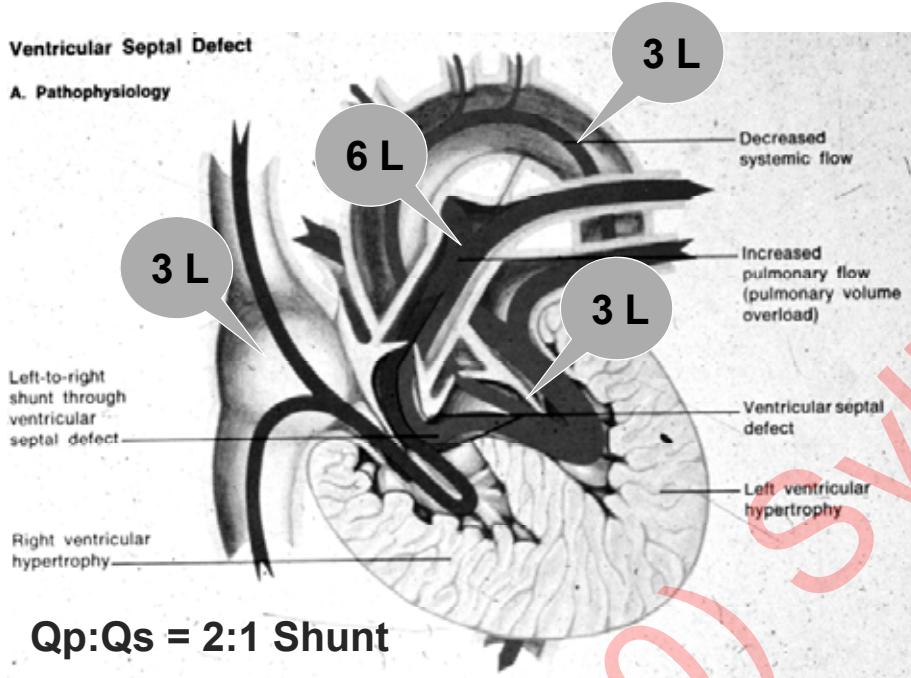


Figure 4 Blood volumes flowing through each chamber of the heart in a patient with a ventricular septal defect and a 2:1 shunt.

2. Obstructive lesions. The most common obstructive lesions are valvar pulmonic stenosis (PS), valvar aortic stenosis (AS), and coarctation of the aorta (CoAo). The common pathophysiologic denominator of these lesions is that, unless the stenosis is severe, cardiac output is maintained, thus, in children, symptoms of heart failure are often not present. This compensation is accomplished by a marked increase in cardiac wall thickness (hypertrophy). Hypertrophy may be detected by subtle radiographic changes in the cardiac silhouette (as compared to the volume lesions), however, left or right ventricular hypertrophy is best detected on the 12-lead electrocardiogram (ECG).
- Severe pulmonic stenosis in the newborn period (critical PS) often leads to right-sided cardiac failure (hepatomegaly, peripheral edema) and to right-to-left shunting across a patent foramen ovale or atrial septal defect and therefore is often classified as a cyanotic heart lesion. The pulmonary vascular markings on the chest X-Ray will be normal or decreased and the ECG will show right ventricular hypertrophy (RVH). Severe aortic stenosis in the newborn period (critical AS) will present with diminished pulses in all extremities and signs of left-sided heart failure (pulmonary edema), right-sided failure (hepatomegaly, peripheral edema), often progressing to total circulatory collapse. If the ductus arteriosus is still open, the oxygen saturation may be



decreased as aortic blood flow may be supplied by a right-to-left ductal shunt. The ECG will show left ventricular hypertrophy (LVH).

Coarctation of the aorta may present solely with a systolic murmur and with diminished pulses in the lower compared with the upper extremities. Thus, it is important to always palpate both the femoral and either the brachial or radial pulses simultaneously during a routine screening examination of any infant or child. A coarctation may be localized to the area of the descending aorta immediately opposite the ductus arteriosus (juxtaductal coarctation). In these patients, in the first few days or weeks of life the ductus arteriosus may remain partially patent and will serve as a conduit for blood flow to partially bypass the obstruction at the level of the coarctation. These infants often become symptomatic when the ductus finally closes. In more severe forms, coarctation involves hypoplasia of the transverse aortic arch, in which case it presents with a more significant obstruction to blood flow and usually causes heart failure and signs of poor perfusion in the neonatal period. The ECG in coarctation, especially in infancy, often shows a combination of both right and left ventricular hypertrophy.

- D. Cyanotic Congenital Heart Lesions (Figure 5). This group of congenital heart lesions can be divided by physiological principles into those associated with decreased pulmonary blood flow (e.g. tetralogy of Fallot, pulmonary atresia with intact septum, tricuspid atresia, total anomalous pulmonary venous return with obstruction) and those associated with increased pulmonary blood flow (transposition of the great arteries, single ventricle, truncus arteriosus, total anomalous pulmonary venous return without obstruction). The chest X-ray is again an important primary initial diagnostic tool for differentiating between these two major categories.
1. Cyanotic lesions with decreased pulmonary blood flow. There are two basic pathophysiologic elements which underlie all of these lesions: First, is an obstruction to pulmonary blood flow at some level (tricuspid valve, sub-pulmonary muscle bundles, pulmonary valve, main or branch pulmonary arteries). Second, is a means by which deoxygenated blood can flow right-to-left to enter the systemic circulation (patent foramen ovale, ASD or VSD). It is important to remember that even with severe pulmonic stenosis, systemic desaturation will not occur unless there is right-to-left shunting at some level.



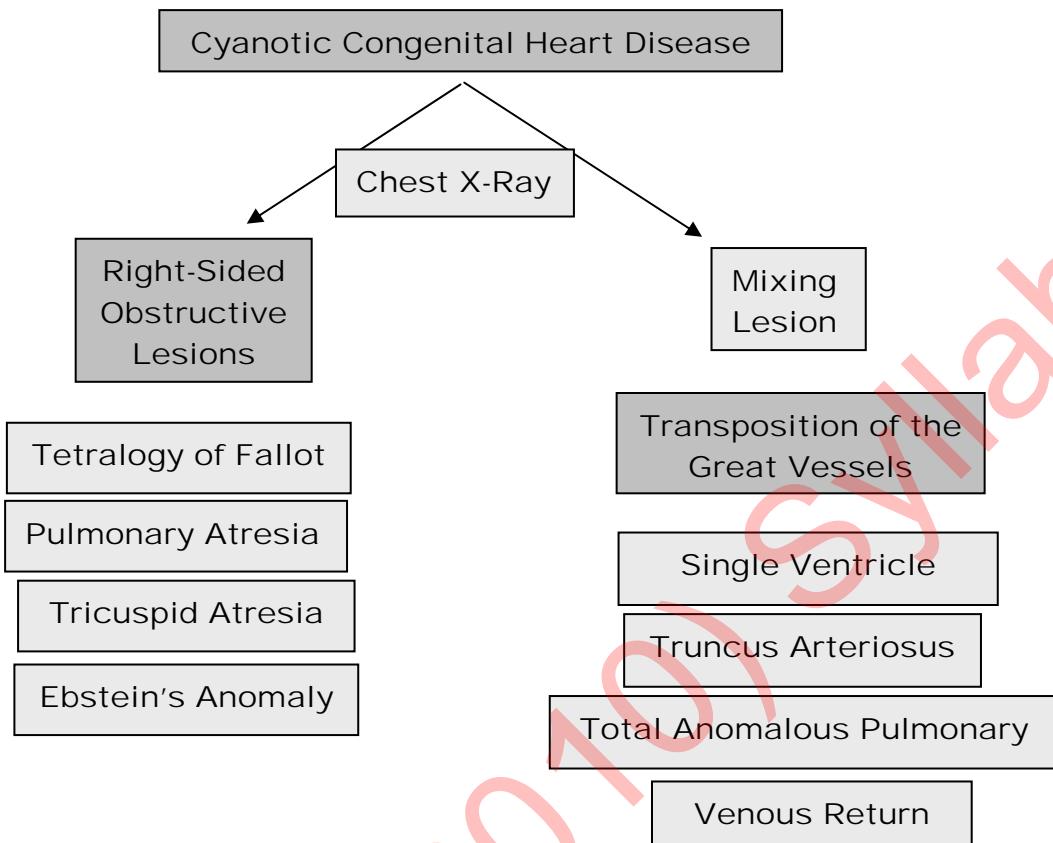


Figure 5. Classification of cyanotic congenital heart lesions based on physiologic perturbation.

In tricuspid atresia, deoxygenated blood shunts right-to-left across either a patent foramen or ASD to the left atrium, where it mixes with pulmonary venous return and enters the left ventricle. Blood enters the lungs either from the right ventricle (via a VSD) or through a patent ductus arteriosus. Tetralogy of Fallot is a constellation of anatomic findings (sub-valvar, valvar and/or supravalvar pulmonic stenosis, VSD, aorta overriding the VSD, and right ventricular hypertrophy). Deoxygenated blood shunts right-to-left across the VSD into the overriding ascending aorta. In these lesions, the degree of clinical cyanosis will depend on the degree of obstruction to pulmonary blood flow. If the obstruction is mild, cyanosis may not be present at rest, but only with stress (these hypercyanotic episodes are known as "Tet spells"). If the obstruction is severe, pulmonary flow may be totally dependent on the patency of the ductus arteriosus. These infants present with profound cyanosis in the newborn period and require pharmacologic manipulation (prostaglandin E1) to maintain ductal patency until surgical intervention.



2. Cyanotic lesions with increased pulmonary blood flow. Unlike the previous group of lesions, pulmonary blood flow is more than adequate in this group, yet because of the defect only a small portion of this oxygenated blood can enter the systemic circulation. Transposition of the great arteries (TGA) is the most common lesion in this group. In TGA, the aorta arises from the right ventricle and the pulmonary artery from the left ventricle. Deoxygenated blood from the body returns to the right side of the heart and is pumped directly back to the body again. Oxygenated blood from the lungs returns to the left side of the heart and is pumped back into the lungs. If not for the persistence of fetal pathways such as the foramen ovale and ductus arteriosus, this lesion would not be compatible with life. These pathways allow for some degree of both left-to-right and right-to-left mixing of oxygenated and deoxygenated blood until surgical intervention can occur.
- Cardiac lesions resulting in a single or common ventricle are known as total mixing lesions. This is because deoxygenated systemic venous blood and oxygenated pulmonary venous blood usually mix totally in the heart resulting in equal oxygen saturations in the pulmonary artery and aorta. Unless pulmonary stenosis is present, pulmonary blood flow will be torrential and these infants usually present with both mild cyanosis and heart failure. If pulmonary stenosis is present, then pulmonary blood flow will be limited, and these infants usually present with more profound cyanosis without heart failure. Truncus arteriosus also results in total mixing of systemic and pulmonary venous blood, however in patients with truncus, mixing occurs at the great vessel level. One additional common lesion, total anomalous pulmonary venous return (TAPVR) with obstruction, causes cyanosis and the appearance of pulmonary edema on chest X-ray, however, this finding is actually secondary to obstruction to blood flowing out of the lungs at the level of the pulmonary veins rather than to an increased volume of pulmonary blood flow. In contrast, total anomalous pulmonary venous return (TAPVR) without obstruction results in increased pulmonary blood flow and cyanosis due to total mixing of systemic venous and pulmonary venous blood at the level of the right atrium.



Last Year's (2010) Syllabus

CONGENITAL MALFORMATIONS OF THE HEART

I. PREFACE

This subject is a large and important one particularly if you are entering a field where you will be routinely caring for children. However, even in many other subspecialties, you may likely be responsible for playing some role in the care of a child with congenital heart disease or an adult who has had repair of congenital heart disease during childhood. There are now, for the first time in history, more adults with congenital heart disease alive in the U.S. than children, reflecting the huge successes in surgical repair over the last 25 years. Whichever subspecialty you choose, it will be necessary to know some of the more common congenital heart diseases and how their cardiopulmonary systems respond to various perturbations, such as fluid shifts, anesthesia and infection, to name a few. While it is impossible in a short period of time to cover the major congenital heart lesions, however, by understanding the basic anatomy and physiology of the major classes of congenital heart disease, you will be well prepared to adopt these basic principals to the specifics of the particular lesion you are managing.

II. INCIDENCE OF CONGENITAL HEART DISEASE

Malformations of the cardiovascular system are the most frequently occurring of all congenital defects. The overall incidence of congenital heart disease (CHD) is approximately 8 per 1,000 newborns. Congenital heart disease is also the leading cause of death due to congenital malformations (accounting for 33% of all mortality). Ventricular septal defect, either alone or in combination with other defects, is the most common congenital heart lesion, followed by patent ductus arteriosus. Tetralogy of Fallot is the most common cyanotic defect (Table I).

III. ETIOLOGY

For years, cardiologists recognized that congenital heart disease had a genetic component, as the incidence of congenital heart disease is higher (4% versus 0.8%) if a first degree relative also has a defect, and even higher if more than one family member are affected. Pedigrees exist with an autosomal transmission pattern for some lesions such as ASD. However, until recently, only a small number of heart lesions were associated with known genetic syndromes, most notably the occurrence of VSD and AV septal defect in children with Trisomy 21. Twin studies show low 'concordance' rate, i.e., in monozygotic twins, the same cardiac defect is only rarely seen in both twins.



IV. GENETIC FACTORS

- A. Specific chromosomal abnormalities which have been associated with congenital heart disease include:
 1. Trisomy 21 (VSD, ASD, PDA, AVSD, Tetralogy of Fallot)
 2. Trisomy 18 (VSD, DORV, PDA)
 3. Trisomy 13 (VSD, ASD, PDA)
 4. (XO) Turner's Syndrome (Coarctation, Bicuspid Aortic Valve)
 5. (XXY) Klinefelter's Syndrome (Tetralogy of Fallot, VSD, PDA)
- B. More recently, a growing list of congenital heart lesions have been associated with specific chromosomal abnormalities, and several have even been linked to specific gene defects (Table 2). The resources of the Human Genome Project combined with powerful new tools of molecular genetics will over the next several years result in the rapid lengthening of this list of congenital heart disease genes. Fluorescent in situ hybridization (FISH) analysis allows clinicians rapid screening of suspected cases once a specific chromosomal abnormality has been identified. Still, even with a known genetic abnormality, the occurrence of heart disease is not a given, and therefore multifactorial etiologies and/or the presence of modifier genes must play a role.

V. ENVIRONMENTAL FACTORS

- A. Thought to represent approximately 10% of etiologies but may play a more substantial role as modifiers of genetic disorders:
 1. Intra-uterine infections:
 - a. Rubella – PDA, peripheral pulmonary stenosis
- B. Coxsackie virus and mumps – cardiomyopathy, endocardial fibroelastosis
 1. Radiation: Teratogenic effect depends on dosage and fetal age.
 2. Clinical evidence suggests only a few cases have history of radiation.
- C. Drugs/Toxins: Essential to take a detailed drug history from the mother.
 1. Alcohol: VSD, ASD, fetal alcohol syndrome
 2. Retinoic acid (conotruncal defects) and dilantin (Ebstein's malformation, pulmonary stenosis) have been associated with heart defects.



3. Non-steroidal anti-inflammatory drugs may cause early closure of the ductus arteriosus during late gestation, leading to physiologic derangements, but not to structural abnormalities.

D. Maternal Disease

1. Diabetes (TGA, Coarctation, VSD)
2. Epilepsy (Pulmonary Stenosis)
3. Phenylketonuria (Tetralogy of Fallot)

VI. CATCH 22

- A. One of the best characterized genetic causes of congenital heart disease is the deletion of a large region of chromosome 22q11, known as the DiGeorge critical region. This region contains over 30 known genes. Recent studies have implicated the transcription factor Tbx1 in the etiology of DiGeorge syndrome and mice with genetic deletion of Tbx1 duplicate many of the clinical findings of patients with this syndrome. Other genes, such as VEGF, are thought to be modifiers, which affect the occurrence and severity of the cardiac defects which occur when Tbx1 is abnormal. The estimated prevalence of 22q11 deletions is 1 in 4000 live births. Cardiac lesions associated with 22q11 deletions are most often seen in association with either the DiGeorge syndrome or the Shprintzen (velocardiofacial) syndrome. The acronym CATCH 22 has been used to summarize the major components of these syndromes (Cardiac defects, Abnormal facies, Thymic aplasia, Cleft palate, and Hypocalcemia). The specific cardiac anomalies fall into the subcategories of conotruncal defects (tetralogy of Fallot, truncus arteriosus, double outlet right ventricle, subarterial ventricular septal defect) and branchial arch defects (coarctation of the aorta, interrupted aortic arch and right aortic arch). Although the risk of recurrence is extremely low in the absence of a parental 22q11 deletion, the risk of recurrence is 50% if one of the parents does carry the deletion.



Table I. Incidence of the most common congenital heart lesions.

Lesion	Percent of Cases of Congenital Heart Disease
Ventricular septal defect (VSD)	30-50
Patent ductus arteriosus (PDA)	10
2° Atrial septal defect (ASD)	7
AV septal defect (AVSD)	3-5
Coarctation of the aorta (CoAo)	6
Aortic stenosis (AS)	5
Pulmonic stenosis (PS)	7
Tetralogy of Fallot (TOF)	5
d-Transposition of the great arteries (d-TGA)	5
Pulmonary atresia	1-2
Tricuspid atresia	1-2
Truncus arteriosus	1
Total anomalous pulmonary venous return (TAPVR)	1
Aortic atresia	1
Double outlet left ventricle	<1
Atrial isomerism	2
Single ventricle	1
Ebstein's malformation	<1

Adapted from Rudolph A.M. Pediatrics 19th ed. Appleton and Lange, Norwalk, 1991, p. 1357.



Table 2. Congenital heart diseases for which chromosomal abnormalities (and some specific gene defects) have been identified.

Congenital Heart Defect or Syndrome	Chromosomal Abnormality	Identified Gene Defect
CATCH 22 (DiGeorge syndrome, Velocardiofacial syndrome)	22q11	Tbx1 (VEGF may be a modifier)
Familial ASD with Heart Block	5q35	NKX2.5
Alagille Syndrome (bile duct hypoplasia, right-sided cardiac lesions)	20p12	JAGGED1
Holt-Oram Syndrome (limb defects, ASD)	12q2	TBX5
Trisomy 21 (AV Septal Defect)	21q22	Not known
Familial TAPVR	4p13-q12	Not known
Noonan (PS, ASD, Hypertrophic Cardiomyopathy)	12q24	PTPN11
Ellis-van Creveld (polydactyly, ASD)	4p16	EVC
Char Syndrome (craniofacial, limb, PDA)	6p12-21.1	TFAP2B
Williams Syndrome (Supravalvar AS, Branch PS, Hypercalcemia)	7q11	Elastin
Marfan Syndrome (Connective tissue weakness, aortic root dilatation)	15q21	Fibrillin
Familial laterality abnormalities (situs inversus, complex congenital heart disease)	Xq24-2q7 1q42 9p13-21	ZIC3 Not known DNAI1



VII. SPECIFIC CONGENITAL HEART LESIONS:

Following are descriptions of the anatomy, clinical presentations, and medical and surgical management of the most common and representative acyanotic and cyanotic congenital heart lesions. Tables 3 and 4 summarize the physical exam, ECG and chest X-ray findings.

VIII. ACYANOTIC LESIONS

- A. Left to Right Shunt (Volume) Lesions
 - 1. Atrial Septal Defect (ASD):
 - a. Anatomy:
 - 1) Secundum ASD in the middle portion of the atrial septum
 - 2) Primum ASD in the inferior, anterior portion of the atrial septum
 - 3) Sinus venosus ASD in the superior portion of the atrial septum adjacent to the SVC. Partial anomalous return of the right upper pulmonary veins to the right atrium is often associated with sinus venosus ASD.
 - 4) Coronary sinus ASD
 - 2. Clinical presentation: With a large ASD, there is equilibration of the right and left atrial pressure. However, because resistance through the pulmonary circulation is lower than through the systemic circulation, left to right shunting will occur. Although pulmonary blood flow may be large, because an ASD does not translate high pressures to the pulmonary circuit (as does a large VSD or PDA), pulmonary hypertension and pulmonary vascular disease are not as common as in these other lesions. Severe heart failure is not common, but children may present with mild symptoms and mild growth limitation; more often the diagnosis is made on the basis of an outflow tract murmur related to the increased flow through the pulmonary valve (note that flow through the ASD does not cause a murmur due to the low pressures at atrial level). Symptoms may begin in the 4th and 5th decades of life: atrial fibrillation, congestive heart failure, and pulmonary hypertension. May be the source of a paradoxical embolus leading to stroke in older adults.



3. Management: Closure of most moderate to large secundum ASDs is now possible with a device placed in the cardiac catheterization lab (Amplatzer, Cardioseal). For those defects too large to close, or for primum or sinus venosus ASDs, surgical closure is low risk and completely curative.

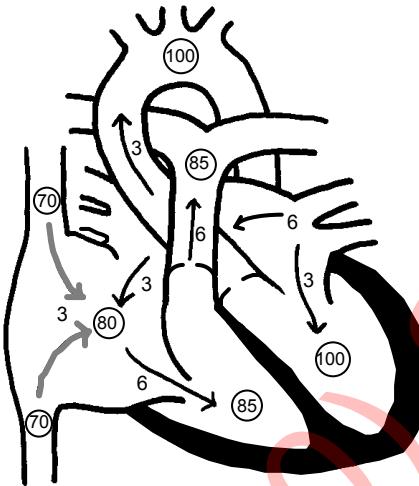


Figure 1: Representative oxygen saturations (circles) and volumes of blood flow (numbers adjacent to arrows) in a patient with a secundum ASD and a Qp:Qs of 2:1.

B. Ventricular Septal Defect (VSD)

1. Anatomy: Four basic types of defect
 - a. Perimembranous (75%)
 - b. Muscular (mid-muscular or apical) (20%)
 - c. Outlet or Supracristal (<5%)
 - d. Inlet (often associated with AV Septal Defects) (5%)
2. Clinical symptoms and time of presentation proportional to:
 - a. size of defect
 - b. ratio of pulmonary to systemic vascular resistances
3. Management:
 - a. Large defects are usually closed surgically during the first six months of life, depending on severity of symptoms (rapid respirations, sweating, trouble eating, failure to thrive).



- b. Small defects will often close spontaneously, especially if the defect is small and muscular in location. Closure of perimembranous defects can also occur and is often associated with the presence of tricuspid valve tissue partially covering the defect (ventricular septal aneurysm or VSA). Spontaneous closure of small defects occurs in 25% by 1.5 yr, 50% by 4 yr, and 60-75% by 10 yr.
- c. Eisenmenger Syndrome. As long as the systemic vascular resistance is higher than the pulmonary vascular resistance, the shunt will be left to right. However, long term exposure of the pulmonary vascular bed to high pressure and high flow will lead to a progressive increase in medial smooth muscle in resistance arterioles (pulmonary vascular disease). Once this occurs, the shunt is reversed and cyanosis occurs. Patients at this time are not suitable candidates for surgical repair and must be considered for heart-lung transplantation.

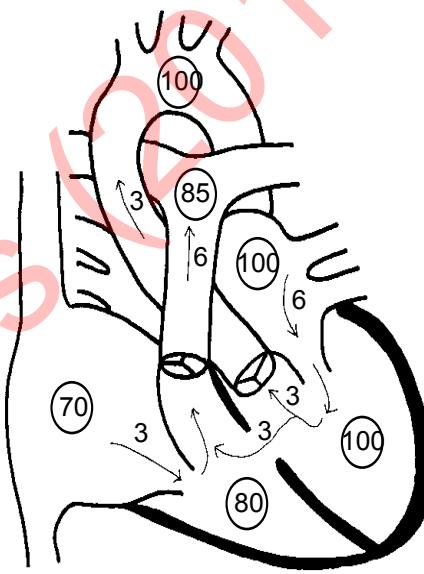


Figure 2: Representative oxygen saturations (circles) and volumes of blood flow (numbers adjacent to arrows) in a patient with a ventricular septal defect and a Qp:Qs of 2:1.

- C. Atrioventricular Septal Defect (AVSD, AV Canal Defect, Endocardial cushion defect)
 - 1. Anatomy:
 - a. Defect in primum atrial septum



- b. Defect in inlet ventricular septum
 - c. Absence of the atrioventricular septum
 - d. Common atrioventricular valve (no separate tricuspid and mitral components)
2. Clinical presentation: often similar to patients with isolated VSD, although presence of left ventricular to right atrial shunting and regurgitation of the common AV valve may lead to marked cardiomegaly (even in the newborn period) and more severe and earlier presentation of heart failure symptoms. Most common congenital heart lesion in patients with trisomy 21.
 3. Management: AVSDs are repaired surgically within the first six months of life. Patients with trisomy 21 are at risk of prematurely elevated pulmonary vascular resistance and more rapid development of Eisenmenger Syndrome.

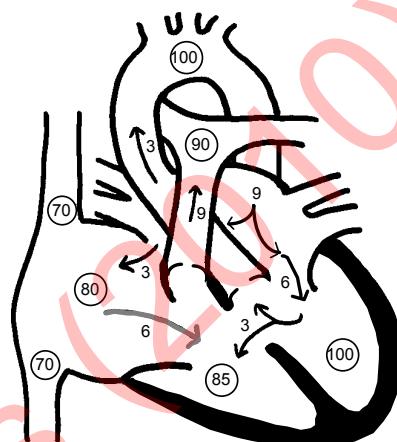


Figure 3: Oxygen saturations and blood flows in a patient with an atrioventricular septal defect and a Qp:Qs of 3:1. Note the presence of left-to-right shunting at both atrial and ventricular levels.

D. Patent Ductus Arteriosus (PDA)

1. Anatomy: In normal newborns, functional closure of the ductus usually occurs within the first 48 hours. Total anatomical closure is complete in 35% of infants at two weeks, 90% at two months and 99% at one year.
2. Clinical presentation: In the first few hours of life, before the pulmonary vascular bed has fully vasodilated, the pulmonary vascular resistance is close to systemic, and the shunt through the ductus is small. As the pulmonary bed dilates in the first day of life, flow through the ductus will increase, left-to-right. Most patients with PDA come to medical attention because of a characteristic "machinery type" murmur.



3. Management: A large PDA may cause symptoms of heart failure due to a large left-to-right shunt, and if left uncorrected may lead to pulmonary vascular disease and Eisenmenger physiology. Large PDAs are usually closed at the time of diagnosis either in the catheterization lab using a coil or closure device, or surgically.
4. A small PDA does not cause symptoms, but puts the patient at risk for a serious infection, subacute bacterial endocarditis (SBE). Small PDAs can be closed electively by a coil inserted in the cath lab.

IX. OBSTRUCTIVE LESIONS

A. Pulmonary Stenosis (PS)

1. Anatomy: The pulmonary valve may be tricuspid with fused leaflets, bicuspid, or unicuspid. Stenosis may occur in the subvalvar area, supravalvar area, or in the peripheral pulmonary arteries.
2. Clinical presentation: Patients usually present with a heart murmur but rarely with clinical symptoms unless very severe. This is an acyanotic lesion unless there is an associated VSD (see tetralogy of Fallot, below). The exception is in the newborn period, where severe PS can lead to right to left shunting through the foramen ovale (known as "critical PS").
3. Management: Mild pulmonic stenosis does not require intervention. Moderate to severe stenosis can usually be treated successfully with balloon valvuloplasty in the catheterization lab.

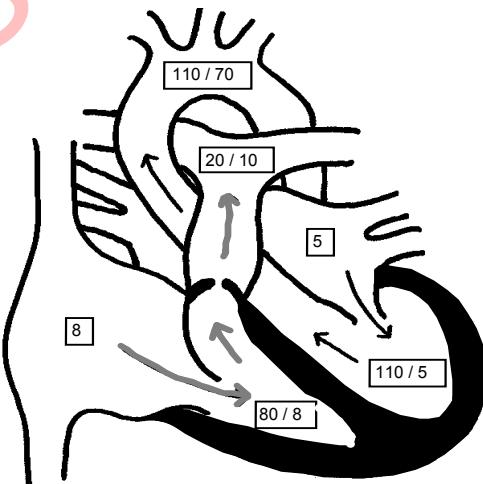


Figure 4: Representative intracardiac pressures in a patient with moderate-severe valvar pulmonic stenosis. Note the elevated RV pressure, the 60 mmHg gradient across the stenotic pulmonary valve. Also note the elevated RA and RV end-diastolic pressures due to decreased compliance of the hypertrophied RV.



B. Aortic Stenosis (AS)

1. Anatomy: The aortic valve may be tricuspid with fused leaflets, bicuspid, or unicuspid (a bicuspid valve is present in up to 2% of the population). Stenosis may occur in the subvalvar area or supravalvar area (often associated with William's syndrome). Severe aortic stenosis can be associated with subendocardial ischemia in fetal life leading to secondary endocardial fibroelastosis (EEF).
2. Clinical presentation: Patients with mild AS usually present with a heart murmur and no clinical symptoms. Moderate to severe AS may present with symptoms of exercise intolerance, chest pain or (if severe enough) cardiovascular collapse after exercise.
3. Management: Mild aortic stenosis does not require intervention, although a bicuspid aortic valve may develop calcification and worsening stenosis in the fourth through seventh decades of life. Moderate stenosis can usually be treated with balloon valvuloplasty in the catheterization lab. Severe stenosis may require either valvuloplasty or surgical valvulotomy. Long term, there is a good likelihood that the valve will need to be replaced.

C. Coarctation of the Aorta (CoAo):

1. Anatomy: Coarctation usually occurs in the region of the descending aorta immediately opposite the insertion of the ductus arteriosus (juxtaductal). Isolated juxtaductal coarctations (formerly known as the "adult" type) can present at any age from newborn to adulthood, depending on how severe the obstruction is. 75% are associated with a bicuspid aortic valve.
2. Clinical presentation: If severe, coarctation can present with respiratory distress, failure to thrive, and even cardiovascular collapse in early infancy; this often occurs when the ductus closes, narrowing the juxtaductal area further. If a coarctation is milder, intercostal arteries enlarge to provide a bypass for blood flow, causing a radial-femoral delay on physical exam and "rib notching" on chest X-ray. Hypertension or decreased femoral pulses are often the only presenting features, although claudication may occur.
3. Management: Surgical correction is the procedure of choice for coarctation of the aorta in infancy and childhood. The abnormal area is excised and the ends of the aorta re-anastomosed. The earlier the time of repair, the higher the likelihood of recurrence later in life. Recurrent coarctation



can usually be treated with balloon angioplasty with or without the placement of an intravascular stent.

X. CYANOTIC LESIONS

A. RIGHT-SIDED OBSTRUCTIVE LESIONS

1. **Tetralogy of Fallot (TOF)**
 - a. **Anatomy:** four components (tetralogy) classically a combination of:
 - 1) Pulmonary stenosis (subvalvar, valvar or supravalvar)
 - 2) VSD (malalignment type)
 - 3) Overriding aorta
 - 4) Right ventricular hypertrophy
 2. **Clinical presentation:** Because of the obstruction to flow through the pulmonary valve, blood passes from the right ventricle through the VSD into the overriding aorta from right to left, causing cyanosis. The degree of cyanosis depends on the severity of the pulmonary stenosis. Infants with severe pulmonary stenosis will present with cyanosis in the immediate newborn period, often as soon as the ductus arteriosus closes. Infants with very mild pulmonic stenosis have a balanced circulation and will not be cyanotic ("pink tets"). Older children in whom the condition has not been corrected will manifest cyanosis, clubbing of the distal fingers (hypertrophic osteoarthropathy) and squatting after exertion.
 3. **Management:** Cyanotic neonates usually undergo complete repair at the time of presentation, although a few centers advocate placement of a Blalock-Taussig shunt between the aorta and pulmonary artery and deferring primary repair until the patient is approximately one year old. Mildly cyanotic or acyanotic patients undergo elective repair within the first 3-6 months of life. Long term outlook is dependent on the degree of pulmonary regurgitation after the repair, the incidence is higher when the valve annulus is small, requiring the surgeon to place a trans-annular patch.



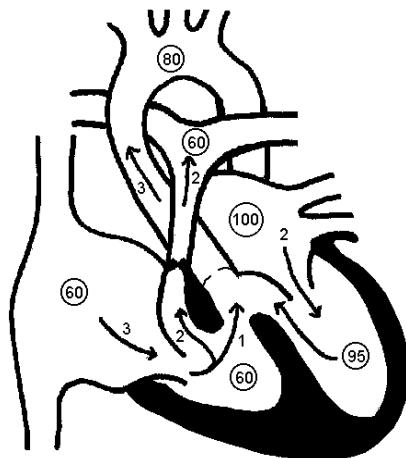


Figure 5: Representative oxygen saturations (circles) and volumes of blood flow (numbers adjacent to arrows) in a patient with tetralogy of Fallot.

XI. MIXING LESIONS

A. d-Transposition of the Great Arteries (d-TGA)

1. Pathology: TGA is one of the conotruncal lesions, the pathogenesis of which is related to the abnormal septation of the embryonic conotruncus. In TGA, the aorta arises from the right ventricle and the pulmonary artery arises from the left ventricle. Physiologically, the systemic and pulmonary circulations are in parallel rather than in series. Life is possible only if admixture of deoxygenated and oxygenated blood occurs via an ASD, VSD or patent ductus arteriosus. TGA can be associated with other lesions, most commonly with ventricular septal defect (VSD), pulmonic stenosis, or with highly complex congenital heart lesions such as single ventricle or tricuspid atresia.
2. Clinical presentation: Patients with simple TGA (no VSD) usually present with cyanosis within the first day or two of life. This may be a sign that the ductus arteriosus is beginning to close. Patients with TGA and a VSD may be only mildly cyanotic due to adequate mixing at the level of the VSD, and these patients may present predominantly with a heart murmur, and some are even not diagnosed until a few weeks of life. Patients with TGA, VSD and pulmonic stenosis will usually present with marked cyanosis in the immediate newborn period.



3. Management: If the ductus begins to close, it can be kept open pharmacologically with an intravenous infusion of prostaglandin E1 (PGE1). In patients with poor admixture of blood despite a PDA, an emergency catheterization procedure to create an artificial ASD (Rashkind procedure) is lifesaving. Surgical repair used to involve creating a baffle between the right and left atria, to tunnel blood flow from the systemic veins to the mitral valve and thereafter from the left ventricle to the pulmonary artery; pulmonary venous return is tunneled to the tricuspid valve, thereafter to the right ventricle and then out the aorta. This operation (Mustard or Senning repair) is done infrequently these days, as total correction of TGA is now feasible (arterial switch or Jatene procedure). An important component of this repair besides switching the aorta and pulmonary artery, is the requirement to also move the coronary arteries from the right ventricular outflow to the left ventricular outflow.

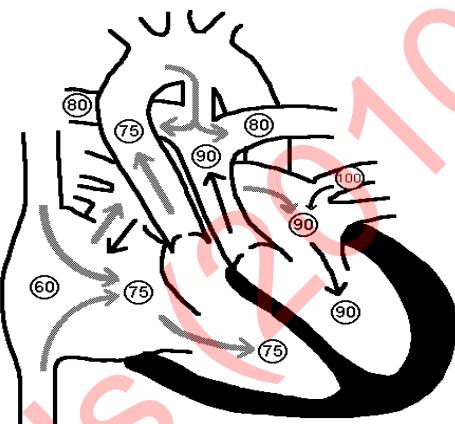


Figure 6: Representative oxygen saturations in a patient with d-transposition of the great vessels and intact ventricular septum. There is mixing at both atrial level and at the ductus arteriosus.



XII. TABLE 3: PHYSICAL FINDINGS IN COMMON ACYANOTIC CONGENITAL HEART LESIONS

Congenital Lesion	Palpation	Auscultation	ECG	Chest X-Ray
Left to Right Shunts				
Atrial Septal Defect (ASD)	RV Impulse	Fixed, wide split S2 Systolic ejection murmur ULSB Mid-diastolic rumble LLSB	Normal; occasionally RSR' in right precordial leads	Large RA,LA,RV, PA Increased pulmonary markings
Ventricular Septal Defect (VSD)	LV Impulse Thrill LLSB	± Widely split S2 Holosystolic (or crescendo-decrescendo) murmur LLSB Mid-diastolic rumble apex		Large LA,LV,PA Increased pulmonary markings
AV Septal Defect (AV Canal)	RV Impulse ± LV Impulse	± Loud S1 Holosystolic murmur LLSB Soft ejection murmur ULSB Mid-diastolic rumble LLSB or apex	Superior, counter-clockwise axis	Large RA,LA,RV,LV Increased pulmonary markings
Patent Ductus Arteriosus (PDA)	LV Impulse Bounding pulses	Continuous murmur ULSB and sub-clavicular area		
Obstructive Lesions				
Pulmonic Stenosis (PS)	RV Impulse Thrill ULSB	Systolic ejection click (mild PS) Soft P2 Systolic ejection murmur ULSB	RVH	Uptilt of cardiac apex (RVH)
Aortic Stenosis (AS)	LV Impulse Decreased pulses Thrill URSB, SSN, carotids	Systolic ejection click (mild AS) Soft A2 Systolic ejection murmur URSB and MLSB	LVH	
Coarctation of the Aorta (CoAo)	Decreased and delayed pulses in lower compared with upper extremities	Systolic ejection click (bicuspid aortic valve) Systolic or continuous murmur LSB and left subscapular area	RVH, LVH	Collateral arteries (Rib notching) Inverted 3 sign Increased pulmonary markings

Adapted from Bernstein D. Pediatrics for Medical Students 2nd Ed. Lippincott Williams and Wilkins, Philadelphia, 2003.



XIII. TABLE 4: PHYSICAL FINDINGS IN COMMON CYANOTIC CONGENITAL HEART LESIONS

Congenital Lesion	Palpation	Auscultation	ECG	Chest X-Ray
Lesions with Decreased Pulmonary Blood Flow				
Critical Pulmonic Stenosis	RV Impulse ± Thrill ULSB	Single S2 ± Systolic ejection murmur ULSB Continuous murmur ULSB (PDA or collaterals)	RVH	Decreased pulmonary flow
Tetralogy of Fallot	RV Impulse ± Thrill ULSB	Loud, single S2 Harsh systolic ejection murmur ULSB and MLSB	RVH, RAD	Decreased pulmonary flow "Boot-shaped" heart R aortic arch (25%)
Tricuspid Atresia	LV impulse	Narrowly split S2, soft P2 Harsh systolic murmur LSB	LVH, Left superior axis	Decreased pulmonary markings Round cardiac silhouette
Ebstein's anomaly of the Tricuspid Valve		Triple or quadruple heart sounds Soft, holosystolic murmur LLSB	RAE, Prolonged PR, Bundle branch block, pre-excitation	Massive RA enlargement, globular cardiac silhouette
Lesions with Increased Pulmonary Blood Flow				
Transposition of the Great Arteries (d-TGV)		Loud or single A2, soft P2 ± Soft systolic ejection murmur MLSB	Normal in newborn period Later RVH, RAD	Normal in newborn; Increased pulmonary markings afterwards; Egg-on-a-string appearance
Truncus Arteriosus	LV impulse RV impulse	Loud single S2 Systolic ejection click MLSB Harsh systolic murmur MLSB Continuous murmur	RVH, LVH	Cardiac enlargement, increased pulmonary markings Right aortic arch (25%)
Hypoplastic Left Heart (HLHS)	RV impulse Poor perfusion Poor peripheral pulses	± Soft midsystolic murmur LSB ± Mid-diastolic rumble LLSB	RAH, RVH	Cardiac enlargement, increased pulmonary markings
Total Anomalous Pulmonary Venous Return (TAPVR)	RV impulse	Gallop rhythm Soft systolic ejection murmur LSB Mid-diastolic rumble LLSB	RVH, RAH	Unobstructed: cardiac enlargement + increased pulmonary markings Obstructed: small heart, diffuse hazy, pulmonary markings

Adapted from Bernstein D. Pediatrics for Medical Students 2nd Ed. Lippincott Williams and Wilkins, Philadelphia, 2003.



XIV. SUGGESTED READINGS

Textbooks and Chapters:

- Bernstein D. Cardiology in Pediatrics for Medical Students 2nd Ed. Lippincott Williams and Wilkins, Philadelphia, 2003, pp. 261-300.
- Bernstein D. The Cardiovascular System in Nelson Textbook of Pediatrics. Saunders, Philadelphia, 2004, pp. 1475-1598.
- Rudolph A. Congenital Diseases of the Heart: Clinical-Physiological Considerations. Futura, Armonk, NY, 2001.
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Figure Credits: Physiology Section:

- Fig. 1. Rudolph A. Congenital Diseases of the Heart. Year Book Medical Publishers. Chicago, 1974, p.10.
- Fig. 2. Behrman RE. Nelson Textbook of Pediatrics. Saunders, Philadelphia, 2004, p. 1603.
- Fig. 4-13. Rudolph A. Congenital Diseases of the Heart. Year Book Medical Publishers. Chicago, 1974, p.107.
- Fig. 1-1. Rudolph A. Congenital Diseases of the Heart. Year Book Medical Publishers. Chicago, 1974, p. 2.
- Fig. 1-2. Rudolph A. Congenital Diseases of the Heart. Year Book Medical Publishers. Chicago, 1974, p. 3.
- Fig 1-5. Rudolph A. Congenital Diseases of the Heart. Year Book Medical Publishers. Chicago, 1974, p. 8.
- Fig. 2-1. Rudolph A. Congenital Diseases of the Heart. Year Book Medical Publishers. Chicago, 1974, p. 18.
- Fig. 2-2. Rudolph A. Congenital Diseases of the Heart. Year Book Medical Publishers. Chicago, 1974, p. 19.
- Fig. 2-3. Rudolph A. Congenital Diseases of the Heart. Year Book Medical Publishers. Chicago, 1974, p. 22.
- Fig. 2-4. Rudolph A. Congenital Diseases of the Heart. Year Book Medical Publishers. Chicago, 1974, p. 23.
- Fig. 3-2. Rudolph A. Congenital Diseases of the Heart. Year Book Medical Publishers. Chicago, 1974, p. 32.



Fig. 3-1. Rudolph A. Congenital Diseases of the Heart. Year Book Medical Publishers. Chicago, 1974, p. 31.

Fig. 19-2. Rudolph CD. Rudolph's Pediatrics. McGraw-Hill, New York, 2003, p. 1520.

Fig. 2-3. Adams FH. Moss' Heart Disease in Infant's, Children, and Adolescents. Williams and Wilkins, Baltimore, 1983, p. 14.

Fig. 1-19. Rudolph A. Congenital Diseases of the Heart: Clinical-Physiological Considerations. Futura, Armonk, NY, 2001, p.44.

Fig. 1-20. Rudolph A. Congenital Diseases of the Heart: Clinical-Physiological Considerations. Futura, Armonk, NY, 2001, p.44.

Figure Credits: Congenital Heart Lesions Section

All figures in this section have subsequently been reprinted in Bernstein D. The Cardiovascular System in Nelson Textbook of Pediatrics. Saunders, Philadelphia, 2004, pp. 1475-1598.



Last Year's (2010) Syllabus

Antiarrhythmic Drugs

Reading assignment: Katzung (10th ed), Ch. 14

LEARNING OBJECTIVES:

- A. Understand the concept of use-dependence.
- B. Understand why some anti-arrhythmic drugs may cause arrhythmias.
- C. Understand how changes in serum potassium ion affect cardiac rhythm.
- D. Learn the pharmacology of the different classes of anti-arrhythmic drugs.

TOPICS

- A. Arrhythmia generation
- B. Antiarrhythmic drugs
 - 1. Sodium channel blockers
 - 2. Calcium channel blockers
 - 3. Potassium channel blockers
 - 4. Beta adrenergic receptor blockers
 - 5. Amiodarone
 - 6. Adenosine



Last Year's (2010) Syllabus

Cardiovascular Pharmacology Case Discussions

Reading assignment: Katzung (10th ed), Ch. 11 – 14, 19, 35, 36 (review)

LEARNING OBJECTIVES:

Review CV pharmacology in preparation for case discussions.

TOPICS

Case discussions



Share only with
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Last Year's (2010) Syllabus

CARDIOVASCULAR LABORATORY II

CASE 1:

Your patient is a newborn resulting from a normal gestation where the mother received good antenatal care. The father had an operation for congenital heart disease and indicates that he was told that he has a deletion of part of one of his chromosomes, but cannot remember which one.

When the baby was born, weighing 2.8 Kg, he was noted to have Apgar scores of 7 (-1 for color, -1 for cry and -1 for tone) and 9 (-1 for color). He then seemed to pink up. At six hours of age, during a bath, he was noted again to be dusky and was taken to the observation nursery. A transcutaneous oxygen monitor showed the oxygen saturation to be 89% and he was given nasal cannula oxygen. You are called to evaluate this infant.

He shows no signs of respiratory distress with a respiratory rate of 55/minute, but appears slightly dusky with an oxygen saturation of 87%. The pulses are equal in the upper and lower extremities. The precordial impulse was notable for a slight accentuation at the lower left lower sternal border. The first heart sound was normal, but the second heart sound was either single. There was a grade III/VI somewhat harsh systolic ejection murmur at the upper left sternal border, radiating equally to both lung fields.

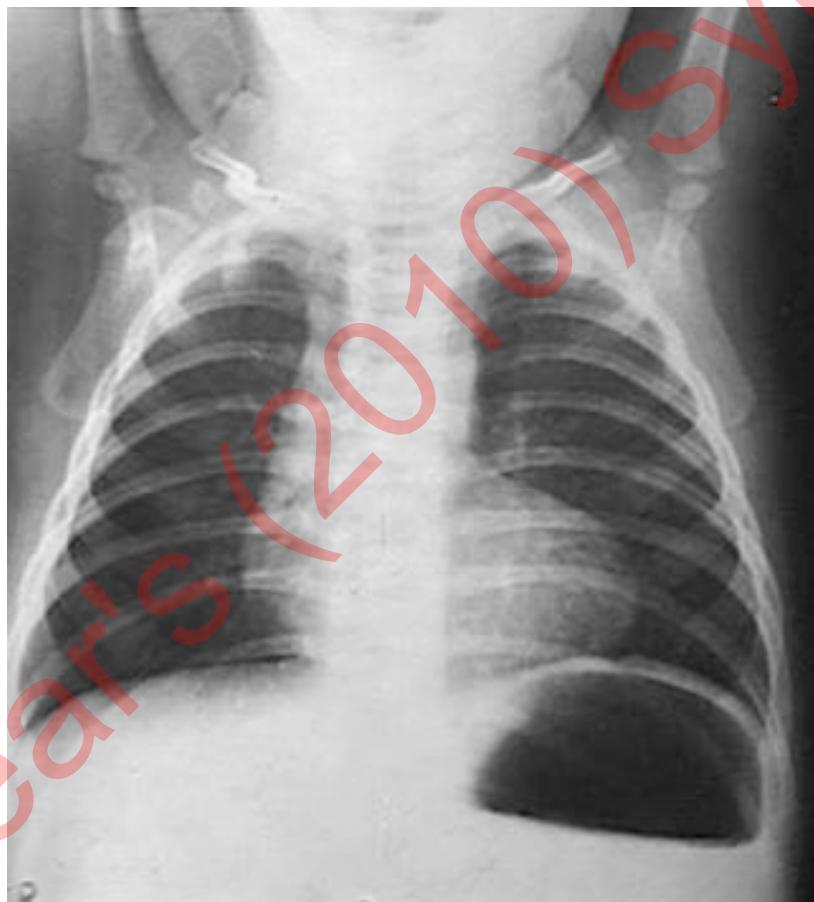
QUESTIONS

1. What is your broad differential diagnosis in this case?

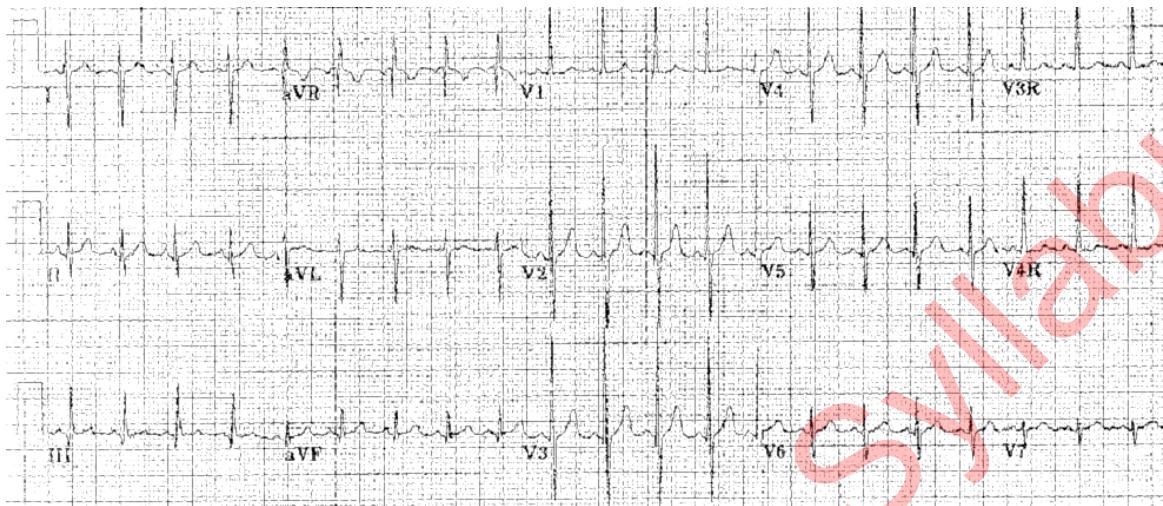


2. What initial studies might you suggest for your evaluation?

3. What features do you recognize in the following study [see CWP for digital original]?



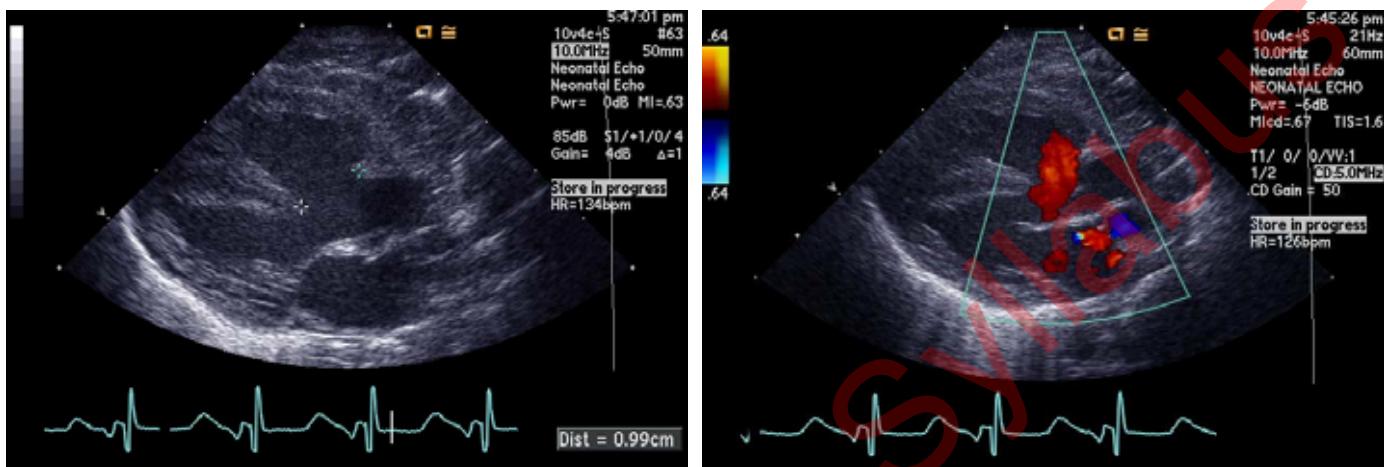
4. What features do you recognize in the following study [original in CWP]?



5. What is your differential diagnosis at this point in the case?



6. Another imaging study is performed. What do you see?

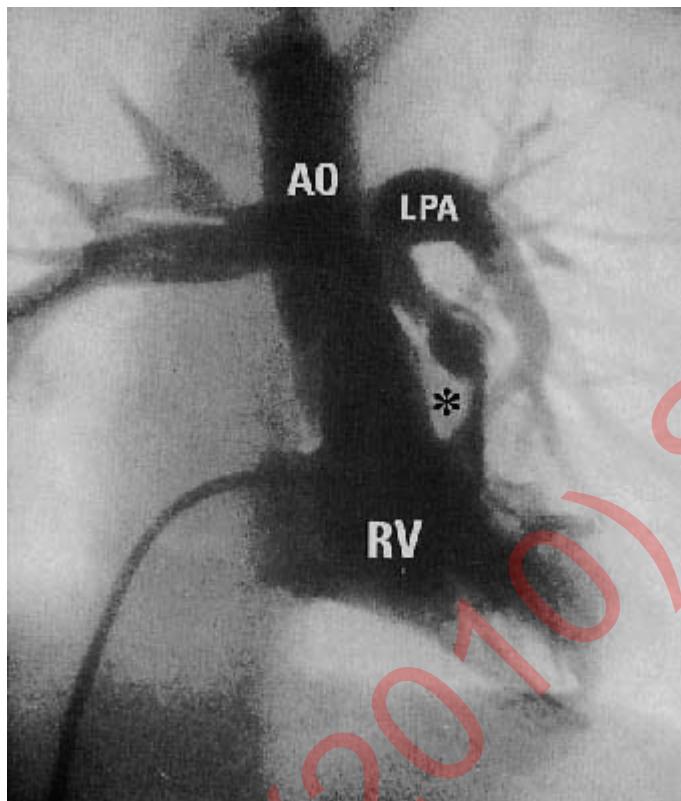


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7. Are there other diagnostic studies that you would order at this time? Below is an image from a cardiac catheterization where contrast dye has been injected into the right ventricle. Describe what this image shows. [original in CWP]



8. What is your final diagnosis?



9. What are the anatomic features of this defect?

10. What corrective operation might be considered?

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CASE 2:

Your patient is a 2.5 mo. old infant girl who was born full term at 3 kg without perinatal complications. She had Apgar scores of 9 and 10 and was sent home on the second day of life. She was noted to have a heart murmur at a routine 1-month check-up with her pediatrician. On close questioning, her mother states that she has been making a grunting sound when breathing for the last several weeks. There is a family history of a cousin with a heart murmur and her grandfather had a heart attack at age 73.

You inquire about the feeding history. Her mother states that the patient is breast fed, but lately has been sweating with feeds and in the past week she falls asleep after 5 minutes at one breast and has to be coaxed to eat more. When she was younger, she used to finish feeding in 15 minutes; now it takes almost 45 minutes.

Physical Exam: Her weight is 3.9 kg and length is 60 cm. Her HR is 155, respirations 75 and blood pressure 70/45 in the right arm. Her oxygen saturation is 97%. She has mild nasal flaring and mild to moderate subcostal retractions. The precordial impulse is diffusely prominent and there is a thrill at the lower left sternal border. The first heart sound is normal. The second heart sound is physiologically split with a loud P2. There is a grade IV/VI blowing holosystolic murmur at the lower left sternal border and a grade II/VI rumbling mid-diastolic murmur at the apex. Her abdominal exam is benign, although the liver is palpated 3 cm below the right costal margin. The spleen is not palpated. Her extremities are warm and well perfused.

QUESTIONS

1. What is your broad differential diagnosis at this point?



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2. What other component of the physical exam is critical at this time?

You feel her pulses in upper and lower extremities simultaneously.

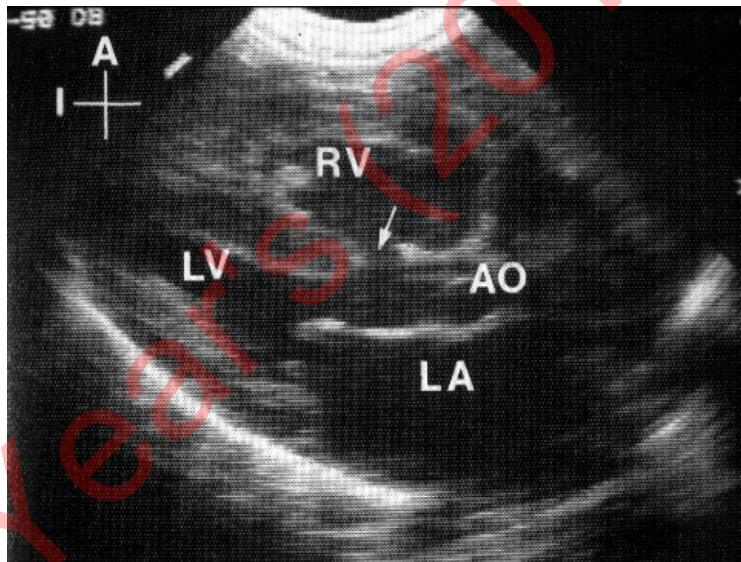
Her pulses are normal in all extremities. There is no delay between the radial and femoral pulses.

3. What additional studies would be helpful?

4. Describe the features found on this X-Ray study, shown below [original in CWP]. What caveats are important to keep in mind in interpreting infant chest X-Rays?



5. How has your differential diagnosis changed by this additional information?
6. Describe the defect found on this echocardiogram and in Echo 1 [CWP: Case 2 Echo 1]. Where is it located? What is the relationship of the defect to the aortic valve? What are the different locations in which this defect can occur?



7. Echo 2 is from a different patient. Describe the location of the defect in Echo 2 [CWP:Inde221 > Lab materials > Cardiac Lab 2 > Case 2 Echo 2].

8. In treating this patient, what therapies should be considered?

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CASE 3:

This 4 year-old girl was in her usual state of excellent health until 7 days ago. At that time she developed a flu-like illness with fever, cough and nasal congestion. Her appetite was diminished but she remained an active toddler. Her vaccination schedule is current and other than usual childhood illnesses she has had no prior serious medical illnesses or conditions. On the day of her admission to the hospital she was brought to the emergency room because she had developed marked fatigue, abdominal pain, and difficulty breathing. She was not noted to be cyanotic.

In the ER she was found to be febrile (38.5 °C), her respiratory rate was 35 per min, heart rate 145 per min, and blood pressure 55/35 mmHg. She looked unwell and appeared weak and sleepy. No neck stiffness, rashes, lymphadenopathy, localizing neurological deficits or oral lesions were found. Crackles were heard in the bases of both lung fields up to the level of the tips of the scapulae. Her cardiac exam was remarkable for an S4 gallop and an occasionally irregular rhythm. No rubs or murmurs were heard. Her liver was palpable 4 cm below the right costal margin and she had 1+ pedal edema.

QUESTIONS

1. What is your differential diagnosis based on the history and physical findings?

2. What studies would you consider at this time?



3. The ECG showed diffuse low voltage and frequent single, unifocal premature ventricular contractions (PVC's). The chest X-Ray demonstrated pulmonary congestion without discrete foci of consolidation. The echocardiogram showed global left ventricular hypokinesis with a fractional shortening of 12%, a dilated LV cavity, and a small pericardial effusion. The interventricular septum was intact and the valves appeared normal. No mural thrombus was seen.

What is your differential diagnosis at this point? What additional studies might be indicated? When would you do the additional studies?

4. An endomyocardial biopsy was performed on the third hospital day without complication. Two days later, she developed a ventricular tachyarrhythmia, and required placement of a Berlin Heart left ventricular assist device (LVAD). She was listed for heart transplant, and a donor heart was obtained after a two month wait. The explanted heart weighed 85 gm (normal 70-80 gm) but showed diffuse myocardial pallor and patchy hemorrhage. The valves, coronary arteries and pericardium appeared normal. The atrial and ventricular septae were intact. A slide (#111) was prepared from the left ventricle of a similar patient. What is the diagnosis?
5. What is the suspected etiology for this lesion?
6. What therapeutic options are available for treatment?

