Update in Nonpulmonary Critical Care

Congestive Heart Failure

ATHENA POPPAS and SHARON ROUNDS

Cardiology Section, The Rhode Island Hospital, Providence, Rhode Island; and Pulmonary/Critical Care Section, Providence VA Medical Center, Department of Medicine, Brown Medical School, Providence, Rhode Island

Congestive heart failure (CHF) complicates the course of a significant proportion of patients in the intensive care unit (ICU). In the ICU, CHF may present as a manifestation of newly diagnosed cardiac disease or as an exacerbation of underlying heart disease, as a result of fluid overload or stress accompanying acute illness, surgery, or trauma. This review highlights recent advances in management of CHF. Most of the data on therapy is from randomized trials of mild to moderate heart failure in the outpatient setting and must be extrapolated to hospitalized patients and to those with advanced disease. There have been surprisingly few studies of the prevalence, causes, and treatment of CHF in the ICU setting.

DIFFERENTIAL DIAGNOSIS

CHF in the ICU typically presents clinically with shortness of breath, hypoxemia, and new or worsening infiltrates on chest radiograph or more insidiously as hypotension or renal insufficiency, or both. The first challenge is to distinguish cardiac from noncardiac causes of pulmonary edema. Causes of noncardiac pulmonary edema include volume overload, renal failure, and capillary leak syndromes. Table 1 lists the differential diagnosis of pulmonary edema.

In evaluating the cause of cardiogenic pulmonary edema, one must first differentiate low or normal output from high output failure (Table 1). The latter is uncommon and is characterized by normal blood pressure, perhaps with increased pulse pressure, tachycardia, and objective evidence of high output, measured as described subsequently. The keystone of treatment of high output failure is correction of underlying cause. This review focuses on systolic and diastolic dysfunction. Systolic dysfunction causes low forward flow and cardiac output, hypotension, and end-organ hypoperfusion. CHF resulting from systolic dysfunction is characterized by pulmonary edema and signs of systemic venous congestion.

Diastolic dysfunction causes CHF with normal to high cardiac output and blood pressure. It is typically precipitated by hypertension, ischemia, or atrial arrhythmias. Diastolic dysfunction can be difficult to diagnose in the ICU patient. The fundamental problem in diastolic dysfunction is that the heart is operating on a steep pressure–volume curve, the slope of which is compliance, and therefore the left ventricle (LV) cannot fill without a significant rise in LV pressure. The diagnosis of diastolic dysfunction requires three conditions: (*1*) the presence of signs or symptoms of CHF; (*2*) the presence of normal LV systolic function (defined as an ejection fraction [EF] $>$ 50%); (*3*) the presence of increased diastolic filling pressure. The prevalence of CHF with normal systolic function is estimated to be 40%, based on meta-analysis of studies over the past 30 yr in which patients met strict criteria for CHF and had normal systolic function (1). A recent study of patients with acute pulmonary edema associated with hypertension revealed that all had similar normal LV ejection fractions (LVEF) both during and after treatment (2), suggesting that CHF complicating hypertension may be the result of diastolic dysfunction. Heart failure with normal systolic function is more common among blacks, women, and the elderly. Although patients with CHF and diastolic dysfunction have a lower annual mortality risk (8.7%) when compared with those with systolic dysfunction (18.9%), their prognosis is still worse than age-matched control subjects without CHF (3 to 4.1%) (3).

DIAGNOSTIC TOOLS

Noninvasive Imaging

Echocardiography can evaluate left and right ventricular systolic function by two-dimensional imaging, and Doppler patterns can differentiate normal from restrictive from constrictive from impaired relaxation physiology. Although transthoracic echocardiograms are the most convenient and readily available means of assessing LV function in the critically ill patient, in the ICU setting, they are often suboptimal owing to patient positioning, mechanical ventilation, lung hyperinflation, and bandages. Intravenous microbubbles can be used for LV opacification, and their use improves assessment of LV wall motion and function (4). High-frequency, multiplane transesophageal echocardiography can further improve assessment of ventricular, valvular, and aortic structure and function with minimal increased risk.

Diastolic function is usually assessed noninvasively by echocardiography. The most widely and readily available methods includes evaluation of Doppler transmitral (E and A waves) and pulmonary venous (S, D, and a waves) inflow patterns, color Doppler m-mode of transmitral flow propagation velocity, and Doppler tissue imaging of mitral annular and myocardial velocities (5). One should alert the echocardiographer if diastolic dysfunction is suspected as a cause of CHF in the ICU.

Radionuclide ventriculography can measure LV filling independent of geometry and may be useful if transthoracic echocardiograms are suboptimal. A less commonly used technique, magnetic resonance imaging (MRI) with tissue tagging, allows evaluation of systolic torsion and diastolic untwisting, which is delayed in patients with hypertrophy owing to pressure overload (6). MRI and computerized tomography (CT)

(*Received in original form February 22, 2001; accepted in final form September 26, 2001*)

Supported by HL 64936, VA Merit Review, and VA/DoD Collaborative Research grants.

Correspondence and requests for reprints should be addressed to Athena Poppas, M.D., The Rhode Island Hospital, 593 Eddy Street, Providence, RI 02903. E-mail: Athena_Poppas@Brown.edu

Am J Respir Crit Care Med Vol 165. pp 4–8, 2002
DOI: 10.1164/rccm2102075
Internet address: www.atsjournals.org

TABLE 1. DIFFERENTIAL DIAGNOSIS OF PULMONARY EDEMA

Noncardiac
Volume overload
Renal failure
Capillary leak
Sepsis
Low oncotic pressure
Toxins
Cardiac
High cardiac output
Anemia
Shunts (cardiac, pulmonary, peripheral)
Beri-beri
Hyperthyroidism
Systolic dysfunction (low cardiac output)
Ischemia
Hypertension
Idiopathic
Tachycardia-mediated
Peripartum
Toxins (e.g., alcohol)
Viral
Hypothyroidism
Diastolic dysfunction (normal to high cardiac output)
Ischemia
Hypertension

can better evaluate pericardial abnormalities, but are not portable techniques and thus are less useful for ICU patients.

Pulmonary Artery Catheterization

In distinguishing cardiac and noncardiac pulmonary edema, the clinical scenario and hemodynamic data (especially pulmonary capillary wedge pressure) are useful. The use of pulmonary artery catheters has decreased since Connors' study suggested higher mortality in ICU patients in whom Swan-Ganz catheters had been placed (7). However, it is not known whether the use of Swan-Ganz catheters is associated with increased mortality of patients with CHF.

For patients with advanced heart failure, invasive monitoring can help guide therapy. The American College of Cardiology/American Heart Association guidelines suggest pulmonary artery balloon catheters in specific instances: clinical deterioration despite use of venodilators and vasodilators, diuretics, and oxygen; slow recovery; high-dose nitroglycerin or nitroprusside; requirement for inotropes; uncertain diagnosis of cardiogenic edema (8).

Cardiac Catheterization

In the catheterization laboratory, contrast ventriculography can measure timing of filling and ejection fractions and can quantify isovolumetric and auxotonic relaxation, chamber compliance, and loading conditions. The latter two techniques are rarely used in clinical practice. Coronary arteriography may be indicated to evaluate acute myocardial ischemia associated with CHF. Newer, more invasive echocardiographic techniques in development include intracardiac echo using a small, high-frequency probe inserted intravenously into the right ventricle for imaging of the left ventricle (9).

MANAGEMENT OF SPECIFIC SYNDROMES

Acute Coronary Ischemia

Suspicion of acute myocardial infarction should prompt an urgent cardiology consult with consideration for thrombolytic therapy or cardiac catheterization and revascularization (10). In non-ST segment elevation, acute coronary syndromes, low-molecular-weight heparin, or platelet glycoprotein GPIIb/IIIa receptor blocking agents have been shown to reduce rates of death and myocardial infarction (11, 12).

Cardiogenic Shock

Mortality exceeds 85% among patients with acute cardiogenic shock, defined as hypotension (systemic blood pressure < 90 mm Hg), hypoperfusion (cardiac index < 2 L/min), and congestion (pulmonary capillary wedge pressure mean > 20 mm Hg). They should be evaluated quickly and aggressively with rapid exclusion or treatment of readily reversible causes of hypotension. Emergency cardiac catheterization and reperfusion is indicated for acute myocardial infarction. The recent trial and registry in shock patients noted a significant reduction in mortality from 88% to 45% for patients treated with acute angioplasty or coronary artery bypass graft (CABG), compared with thrombolytic therapy or intra-aortic balloon counter-pulsation (13). Correctable mechanical lesions can be quickly identified with transthoracic echocardiograms. These include acute ventricular septal defect (VSD), free wall rupture, ruptured chordae tendineae or papillary muscles with severe mitral regurgitation, acute aortic insufficiency, acute aortic dissection, acute prosthetic valve obstruction, or incompetence. MRI or transesophageal echocardiogram may be needed to precisely define the structural abnormality of aortic dissection or mechanical prosthetic valve dysfunction.

Diastolic Dysfunction

There have been few randomized trials of treatment of diastolic dysfunction because of difficulty in diagnosis and occurrence in elderly patients with multiple comorbidities. Therefore, treatment remains empirical and includes avoidance of sodium intake, cautious use of diuretics, restoration of sinus rhythm at a heart rate that maximizes ventricular filling, and correction of precipitating factors, such as acute ischemia and hypertension. Diuretics should be used cautiously to avoid excessive preload reduction. Although calcium channel blockers, nitrates, and angiotensin-converting enzyme (ACE) inhibitors are frequently used to treat diastolic dysfunction, there have been no large prospective trials proving either acute or long-term efficacy.

TREATMENT/MEDICATIONS

Most randomized studies have focused on systolic dysfunction. The treatment goals in acute, decompensated heart failure are to relieve symptoms and stabilize hemodynamics, and there is a strong correlation between the two goals.

Nitrates

Sublingual, oral, and intravenous nitrates provide exogenous nitric oxide and are endothelial-independent vasodilators. Vasodilatation of arteriolar resistance vessels and venous capacitance vessels effectively unloads the heart, reduces LV wall stress, relieves coronary artery constriction, and redistributes flow through collaterals to reduce myocardial ischemia. Morphine sulfate is also an effective venodilator in patients with acute pulmonary edema but must be administered with caution in patients with tenuous respiratory status because of the potential for suppression of ventilatory drive.

Diuretics

Intravenous diuretics have a clear role in reducing the acute symptoms of acute congestion, and when used chronically, may retard biventricular chamber dilation by reducing preload. Loop diuretics, which reversibly inhibit the Na^+, K^+, 2Cl cotransporter, are more effective and preferred in the patient

with acute pulmonary edema caused by CHF. Within minutes of a bolus infusion, pulmonary capillary wedge pressure is reduced and venous capacitance is increased. For patients with refractory heart failure or diuretic resistance, beneficial options include continuous infusion of furosemide to prevent rebound, or the addition of metolazone or spironolactone, which have different sites and mechanisms of action from loop diuretics (14). Spironolactone, an aldosterone-receptor blocker, reduces long-term cardiovascular mortality. In an outpatient, randomized trial of 1,663 patients with EF $< 35\%$, the addition of spironolactone to a regime of ACE inhibitors and loop diuretics reduced morbidity by 35% and mortality by 30% at 24 mo (15). Potential adverse effects included hyponatremia, hypokalemia, azotemia, and hypovolemia.

Vasodilators

Vasodilators reverse maladaptive neurohumoral and hemodynamic responses in heart failure; they are well tolerated, improve signs and symptoms, and reduce mortality by 15 to 40% depending upon the degree of initial functional impairment. The long-term morbidity and mortality benefits of ACE inhibitors (captopril, enalapril, trandolapril, ramipril) have been demonstrated in large randomized, controlled trials in the last 15 yr (16, 17). Hyponatremic and hypovolemic patients are more apt to develop worsening renal function or hypotension when ACE inhibitors are initially prescribed. If this occurs, diuretics should initially be reduced and some degree of prerenal azotemia must be tolerated. For the 5 to 10% of patients who experience side effects of ACE inhibitors, such as cough, angiotensin II receptor blockers (ARB) acutely improve hemodynamics and probably improve long-term morbidity and mortality (18). There are ongoing, outpatient mortality trials of a number of ARBs.

The isosorbide dinitrate–hydralazine combination is an alternative treatment for patients who cannot tolerate ACE inhibitors; morbidity and mortality benefits were shown to be greater than placebo, but less than enalapril, in the V-HeFT trials (19). The use of calcium-channel blockers for CHF is circumscribed. Nifedipine, nicardipine, and diltiazem may worsen morbidity and mortality. Two dihydropyridines, amlodipine in one study and felodipine in a VA hospital trial, have shown neutral effects on morbidity and mortality (20). These can be considered safe fourth-line agents for patients with persistent ischemia or hypertension.

Sodium nitroprusside is a potent vasodilator which decreases vascular resistance and thereby decreases oxygen consumption with resultant increase in cardiac output. It is particularly effective in pulmonary edema caused by severe valvular regurgitation or systemic hypertension. The risks of the drug include rapid and dramatic drops in systemic blood pressure and cyanide toxicity, particularly in the elderly or in those with reduced renal function. In patients with pulmonary edema complicating malignant hypertension, the dopamine (DA1) antagonist, fenoldopam, is an alternative vasodilator which has the advantages of improved renal blood flow and natriuresis without cyanide toxicity (21).

β-Adrenergic Blocking Agents

In outpatients, β-blockers improved survival and reduced rates of rehospitalization and worsening of CHF (22, 23). Importantly, this class of drugs causes an initial deterioration in hemodynamics, symptoms, and LVEF with subsequent improvement over the next 6 to 12 mo. When patients are admitted to the ICU with an acute exacerbation of CHF, β-blockers should not be initiated and chronic doses should be reduced by half. Very low doses can be initiated in patients who have recovered from their acute episode of CHF and show no signs of fluid retention. The use of β-blockers in patients with chronic obstructive pulmonary disease is usually well tolerated, but they should be avoided in severe asthmatics.

Inotropes

Acute treatment of CHF may require parenteral inotropic medications guided by pulmonary artery catheter–derived hemodynamic information. Inotropes temporarily improve cardiac output and renal blood flow and may break the negative neurohumoral feedback partially produced by renal hypoperfusion. Dobutamine has potent inotropic and mild chronotropic and vasodilatory actions through its effects on β_1 and β_2 and α_2 receptors. Doses less than 10 μg/kg/min are less likely to cause side effects that include tachycardia, ventricular arrhythmias, and myocardial ischemia. Improvement in ventricular function and symptoms after 48 to 72 h of dobutamine may persist for weeks to months (24). Enthusiasm for long-term intermittent or continuous infusion has been tempered by a number of studies showing increased mortality with no significant morbidity benefits, similar to findings with a number of oral inotropes (25). However, these drugs can be used for continuous support as a bridge to transplant.

Low-dose dopamine (2 to 5 μg/kg/min) stimulates β_2 receptors, improving ventricular contraction and increasing renal cortical blood flow and diuresis. At higher doses, stimulation of α_1-adrenergic receptors causes peripheral arterial constriction and increases afterload, wall stress, and myocardial oxygen consumption. This can be counteracted by concomitant administration of nitroprusside or nitroglycerin (24).

Newer phosphodiesterase inhibitors (PDIs), such as milrinone and amrinone, prevent degradation of cyclic adenosine monophosphate in myocytes and vascular smooth muscle cells and therefore are potent inotropes and vasodilators. Their effects on systemic vascular resistance help prevent increases in myocardial oxygen consumption, and the reduction in pulmonary vascular resistance can significantly unload the right ventricle (26). Conversely, patients with sepsis or hypovolemia may not tolerate the peripheral effects of these drugs. Unlike the β-adrenergic receptor agonists and dobutamine, PDIs act downstream to the receptor and therefore are not associated with tachyphylaxis and are effective in patients on β-blockers.

Digoxin has neurohumoral and electrophysiologic effects that improve hemodynamics acutely and chronically and reduce hospitalizations in patients with either atrial fibrillation or sinus rhythm. In the recent Digitalis Investigation Group (DIG) study, digoxin had a neutral effect on mortality; this appeared to be due to a reduction in mortality from heart failure but an increase in probable arrhythmic deaths (27). Digoxin should not be initiated in inpatients with acute coronary syndromes, as ischemia appears to lower the threshold for arrhythmias.

Investigational Agents

Some investigational drugs have shown promise in CHF. In chronic CHF, antidiuretic hormone is inappropriately elevated, leading to water retention. Arginine-vasopressin receptor antagonists have natriuretic and vasodilatory effects and had good safety and hemodynamic profiles in Phase II trials (28). In 370 patients with severe Class III–IV CHF treated with an endothelin receptor antagonist, versus placebo for 6 mo, 27% versus 19% of patients noted improvement in the composite endpoint of symptoms and cardiovascular events (29). Natriuretic peptides regulate adrenergic tone, natriuresis, vasodilation, venodilation, hypertrophy, and myocardial relaxation. In Phase

II and III trials of decompensated heart failure, continuous infusions of brain natriuretic peptide (BNP) caused dose-related decreases in pulmonary capillary wedge pressure and systemic vascular resistance. Cardiac output and urine output increased without a change in heart rate and with less renal impairment and ventricular arrhythmias, as compared with placebo (30).

Antiarrhythmic Agents

Although patients with heart failure are at risk for sudden cardiac death, prophylactic antiarrhythmic drugs have been shown to increase mortality. Intravenous amiodarone is the preferred agent for treating sustained or hemodynamically significant ventricular tachycardia or for suppressing or converting atrial arrhythmias associated with hemodynamic instability. In a randomized trial of 674 CHF outpatients with asymptomatic ventricular arrhythmias, oral amiodarone did not increase the risk of death when compared with placebo. In the subgroup with nonischemic cardiomyopathy, there was a decrease in all-cause mortality and rehospitalization (31). Amiodarone has gastrointestinal side effects, particularly during loading, as well as risk of pulmonary fibrosis and thyroid disorders when used long-term.

TREATMENT/INTERVENTIONS

Positive Pressure Ventilation

The beneficial effects of positive pressure ventilation on CHF have been known for over 50 yr. Intubation can be life-saving. Positive pressure ventilation with positive end-expiratory pressure (PEEP) recruits edematous lung, improving compliance and gas exchange and decreasing work of breathing. Positive pleural pressure decreases preload and LV afterload immediately.

Continuous positive airway pressure (CPAP) delivered by face mask reduced need for intubation and mechanical ventilation in patients with acute CHF, and this conclusion was validated in a recent meta-analysis (32). The effects of bilevel positive airway pressure (BiPAP) are less clear since a recent controlled comparison of BiPAP versus CPAP had to be terminated because of increased risk of myocardial infarction in the BiPAP group, despite more rapid improvement in ventilation and vital signs (33).

Mechanical Ventricular Support

In persistent shock despite inotropes with a potentially reversible cause (such as acute myocardial infarction, VSD, or valvular regurgitation) intra-aortic balloon counterpulsation (IABP) is a useful bridge to stabilize the patient before diagnostic or therapeutic intervention or to allow the heart to recover function (10). It can be inserted percutaneously under fluoroscopy. IABP is contraindicated in aortic dissection, severe aortic insufficiency, and thrombocytopenia. Its use carries significant morbidity, including bleeding infection, and limb ischemia, which increases with length of use. Hence, for patients awaiting transplantation, mechanical left ventricular assist devices are promising alternatives. These surgically implanted devices are mechanical pumps that take over the function of the failing heart, restoring hemodynamics and reversing end-organ deterioration (34).

Cardiac Transplantation

Heart transplantation improves survival compared with traditional therapy in patients with acute or chronic New York Heart Association (NYHA) functional Class III–IV. Ten-year survival rates are approximately 50%. Unfortunately, more than 10% of outpatients and 30% of inpatients awaiting transplantation die because of shortage of donor organs. Hemodynamic and functional indices of prognosis and comorbid conditions help identify patients who are likely to derive the maximum benefit from transplantation (35). Conditions that limit survival independent of heart disease or negatively affect outcome after transplantation are considered relative contraindications.

POST-ICU CARE

Patients should be stabilized on an oral regimen of ACE inhibitors, β-blockers, and possibly diuretics and digoxin. Anticoagulation with warfarin is beneficial in the subgroup of patients with atrial fibrillation, a history of embolic events, and probably with LV thrombi and very low (< 20%) EFs. There have been no randomized, long-term, prospective trials to evaluate anticoagulants in all patients with LV dysfunction (36). Patient education about the nature of their disease, low-salt diet, and careful follow-up are important for minimizing morbidity and mortality (8).

SUMMARY/APPROACH TO THE PATIENT WITH CHF

The diagnosis of CHF caused by systolic or diastolic dysfunction relies upon a careful history and physical examination for signs and symptoms as well as hemodynamic assessment by noninvasive or invasive measures. Systolic dysfunction should be treated with preload reduction using venodilators and diuretics, afterload reduction with vasodilators, and improvement of peripheral perfusion, if necessary, with inotropes. Diastolic dysfunction should be treated with cautious diuresis, control of increased blood pressure, and treatment of myocardial ischemia with nitrates and β blockade. Further work is needed to characterize the prevalence, precipitating causes, and treatment of CHF among patients in the ICU.

References

1. Vasan R, Benjamin E, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. *J Am Coll Cardiol* 1995;26:1565–1574.
2. Gandhi SK, Powers JC, Nomeir A-M, Fowle K, Kitzman DW, Rankin KM, Little WC. The pathogenesis of acute pulmonary edema associated with hypertension. *N Engl J Med* 2001;344: 17–22.
3. Vasan R, Larson M, Benjamin E, Evans J, Reiss C, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction. *J Am Coll Cardiol* 1999;33:1948–1955.
4. Reilly J, Tunick P, Timmermans R, Stein B, Rosenzweig B, Kronzon I. Contrast echocardiography clarifies uninterpretable wall motion in intensive care unit patients. *J Am Coll Cardiol* 2000;35:485–490.
5. Mandinov L, Eberli F, Seiler C, Hess O. Diastolic heart failure. *Cardiovasc Res* 2000;45:813–825.
6. Stuber MB, Scheidegger MB, Fischer S, Nagel E, Steinmann F, Hess OM, Boesiger P. Alterations in the local myocardial motion pattern in patients suffering from pressure overload due to aortic stenosis. *Circulation* 1999;100:361–368.
7. Connors AF Jr, Speroff T, Dawson NV, Thomas C, Harrell FE Jr, Wagner D, Desbiens N, Goldman L, Wu AW, Califf RM, *et al.* The effectiveness of right heart catheterization in the initial care of critically ill patients. *J Am Med Assoc* 1996;276:889–897.
8. Williams J, Bristow M, Fowler M, Francis G. Guidelines for the evaluation and management of heart failure. Report on the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Evaluation and Management of Heart Failure). *Circulation* 2000;92:2764–2784.
9. Allan J, Smith R, DeJong S, McKay C, Kerber R. Intracardiac echocardiographic imaging of the left ventricle from the right ventricle: quantitative experimental evaluation. *J Am Soc Echocardiogr* 1998;11:921–928.
10. Ryan TJ, Anderson JL, Antman EM, Braniff BA, Brooks NH, Califf RM, Hillis LD, Hiratzka LF, Rapaport E, Riegel BJ, *et al.* Guidelines for the management of patients with acute myocardial infarction. *J Am Coll Cardiol* 1996;28: 1328–1428.
11. Zed P, Tisdale J, Borzak S. Low-molecular-weight heparins in the man-

agement of acute coronary syndromes. *Arch Intern Med* 1999;159: 1849–1857.
12. Lincoff A, Califf R, Topol E. Platelet glycoprotein IIb/IIIa receptor blockade in coronary artery disease. *J Am Coll Cardiol* 2000;35:1103–1115.
13. Hochman J, Sleeper L, Webb J. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. *N Engl J Med* 1999; 341:625–634.
14. Kramer B, Schweda F, Riegger G. Diuretic treatment and diuretic resistance in heart failure. *Am J Med* 1999;106:90–96.
15. Pitt B, Zannad F, Remme W, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;341:709–717.
16. AIRE Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;342:821.
17. Kober L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K, Videbaek J, Cole DS, Auclert L, Pauly NC. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995;333:1670–1676.
18. Pitt B, Segal R, Martinez F. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of losartan in the elderly study, ELITE). *Lancet* 1997;349:747–752.
19. Cohn J, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, Smith R, Dunkman WB, Loeb H, Wong M, *et al.* A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;325:303–310.
20. Packer M, O'Connor CM, Ghali JK, Pressler ML, Carson PE, Belkin RN, Miller AB, Neuberg GW, Frid D, Wertheimer JH, *et al.* Effect of amlodipine on morbidity and mortality in severe chronic heart failure. *N Engl J Med* 1996;335: 1107–1114.
21. Varon J, Marik P. The diagnosis and management of hypertensive crises. *Chest* 2000;118:214–227.
22. Bristow M. β-adrenergic receptor blockade in chronic heart failure. *Circulation* 2000;101:558–569.
23. Lechat P, Packer M, Chalon S, Cucherat M, Arab T, Boissel J. Clinical effects of β-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. *Circulation* 1998;98:1184–1191.
24. Om A, Hess M. Inotropic therapy of the failing myocardium. *Clin Cardiol* 1992;16:5–14.
25. Ewy G. Inotropic infusions for chronic congestive heart failure. *J Am Coll Cardiol* 1999;33:572–575.
26. Givertz M, Hare J, Loh E, Gauthier D, Colucci W. Effect of bolus milrinone on hemodynamic variables and pulmonary vascular resistance in patients with severe left ventricular dysfunction: a rapid test for reversibility of pulmonary hypertension. *J Am Coll Cardiol* 1996;28: 1775–1780.
27. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;336: 525–533.
28. Abraham W, Oren R, Crisman T, Robertson A, Shakur S. Effects of an oral, non peptide, selective V2 receptor vasopressin antagonist in patients with chronic heart failure. *J Am Coll Cardiol* 1997;29(Suppl. A):169A.
29. Packer M, Caspi A, Charlon V, Cohen-Solal A, Kiowski W. Multicenter, double-blind, placebo-controlled study of long-term endothelin blockade with bosentan in chronic heart failure: results of the REACH-1 trial. *Circulation* 1998;98(Suppl):I–3.
30. Mills RM, LeJemtel TH, Horton DP, Liang C, Lang R, Silver MA, Lui C, Chatterjee K. Sustained hemodynamic effects of an infusion of nesiritide (human B-type natriuretic peptide) in heart failure: a randomized, double-blind, placebo-controlled clinical trial. Natrecor Study Group. *J Am Coll Cardiol* 1999;34:155–162.
31. Singh SN, Fletcher RD, Fisher SG, Singh BN, Lewis HD, Deedwania PC, Massie BM, Colling C, Lazzeri D. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmias. *N Engl J Med* 1995;333:77–82.
32. Pang D, Keenan S, Cook D, Sibbald W. The effect of positive pressure airway support on mortality and the need for intubation in cardiogenic pulmonary edema: a systematic review. *Chest* 1998;114:1185–1192.
33. Mehta S, Jay GG, Woolard RH, Hipona RA, Connolly EM, Cimini DM, Drinkwine JH, Hill NS. Randomized, prospective trial of bilevel versus continuous positive airway pressure in acute pulmonary edema. *Crit Care Med* 1997;25:620–628.
34. Goldstein D, Mehmet C, Rose E. Implantable left ventricular assist devices. *N Engl J Med* 1998;339:1522–1533.
35. Costanzo MR, Augustine S, Bourge R, Bristow M, O'Connell JB, Driscoll D, Rose E. Selection and treatment of candidates for heart transplantation. A statement for health professionals from the Committee on Heart Failure and Cardiac Transplantation of the Council on Clinical Cardiology, American Heart Association. *Circulation* 1995;92:3593–3612.
36. Koniaris L, Goldhaber S. Anticoagulation in dilated cardiomyopathy. *J Am Coll Cardiol* 1998;31:745–748.