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# A CRITICAL ASSESSMENT OF ENDPOINTS OF SHOCK RESUSCITATION

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In recording observations made while caring for a trauma victim in the late nineteenth century, Warren[78] characterized what we now term shock as a *momentary pause in the act of death*. Great strides have been made in our understanding of shock since that description. The current concept of shock is a series of sequellae of tissue perfusion that is inadequate to maintain normal metabolic and nutritional functions.[50] Blalock's work,[9] which established an etiologic classification of shock, was the major contribution to the field of shock research before 1945. Although his original classification has been expanded and modified (Table 1), this paradigm persists as a valuable starting point for understanding the fundamental concepts of shock. Many of the primary descriptive features of the shock states remain clinical in nature—a series of bedside patient observations, vital signs, urine output, and so forth. This certainly makes sense in view of the fact that the pioneers of clinical shock research had little in the way of more invasive monitoring systems and were reliant on developing their insights based on little more than physical examination.

From this perspective, it stands to reason that the success or failure of a given therapeutic measure developed to resuscitate a patient from shock has historically been based on whether it induced a "normalization" of overtly abnormal clinical variables. One need look no further than the World Wars to confirm the clinical success of transfusion and fluid resuscitation in soldiers who would have otherwise succumbed to hemorrhagic shock before surgical control of their bleeding sites. Despite continued improvements in resuscitative prehospital care, transfusion and fluid therapy, and surgical approaches, resuscitation

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Table 1.

| Diagnostic Information | Hypovolemic | Cardiogenic | Neurogenic | Septic (Hyperdynamic) State |
|---|---|---|---|---|
| Signs and symptoms | Pallor; skin clammy, cold; tachycardia; oliguria; hypotension; increased peripheral resistance | Skin clammy, cold; tachy- and brady-arrhythmias; oliguria; hypotension; increased peripheral resistance | Skin warm, normal/low heart rate, normal/low urine output, hypotension, decreased peripheral resistance | Rigors, fever, skin warm, tachycardia, oliguria, hypotension, decreased peripheral resistance |
| Laboratory data | Low hematocrit (late) | Cardiac enzymes, ECG | Normal | Neutrophil count, Gram stain, cultures, ↓ AVDO, |

AV = arteriovenous.

directed at normalization of bedside tests in patients presenting with shock from any cause fails. Death or significant morbidity occurs because of secondary organ failure in 12% to 18% of patients initially presenting with severe shock.[76] Meanwhile, basic laboratory research efforts have confirmed a 20% mortality rate, over the long term, in animals successfully resuscitated using fluid volumes based on direct measurements of intravascular and extravascular fluid deficits.[64] Other studies have provided key insights as to the pathophysiology of shock states, yielding concepts such as tissue acidosis, "irreversible" shock, and tissue oxygen debt—none of which can be quantified using traditional clinical observations.[67] In addition, tremendous advances in invasive and noninvasive monitoring systems design allow clinicians to recruit far more sensitive and specific organ and cellular data to assist in treating established shock.[72] Given the clear record of successful treatment of most patients in shock using nothing more than clinically evident outcomes, however, whether one need progress beyond the use of bedside tests to resuscitate patients in shock, whatever the cause, remains controversial. Because any adjunctive assessment or intervention chosen to supplement bedside testing and conventional management must lead to improved outcomes and be usable and efficient in the hectic environment of the care of shock patients, each should be evaluated and chosen carefully.

## CLINICAL SIGNS OF SHOCK

Clinical recognition of shock in its preterminal stages—severe hypotension, agonal respirations, a thready pulse, tachy- and bradyarrhythmias—is simple, but the firmly established pathophysiology is difficult to overcome regardless of the means used to gauge the success of resuscitative measures. As a corollary, the management of patients in the early stages of shock has a higher success rate if the clinical index of suspicion is sufficiently focused to recognize the presence of shock before the onset of arterial hypotension. Clinically evident arterial hypotension means that all compensatory mechanisms have been overcome because of the absolute volume of blood lost, rapidity of bleeding, severity

| Septic (Hyperdynamic) State |
|---|
| Rigors, fever, skin warm, tachycardia, oliguria, hypotension, decreased peripheral resistance |
| Neutrophil count, Gram stain, cultures, ↓ $AVDO_2$ |

of tissue trauma, underlying cardiopulmonary disease, or a combination of all of these. Arterial hypotension signals the premorbid state. In this regard, several limitations to the use of vital signs to establish the presence of "early" shock exist. Because hypotension and tachycardia are considered primary clinical features of most shocklike states, magnification of these clinical signs using gravity (e.g., orthostatic changes) seemingly might be useful early indicators of shock states. Unfortunately, data show that almost half of normovolemic patients demonstrate positive orthostatic changes,[46] calling to question the accuracy of this bedside test in the diagnosis of early shock. Moreover, in a series of critically ill patients who presented to an emergency department for evaluation, Shoemaker et al[69] found that the average mean arterial pressure (MAP) initially recorded in survivors was only slightly higher than that of nonsurvivors. Finally, the individual means by which arterial pressures are recorded seem to vary greatly, distorting the interpretation of this variable. Creamer et al[16] demonstrated that the cuff pressures of patients in cardiogenic shock were poorly correlated with those obtained by direct monitoring of MAP using radial artery catheters before and after efforts directed at resuscitating patients.

For a variety of reasons, the use of heart rate (HR) as an indicator of shock possesses limitations similar to those just described for MAP. Although tachycardia typically accompanies early shock states, myriad factors may alter HR independently of the presence of shock. Many medications can have a profound effect on a patient's HR in health and in disease, including digitalis preparations, β-blockers, calcium channel antagonists, phosphodiesterase inhibitors, and caffeine, to name a few. The bradycardic response to cocaine has become an important confounding variable in the interpretation of HR during the management of traumatic (hemorrhagic) shock victims.[11] Finally, age alone may, to an extent, define the cardiovascular response to shock. Banic et al.[4] found that, although the decrease in MAP in response to graded hemorrhagic shock was similar in young and old rats, older animals exhibited a significant decrease in HR with progressive hemorrhage compared with that of their younger counterparts.

Originally described by Allgower and Buri,[2] the shock index (HR/systolic blood pressure) is a measurement developed to overcome the inaccuracy of conventional vital signs in defining shock states. Several investigators have suggested that the shock index bears a reliable inverse relationship to left ventricular stroke work in acute circulatory failure.[58] Rady et al[59] supplied clinical data to suggest that, in acutely ill patients with apparently stable initial vital signs, the presence of an abnormal shock index (> 0.9) was a specific indicator of acute circulatory failure that would later require intensive resuscitative therapy. Unfortunately, patients can present with an abnormal shock index in the presence of normal vital signs. Hence, the lack of sensitivity of the shock index has limited its clinical utility.[59]

As suspect as these traditional bedside tests seem to be in defining shock states, even more controversy exists as to their value when used to guide the process of resuscitating patients in shock. In an early study involving repeated analysis of blood-volume status (using radiolabeled albumin) in hypovolemic shock patients, Shippy et al[63] found that MAP, HR, and urine output (UO) were potentially useful guidelines of volume status only during the initial stages of resuscitation; that is, for patients who present in a state of hypovolemic shock (e.g., hypotension, tachycardia, and low UO), improvement in each of these monitored variables, in concert with immediate volume infusion, remains a reliable indicator of the success of therapy; however, the investigators also provided data to suggest that, if these variables are used as the sole means of

guiding resuscitative efforts beyond this initial phase, many patients thought to be fully resuscitated in terms of a return to normal or near-normal values have a much reduced intravascular volume and are therefore at risk for incurring the morbidity of untreated shock. Fiddian-Green[29] stated that this condition, recognized as compensated shock, would be most difficult to detect based on the aforementioned clinical grounds because on resuscitation from hypotensive shock, MAP is normal or near normal, HR may be normal, UO is restored, and peripheral vasoconstriction is reversed[24]; however, the oxygen debt incurred at the tissue and organ levels has yet to be repaid, leading to continued high morbidity and mortality rates unless more effective monitoring systems are used.

This concern was addressed in several clinical studies, including one in which 58 critically ill surgery patients underwent comprehensive serial monitoring of their routine vital signs and, with a pulmonary artery catheter, cardiac and oxygen transport variables.[65] The authors found that, as expected, MAP and cardiac output (CO) decreased while patients were in shock and increased immediately on resuscitation; however, beyond that initial time period, these variables bore no consistent relationship. Moreover, despite maintenance of normal or near-normal MAPs following resuscitation, numerous episodes of alterations in CO and in oxygen transport variables occurred that would have clearly gone undetected without invasive monitoring. Unfortunately, these investigators did not attempt to correlate these untoward observations (and management thereof) with patient outcome. Later, Bishop et al[7] reported their observations on a series of 90 severely injured patients (33% hospital mortality rate) in whom pulmonary artery catheters were routinely placed early in the course of management. MAPs were rapidly restored in all patients, and the mean values for MAP and heart rate did not significantly differ among survivors and those who died until the onset of terminal decompensation. In contrast, survivors were found to have significantly higher cardiac indices and oxygen transport variables throughout their hospital courses. The investigators hypothesized that, although routine clinical signs may indicate the presence of uncompensated shock, their value as resuscitation endpoints would be of limited value.

These data notwithstanding, some investigators have suggested that the shock index (ratio of HR to systolic arterial pressure) provides a means of using readily available bedside tests to gauge clinicians' resuscitative efforts. In clinical and experimental studies, Rady[57] has demonstrated that the shock index correlates well with left ventricular stroke work during resuscitation from hypovolemic (not septic) shock, although it bore no relationship to any measurement of oxygen transport. Hence, although the presence of a persistently abnormal shock index in a patient who has been resuscitated to normal vital signs may suggest the need for more invasive monitoring systems, this variable possesses little value in the long-term management of shock patients.[57]

That resuscitation guided by bedside tests might result in a more adverse outcome than that driven by cardiac function and oxygen transport variables was suggested by Shoemaker et al[66] in a clinical study of critically ill surgical patients. In a prospective, semirandomized fashion, the perioperative resuscitative management of patients of similar demographics and baseline vital signs was guided by the use of one of three protocols: (1) traditional clinical bedside tests in addition to data obtained through a central venous catheter with the goal of normalizing these variables; (2) cardiac and oxygen transport data obtained from a pulmonary artery catheter with the goal of achieving and maintaining normal values for each; and (3) similar data gained from a pulmonary artery catheter, with the goal of reaching supranormal values for oxygen transport and consumption. In terms of morbidity and mortality, the outcomes

of groups 1 and 2 were identical, but both were significantly worse than the group resuscitated to supernormal cardiac and oxygen transport values. From these observations, the investigators concluded that, although clinical bedside tests are valuable indicators of acute shock states and of shock in its terminal stages, they are inadequate variables for monitoring the success or failure of the management of shock patients within the often more critical time interval between these two stages. These conclusions were confirmed in a prospective, randomized trial of 125 severely injured patients conducted by Bishop et al.[6] Morbidity and mortality rates of patients whose management was directed toward normalization of vital signs, UO, and central venous pressure were significantly higher than those whose resuscitation was guided by maximizing their cardiac and oxygen transport variables.

From all of the aforementioned data, the use of traditional bedside clinical tests in the management of shock patients seemingly should be relegated to the affirmation of shock in its uncompensated state. Also, because a more rapid reversal of oxygen debt may result in an improvement in patient outcome, resuscitative efforts should not be delayed until more invasive monitoring systems are in place and may, therefore, best proceed under the direction of basic vital signs after the shock state is properly classified. Beyond these parameters, however, the use of bedside tests often fails to adequately address those intricacies of shock states, compensated shock, uneven distribution of oxygen and nutrients to tissues, and reperfusion injury, and leads to high morbidity and mortality rates.

## LABORATORY STUDIES OF SHOCK

The role of the clinical laboratory in assisting clinicians managing patients in shock is unclear. With the exception of the tests listed in Table 1, the accrual of baseline laboratory data is not helpful in the specific diagnosis or management of patients in shock. Perhaps, at best, they may function as confirmatory data to the overall impression. For example, the hematocrit is an extremely unreliable test. The hematocrit is normal during the early stages of profound shock, even in the presence of massive hemorrhage. Alternatively, because of the diuretic effect of alcohol, an elevated hematocrit may be observed in acute alcohol users who are the victims of blunt trauma. Sequential hematocrit levels may be of assistance, although the interpretation of these results must take into account the presence of ongoing bleeding and the volume and type (e.g., blood versus crystalloid) of resuscitation fluid being used. Finally, the absolute neutrophil count may be elevated, normal, or low on initial evaluation of patients in septic shock, making this test neither sensitive nor specific.

Because *shock* is defined as inadequate perfusion to meet tissue metabolic demand, a laboratory test that reflects cellular metabolism is of major value. One consequence of shock states is anaerobic metabolism, which results in the production of lactic acid, which, in turn, may accumulate in the serum when clearance mechanisms have been overcome. Lactate can be directly measured in serum and pH can be assessed from arterial blood samples. Base excess (deficit) may be calculated, and this value will reflect the extent to which body buffers have been exhausted.

Several reports have documented that normalization of serially measured levels of arterial lactate, pH, and base deficit in shock patients each provide valid targets for resuscitative efforts and that failure to reach these targets correlates with morbidity and mortality.[1, 19, 77] Davis et al[29] provided data to

suggest that the rapidity of normalization of base deficit decreases morbidity and mortality rates. Clearly, such data must be carefully interpreted because many, if not most, patients in shock are at least partially compensated and have arterial pH, base deficit, and lactate levels that are within the normal range. Also, some patients have preexisting conditions (e.g., diabetes mellitus, chronic pulmonary disease, or liver disease) that can alter any or all of these variables. Available data suggest that the presence of metabolic acidosis, elevated lactate, and significant base deficit are markers of a poor prognosis; in contrast, the ability to correct these abnormalities portends an improved outcome; however, specific treatment (e.g., infusion of sodium bicarbonate) is not routinely used because it does little to positively affect morbidity and survival. Clearly, the treatment of shock is best directed toward reversal of the conditions that have caused those laboratory abnormalities.

## THE SWAN-GANZ CATHETER IN THE DETECTION AND TREATMENT OF SHOCK

Over the past 2 or 3 decades, much forward progress has been made in the application of technology to the hemodynamic management of critically ill patients. We have gone from the simple taking of the pulse and blood pressure to using several invasive and noninvasive techniques to assess the adequacy of oxygen delivery ($Do_2$) and to determine how to correct deficiencies. This section reviews the application of commonly used and new technologies to the problem of assessment of hemodynamic status and treatment of shock.

The first step in managing shock, defined as the inadequate delivery of nutrients to the cells of the body, requires its recognition. The ability to use invasive monitoring has enhanced the ability to determine the presence of shock. Because oxygen is the only nutrient that cells cannot store in any appreciable quantity, shock is also equivalent to inadequate $Do_2$. Many clinical and laboratory indicators of shock exist, but, unfortunately, none is specific. It is helpful, therefore, to consider whether other indicators of shock may be assessed using information from invasive monitoring devices.

The Swan-Ganz catheter allows for the direct measurement or calculation of several parameters that may be helpful in detecting shock, including thermodilution CO, mixed venous oxygen tension ($P\bar{v}o_2$) or saturation ($Svo_2$), arteriovenous oxygen content difference ($AVDO_2$), and oxygen-extraction ratio. $Do_2$ and oxygen consumption ($\dot{V}o_2$) are also possible to calculate.

Thermodilution CO is determined by using the Fick principle, in which a known quantity and concentration of a detectable marker travels a known distance, at which point its concentration is determined. From this information, the quantity of blood passing the reference point may be calculated, which in this case is the CO. In the case of thermodilution CO, temperature is the marker and is given as a bolus of saline through the proximal central venous port of the Swan-Ganz catheter. It travels to the Swan-Ganz's thermistor (≈ 30 cm), at which point the change in blood temperature is detected. In general, the greater the difference in temperature between the saline bolus and the blood, the more accurate the CO determination. Swan-Ganz catheters with continuous cardiac output (CCO) have been shown to function with accuracy similar to standard Swan-Ganz catheters in determining the CO. Their function is also based on the Fick principle, but instead of giving a bolus of cold saline, the CCO Swan-Ganz catheters have a copper coil proximal to the thermistor that heats the blood passing by it a few hundredths of a degree Celsius. The heated blood travels a

known distance to the thermistor, where the change in temperature is measured. The change in temperature at the thermistor allows for the calculation of CO in the same way as it is calculated with bolus CO. This technique does not really result in CCO, but the process is repeated so frequently that it is, for all practical purposes, continuous. Comparison with bolus thermodilution CO is useful to make certain of the validity of the data obtained.

Cardiac output is most useful in determining the presence of shock in patients with shock caused by primary cardiac disease. CO measurements below the normal range are likely to be associated with shock; however, in patients who have shock related to sepsis syndrome or severe trauma, the CO is almost always elevated if a patient has been adequately volume resuscitated. Unfortunately, it is impossible to make a determination as to a sufficiently high CO in these patients, so CO is a poor indicator of shock in the patients who most commonly populate a surgical ICU.

Mixed venous blood may be drawn from the pulmonary artery port of the Swan-Ganz catheter and a blood gas determination will yield the $P\bar{v}O_2$ and saturation ($Sv_{O_2}$) of the mixed venous blood. Mixed venous blood represents the venous effluent of *all* of the body's organs and tissues. Therefore, to obtain mixed venous blood, one must draw it after the venous return of the heart (coronary sinus) but before the blood enters the pulmonary capillaries for reoxygenation. The pulmonary artery port of the Swan-Ganz catheter is the most convenient site.

A decreased $P\bar{v}O_2$ or $Sv_{O_2}$ may indicate the presence of shock because both imply that the content of oxygen in the mixed venous blood is lower than normal, indicating that insufficient oxygen is being delivered (the definition of shock) to the peripheral tissues. Treatment is directed at increasing $D_{O_2}$; however, in several settings, these parameters may be "artificially" elevated and, therefore, a normal or even elevated $P\bar{v}O_2$ or $Sv_{O_2}$ may not rule out shock. Patients with cirrhosis and sepsis syndrome fall into this category. In the case of cirrhosis, shunting of blood seems to occur around the capillary beds in the liver and other tissues so that the oxygen carried in this blood is unavailable for metabolism, thereby leaving a higher venous oxygen content than would otherwise be present. Similarly, in patients with sepsis, investigators believe that blood may be shunted around capillary beds as in cirrhosis or that a cellular disorder of oxygen utilization may be present. In either case, the effect would be to artificially elevate the $P\bar{v}O_2$ and $Sv_{O_2}$, in which case neither laboratory test would truly reflect the adequacy of tissue perfusion.

Many parameters can be calculated from data gathered from the Swan-Ganz catheter and other sources that may be used to assess for the presence or absence of shock. Probably the ones used most commonly are the $AVDO_2$ and the oxygen-extraction ratio. The former is the difference between the oxygen content of arterial and mixed venous blood. If it is increased, it is indicative of shock, but the limitations and problems with $P\bar{v}O_2$ and $Sv_{O_2}$ apply to $AVDO_2$ also. The same conditions that cause artificially elevated $P\bar{v}O_2$ and $Sv_{O_2}$ artificially elevate the mixed venous oxygen content and, therefore, artificially decrease the $AVDO_2$, giving the impression that perfusion is adequate when it may not really be.

Under normal circumstances, global oxygen extraction is less than 25% of the oxygen delivered to tissue by arterial blood (oxygen-extraction ratio $< 25\%$). Elevated oxygen-extraction ratios are associated with inadequate oxygen delivery and shock; however, the same factors that act to modify $P\bar{v}O_2$, $Sv_{O_2}$, and $AVDO_2$ may act on the oxygen-extraction ratio, so this ratio is probably no more useful than any of the other variables that have been discussed.

Over the past decade, Shoemaker has helped popularize the concept of

flow-dependent $VO_2$ and has suggested that adequate resuscitation from shock requires that the patient's hemodynamic status must be pushed to the state of flow-independent $VO_2$ (Fig. 1). It is difficult to construct a $DO_2$–$VO_2$ curve for individual patients (or populations of patients). The reported data suggest that most patients reach the state of flow-independent $VO_2$ with a cardiac index of 4.5 L/min/m² or more, a DO index of 750 mL/min/m² or more, and a $VO_2$ index of 180 mL/min/m² or more. These endpoints of resuscitation from shock are controversial. Shoemaker et al[6, 68, 73] published several studies that show that groups of critically ill patients randomized to these high hemodynamic goals have improved outcome compared with patients treated in a "standard" manner. Boyd et al[18] also demonstrated that, in an elderly patient population, maintaining patients' hemodynamic status above these limits with dopexamine was associated with improved outcome. Most other randomized, prospective studies of this subject by other investigators have failed to demonstrate a survival advantage to this "supranormal" approach, although the studies have not been designed exactly as those reported by Shoemaker et al. Another concern pertaining to studies of the relationship between $DO_2$ and $VO_2$ relates to the concept of mathematic coupling. *Mathematic coupling* is a term used to describe the apparent, but false, relationship between two parameters (in this case, $DO_2$ and $VO_2$) that share common variables. Phang et al[34] studied mathematic coupling in a cohort of patients with acute respiratory distress syndrome. They found that the relationship between the calculated (Fick) $VO_2$ and $DO_2$ was much different than the relationship between $VO_2$ obtained by indirect calorimetry and $DO_2$. Hanique et al[34] also found the same to be true in patients with acute respiratory distress syndrome, sepsis syndrome, and fulminant hepatic failure. The authors' experience indicates that, in patients with good cardiovascular reserve (e.g., young trauma patients who are resuscitated from shock), correction of the obvious signs of shock (e.g., oliguria, tachycardia, and metabolic acidosis) commonly is accompanied by the achievement of the hemodynamic goals suggested by Shoemaker.

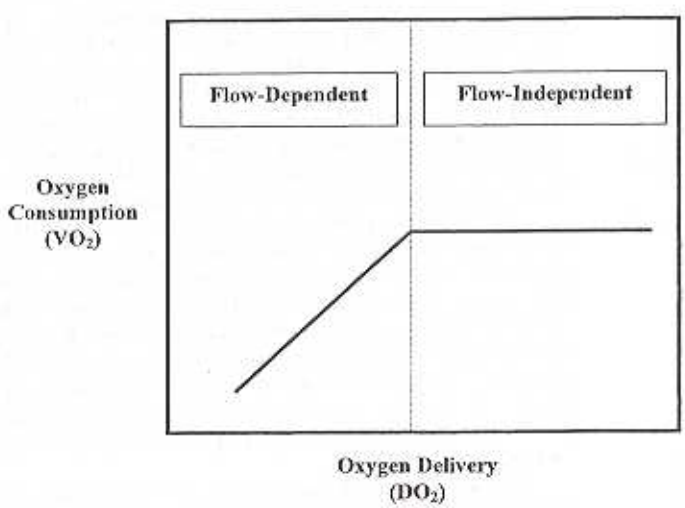


**Figure 1.** Theoretic relationship between oxygen delivery and consumption.

## ASSESSMENT OF TISSUE PERFUSION AND OXYGENATION

All of the parameters discussed thus far suffer from the fact that, singly or as a group, they represent global, whole-organism assessments of the adequacy of tissue perfusion. It is extremely difficult to prove that correcting abnormalities of any one or any group of these is associated with any improvement in outcome. Attempts have been made to assess the adequacy of perfusion of regional vascular beds. The two vascular beds most studied have been the mesenteric circulation and the skin or subcutaneous (SC) tissue. The concept underlying using these two regional vascular beds to assess adequacy of resuscitation is that blood flow is selectively shunted away from the splanchnic and SC circulations early in shock. This fact leads to the hypothesis that restoration of perfusion to these two vascular beds should indicate restoration of blood flow to all the other vascular beds. A host of experimental studies have shown that restoration or maintenance of blood flow to such vascular beds as the kidneys, brain, and heart does not necessarily indicate that optimum blood flow to all organ systems and tissues has been achieved.[13, 17, 25, 26] On the other hand, restoration of flow to intestines and skin usually is accompanied by restoration of flow to the other vital regional circulations.[15, 23, 28] Tissue-specific measurements of perfusion have the potential to overcome many of the limitations of global indices. Instead of the body's normal physiologic response obscuring the recognition of inadequate delivery of nutrients to the tissues, this response can be exploited to the clinician's advantage.

### Gastric Tonometry

Fiddian-Green et al[27] were probably the first major proponents of tonometry to assess adequacy of perfusion to the gut mucosa. They applied the principle that, in shock, splanchnic blood flow rapidly decreases, and actively metabolizing mucosal cells make the transition to anaerobic metabolism, leading to mucosal acidosis.

Gastric tonometry uses the principle of equilibration of intracellular $P_{CO_2}$ of the mucosal cells of the stomach with saline contained in a Silastic balloon resting within the stomach lumen attached to a modified nasogastric tube. This technique has evolved from initial studies done in 1964 by Bergofsky that proved the feasibility of estimating tissue partial pressure of oxygen ($P_{O_2}$) and $P_{CO_2}$ by its equilibration with saline within hollow viscera.[5] By means of the Henderson-Hasselbalch equation:

$$pH = 6.1 + \log [HCO_3^- / (0.03 \times P_{CO_2})]$$

the intramucosal pH can be determined using the measured $P_{CO_2}$, after correction for equilibration when the bicarbonate concentration is known. For purposes of the calculation, the mucosal bicarbonate concentration is assumed to be equal to the arterial bicarbonate concentration.

The splanchnic circulation is one of the first regional vascular beds to experience decreased blood flow in shock states. This allows the intramucosal pH ($pH_i$) to be used as an early assessment of oxygen utilization by the mucosal cells. Under resting conditions, the delivery of oxygen to the splanchnic bed is sufficient to meet the metabolic demands of the tissue, which is reflected by a normal tissue $pH_i$; however, when perfusion decreases and the delivered substrates can no longer support aerobic metabolism, $pH_i$ decreases, reflecting the increased production of lactic acid and potentially the decreased washout of

carbon dioxide.[31] By this mechanism, the gastrointestinal tract may act as the body's canary, assisting in the early determination of the adequacy of tissue oxygenation and perfusion.[18]

The assessment of mucosal acidosis has been used in numerous clinical situations in addition to the evaluation of resuscitation status. Some of these include identification of sigmoid ischemia following aortic surgery, prediction of ICU course, prediction of successful weaning from mechanical ventilation, and identification of the presence of complications following surgery or trauma.[8, 23, 40, 50, 51, 62] These studies have helped to delineate a lower limit $pH_i$ value of approximately 7.3. When the mucosa remains consistently more acidic, a worse outcome may be predicted.

In prospective clinical studies in which gastric intramucosal pH has been examined as an index of tissue oxygenation, all found gastric tonometry useful as a supplement to other forms of assessment. Roumen et al[49] followed gastric $pH_i$ values in 15 multiple-trauma patients who required surgery because of one or more injuries. All seven patients who maintained normal $pH_i$ values recovered without complications, whereas of eight patients who demonstrated a low $pH_i$, three developed major complications, and two died. The investigators were unable to demonstrate significant correlation between $pH_i$ values and lactate levels, base deficit, severity of shock, or Acute Physiology and Chronic Health Evaluation (APACHE) II scores. Likewise, Chang et al[13] found a poor correlation between $pH_i$ and systemic hemodynamic and oxygen transport variables, including base deficit, lactic acid level, $Svo_2$, $Do_2$, and $Vo_2$ in 20 critically ill trauma patients whom they followed up prospectively. Organ dysfunction and mortality also were predicted by a low $pH_i$ that failed to correct within the first 24 hours. A report by Chang and Meredith[14] confirmed the increased incidence of organ failure and death in patients with persistently low $pH_i$.

Only two clinical studies report the use of gastric tonometry to guide resuscitation. One examined its use in a heterogeneous group of ICU patients from several institutions.[32] The study was able to show an improved outcome with therapy to increase $Do_2$ or decrease oxygen demand in patients with a normal $pH_i$ on admission to the ICU but who subsequently developed mucosal acidosis. No benefit was demonstrated for patients with a low $pH_i$ on admission to the ICU who had their resuscitation guided by level of mucosal acidosis. The investigators believed that this lack of improvement may have been caused by irreversible deleterious effects caused by longstanding hemodynamic deficits. Ivatury et al[30] compared global oxygen transport indices with $pH_i$ as endpoints of resuscitation in 57 trauma patients. Attempts were made to achieve supranormal levels of $Do_2$ consumption, or both, or a $pH_i$ of 7.3 or more depending into which group patients were randomized. Although the prevalence of multiorgan failure and death—the primary outcome variables--did not differ among the groups, a subset analysis of the $pH_i$ value at 24 hours and the time to optimization of $pH_i$ show potential as markers of inadequate response to resuscitation. Significantly more time was required to optimize $pH_i$ in the group of nonsurvivors, with this optimization time being found predictive of mortality on multiple regression. Global oxygen transport indices had a low correlation with $pH_i$, indicating that gut mucosal acidosis may not always be reversed by achieving supranormal levels of $Do_2$ and $Vo_2$. These studies have attempted to improve intramucosal pH by manipulating systemic hemodynamics. No attempt was made to gear the therapy toward improving the splanchnic circulation in particular. The results of an interesting approach designed to specifically alter gut perfusion were recently presented in an abstract by Kirton et al.[44] They attempted pharmacologic splanchnic dilatation and added systemic and luminal agents

thought to minimize gut reperfusion injury. They were able to demonstrate a reduced incidence of multiorgan failure in the small patient population studied. It will be interesting to see what elements of their therapy account for the improved outcome as new studies are completed.

Although clinical evidence supporting gastric tonometry as a monitoring tool continues to grow, it is not without its limitations. Unfortunately, the tonometer cannot distinguish between intramucosal carbon dioxide and that residing within the lumen of the stomach. Therefore, carbon dioxide that enters the stomach through a vented nasogastric tube, or is produced in the stomach when gastric acid is neutralized by duodenal or exogenous bicarbonate, increases the measured $P_{CO_2}$ value and gives a falsely low $pH_i$ when calculated from the Henderson-Hasselbalch equation. Although some have shown that the use of $H_2$ blockers eliminates this problem, others have not been able to confirm this finding.[36, 49, 52]

A second area of debate regards the effects of the assumption that the mucosal bicarbonate level is equal to the easily measured arterial value. This calls into question the calculated $pH_i$ during low flow states, when arterial bicarbonate is thought to overestimate the depleted stores found in the mucosa, thus underestimating mucosal acidity.[3] In an attempt to minimize this error and also the effects of systemic acid–base derangements, some clinicians recommend the use of the pH or $P_{CO_2}$ gradient or gap, which represents the difference between the arterial and tonometric values.[51] Data are inadequate to support a recommendation for its use. In the recent prospective trial by Ivatury et al,[40] these gaps did not significantly enhance data gained from direct $pH_i$ determinations, even in some patients receiving permissive hypercapnia for acute respiratory distress syndrome with significantly elevated levels of $Paco_2$. Thus, reported data support $pH_i$ as an accurate reflection of mucosal acidosis that is not significantly affected by systemic acid–base balance.

Other limitations of gastric tonometry, such as the need for intermittent measurements and for special tonometry catheters, are being addressed. One device, a capnometric recirculating gas tonometry system, replaces saline with a circulating gas in a closed circuit that allows for continuous $P_{CO_2}$ measurements.[33] The system detects changes in intramucosal $P_{CO_2}$ in as little as 5 minutes instead of after the prolonged equilibration period needed with the saline tonometer. A second method uses "balloonless" air tonometry that can use a conventional nasogastric tube to obtain samples for measurement.[61] This technique has also been found to accurately estimate mucosal $P_{CO_2}$. As tonometers become easier to operate and their limitations better characterized and overcome, they should enjoy a more widespread use in clinical practice.

## Tissue Oximetry

A second tissue-specific method of assessing the adequacy of resuscitation is tissue oximetry. Measurements of tissue oxygen tensions can be obtained from electrodes or fluorescent quenching optodes placed on or through the skin into particular tissue beds, such as SC tissue or skeletal muscle. These devices, commonly used in conjunction with saline-filled Silastic tonometers, continuously monitor the $P_{O_2}$ of the tissues in which they reside. The electrode or optode sits within the implanted tonometer or in the tissue and measures the tissue $P_{O_2}$. The rationale for its use is simple: the basic tenet of resuscitation is to avoid or correct cellular hypoxia. These devices allow for the direct measurement of tissue $P_{O_2}$. Because tissue oxygenation varies among different organs as

a reflection of their perfusion status,[28-30, 41, 43, 48, 55, 56, 80] following these values may be of benefit as a guide to resuscitation.

Tissue oximetry has, to date, found most of its use in the research laboratory, mainly in the investigation of wound healing and resistance to infection.[38, 39, 42, 45] During these investigations, SC oxygen tensions improved when perfusion status of the tissues improved. This led to the evaluation of tissue $P_{O_2}$ as a marker of tissue perfusion. Several laboratory studies support its use as an assessment of tissue oxygenation and perfusion.[28-30, 35, 48, 55, 56] Gosain et al[29] compared global indices to transcutaneous and SC oxygen tensions during graded hemorrhage in dogs. They also examined tissue blood flow at each stage of blood loss using radiolabeled microspheres in an attempt to delineate the tissue-specific blood flow response to hemorrhage. SC $P_{O_2}$ was found to be a relatively sensitive predictor of blood volume loss of up to 40%, with a higher correlation than arterial pressure, CO, or transcutaneous $P_{O_2}$. Blood flow in the SC tissue decreased early and precipitously, unfortunately to a point too low to collect sufficient microspheres for an accurate assessment of blood flow as the hemorrhage volumes increased.

In a study of the relationship between systemic $D_{O_2}$ and tissue oxygen tension in hypovolemic shock, Pianim et al[55] compared SC $P_{O_2}$ to small bowel submucosal $P_{O_2}$ and intramucosal pH and related them to global indices.[55] They found that the degree of gut and SC tissue ischemia paralleled each other. They also found SC tissue oximetry to be better correlated with systemic parameters than was $pH_i$.

Clinical experience with oximetry in the assessment of tissue perfusion is limited. Chang et al[15] reported in 1983 on evidence of tissue hypoxia thought to be related to hypovolemia in postoperative patients. Although evidence of global tissue hypoxia was lacking, 19 of 19 patients with depressed tissue $P_{O_2}$, as measured by an SC silastic catheter containing a Clark electrode, responded positively to a bolus fluid infusion by increasing their tissue $P_{O_2}$. The investigators concluded that hypovolemia was a common cause of tissue hypoxia postoperatively. This link between volume status and SC oxygen tension was also noted in nine patients undergoing hemodialysis.[41] As a technique to assess the adequacy of tissue perfusion, Jonsson et al[43] examined the response of tissue $P_{O_2}$ in postoperative patients to an increase in inspired oxygen concentrations ($FI_{O2}$). They postulated that a lack of response would indicate increased oxygen extraction caused by a perfusion deficit. Of the 12 patients who were thought to demonstrate inadequate tissue perfusion by this criterion, 10 responded to fluid boluses by increasing their tissue $P_{O_2}$. No mention is made, however, about whether any patients thought to be without perfusion deficit were given fluid boluses and how they may have responded.

Two other groups have used a similar "oxygen challenge test" to assess adequacy of perfusion. Hopf et al[22, 37] have used the method to estimate resuscitation status of trauma patients thought to have adequate tissue perfusion by global criteria. As many as 75% were found to fail the oxygen challenge test within the first 48 hours of hospitalization, although they were thought to be adequately resuscitated by standard criteria. In an attempt to use this test to guide resuscitation, Waxman et al[79] examined 29 trauma patients within 48 hours of their injuries, 15 of whom were still in the emergency department, for evidence of inadequate resuscitation. The investigators placed their probes directly into skeletal muscle and did not use tonometers. The premise of the study is supported by the data showing that those who initially had increased tissue $P_{O_2}$ in response to higher $FI_{O_2}$, indicating adequate perfusion, had lower Injury Severity Scores and lengths of stay compared with the nonresponders. No firm

conclusions can be drawn regarding this method as an assessment of resuscitation, however, because of the absence of a standard control group in its design and lack of clear characterization of the patients and their injuries.

Limitations of tissue oximetry are numerous. They include reliance of tissue $P_{O_2}$ on $D_{O_2}$ and consumption; characteristics of the tissue site; technical aspects of the devices; the influences of conditions such as pain and cold on tissue perfusion, type of shock, and the lack of a clearly described "normal range" of values by which to interpret the findings. The method of tissue $P_{O_2}$ monitoring that has found the most favor involves placing a silastic tonometer into the SC tissue with the insertion of an optode or an electrode into the tonometer. Although this method is invasive, it allows for ease of recalibration and provides an averaging of the $P_{O_2}$ from the tissue surrounding the tonometer. Also, more research is needed to design the optimal provocative test that can accurately define hypoperfusion in a sensitive and specific fashion. Nonetheless, tissue oximetry holds merit and promises to find use as a tissue-specific assessment of the adequacy of resuscitation.

Clinicians are painfully aware of how difficult it is to accurately assess the perfusion status of critically ill patients by using global indices. This makes the theoretic benefits of tissue-specific guides to resuscitation, such as gastric tonometry and tissue oximetry, in contrast to UO, blood pressure, CO, or oxygen-extraction ratio, readily apparent. Techniques to assess tissue perfusion will continue to be refined and eventually play a major role in the recognition and treatment of shock.

## CORRECTION OF SHOCK-INDUCED HEMODYNAMIC ABNORMALITIES

After shock is detected, whether it be by gross assessments, such as hypotension or oliguria, or by tissue-specific measures, such as gastric tonometry or tissue $P_{O_2}$, the next step is its correction. This is accomplished by following an algorithm that accounts for the variables that make up the following mathematic equation for $D_{O_2}$ that includes $Pa_{O_2}$, $Sa_{O_2}$, HR (and heart rhythm), hemoglobin concentration, and stroke volume:

$$D_{O_2} = \text{cardiac output} \times Ca_{O_2} \times 10$$

$$D_{O_2} = (HR \times SV) \times [(1.34 \times [Hb] \times Sa_{O_2}) + (Pa_{O_2} \times 0.0031)] \times 10$$

Stroke volume is controlled by preload, afterload, and contractility.

### $Pa_{O_2}$ and $Sa_{O_2}$

Although it is important to treat hypoxia, one must realize that little in the way of improvement in $D_{O_2}$ will occur. Arterial oxygen tension contributes little to $D_{O_2}$ because, at normal atmospheric pressure, little oxygen is dissolved in plasma. Even in patients who are very hypoxic, it is rare to have $Sa_{O_2}$ levels of less than 85%. For example, increasing $Sa_{O_2}$ from 85% to 95% only increases $D_{O_2}$ by 10% if the other variables of the $D_{O_2}$ equation remain unchanged.

### Heart Rate and Rhythm

Sometimes modifying HR or heart rhythm is associated with significant improvements in CO and $D_{O_2}$. Patients in nonsinus rhythms (e.g., atrial fibrilla-

tion or flutter or nodal rhythms) may lose 10% to 25% of their CO based only on rhythm. HRs of more than 150 or less than 50 may compromise CO by not allowing time for adequate filling of the left ventricle or by being so slow that, even at maximal stroke volumes, the heart cannot generate adequate CO. Under these circumstances, correction of abnormal HRs and rhythms may significantly improve CO and $Do_2$.

### Hemoglobin Concentration

Patients who are extremely anemic may receive significant boosts in $Do_2$ from transfusion by increasing oxygen carrying capacity. For example, if a patient with a hemoglobin concentration of 8 is transfused to 12, $Do_2$ increases by 50%, assuming that other variables remain unchanged.

### Stroke Volume

Although optimization of each of the earlier-mentioned variables may lead to the correction of shock states depending on the circumstances and type of shock, the one that requires optimization most frequently is stroke volume. Stroke volume is controlled by preload, afterload, and contractility. If attempts to increase stroke volume are made, it is important to optimize preload first because if afterload is reduced in the face of inadequate preload, the patient becomes hypotensive and perfusion is further compromised. Increasing contractility in the face of inadequate preload results in only minimal, if any, increase in stroke volume.

Preload is the amount of stretch on muscle fibers at the time of contraction and is a property of skeletal and myocardial muscle. In general, the greater the stretch on the muscle, up to a point, the greater the contraction. If the muscle is overstretched, contractility decreases. This is the basis for the Frank-Starling curve. In the case of the left ventricle, because blood is not compressible, preload is defined by the left ventricular end-diastolic volume (LVEDV). Unfortunately, no bedside method that measures LVEDV is available. Even echocardiography gives only an estimate based on the echocardiographer's educated but subjective assessment. The authors' attempts to assess preload have included clinical indicators, such as jugular venous distension; use of various pressure determinations, such as central venous pressure (CVP) or pulmonary capillary wedge pressure (PCWP); right ventricular end-diastolic volume index (RVEDVI), transthoracic or transesophageal echocardiography, and esophageal Doppler sonography.

Studies designed to assess clinicians' ability to determine preload on clinical acumen alone have all demonstrated that the correlation between the clinical assessment and assessment using invasive monitoring is poor. Clinicians can expect their estimates of preload to jibe with the PCWP in only approximately 50% of cases and that the use of invasive monitoring to assess preload mandates a significant change in therapy in approximately 50% of cases.[12, 74]

Because of the problems in using clinical acumen to determine preload, the authors have relied more heavily on invasive monitoring for that assessment. The two most commonly used parameters are CVP and PCWP. CVP and PCWP correlate well at low pressures, but as CVP increases to more than 8, its correlation with PCWP becomes increasingly tenuous so as to be totally unreliable in most instances. In patients with relatively normal hearts, PCWP correlates rela-

tively well with cardiac index; however, the relationship between PCWP and LVEDV, which is what a physician is attempting to assess in using PCWP to estimate preload, is affected by changes in left ventricular compliance. Any change in ventricular compliance disrupts the linear relationship between PCWP and LVEDV and, therefore, interferes with the ability to use PCWP as an assessment of preload. Left ventricular compliance decreases significantly in many critically ill patients, including those with myocardial infarction and sepsis; therefore, in the sickest patients, PCWP is the least helpful and it is impossible to predict, a priori, the optimal PCWP for any patient. So, especially in septic patients, a physician is left to give an empiric fluid challenge almost regardless of what the PCWP is and then assess its effect on CO. If CO increases after such a challenge, the authors conclude that preload is inadequate and continue to give fluid until the indicators of shock have been reversed or the patient stops responding to fluid.

The volumetric Swan-Ganz, which calculates the RVEDVI, was developed with the hope that RDEDV would better reflect LVEDV (preload) than does PCWP. Correlation coefficients of PCWP and cardiac index are typically between 0.01 and 0.30, which is close to no relationship whatsoever. Most studies show that the $r$ value for RVEDVI and cardiac index (0.50–0.60) is much better, and many intensivists therefore have concluded that volumetric Swan-Ganz catheters should be used more frequently to assess preload; however, one must recognize that statistics apply to populations of patients and that significant problems occur when trying to apply RVEDVI to individual patients in an attempt to assess preload. For example, Durham et al[23] found that there was much better correlation between RVEDVI and cardiac index ($r = 0.60$) than between PCWP and cardiac index ($r = 0.01$); however, of the 38 critically ill patients investigated, no correlation was found between RVEDVI and cardiac index in 11 patients therefore rendering RVEDVI useless as a predictor of preload in those patients. The RVEDVI that was associated with the highest CI in the other 27 patients was 80 to 160 mL/m$^2$, much too great of a range for the RVEDVI to be used as an endpoint for evaluation of preload in individual patients without constructing a Starling curve for each patient. Also, the correlation between RVEDV by volumetric Swan-Ganz and the RVEDV and LVEDV assessed by echocardiography is poor. A difference in RVEDV and LVEDV of up to 100% has been reported.[47] So, although RVEDVI correlates better with CI than does the PCWP, physicians are left to treat individual patients similarly: administer an empiric fluid challenge and see whether the CO increases.

Transthoracic or transesophageal echocardiography may be used to assess preload by evaluating cardiac chamber size at end-diastole. This technique provides an assessment of myocardial and valvular function and detects whether pericardial fluid is present; however, its disadvantages are numerous. First, it is operator dependent, and assessment of the images may vary significantly among observers. Second, it gives only a single snapshot in time. To assess trends, the test must be repeated. Last, it is extremely expensive compared with the other modalities discussed.

The newest technique used to assess preload is esophageal Doppler sonography. It is a relatively noninvasive technique in which a Doppler sonography device is placed within the lumen of the esophagus and focused on the descending thoracic aorta. The device measures velocity (V) of blood flow in the aorta on a beat-to-beat basis. Using an assumption as to the aortic diameter (D), flow can be calculated:

$$\text{Flow} = \pi D^2/4 \times \text{Vmean} \times 60$$

Flow per heart beat is equal to stroke volume. CO may be calculated from stroke volume multiplied by HR, and direct measurements of flow time and peak velocity allow one to draw conclusions concerning preload, contractility, and afterload. Excellent correlation seems to exist between thermodilution CO and the calculated CO obtained from the esophageal Doppler, with $r = 0.95$.[75] Limited information is available using this technique in critically ill patients. In 43 mechanically ventilated patients, the esophageal Doppler probe seemed to give accurate information concerning preload whether patients were hypovolemic or hypervolemic.[71] If this new device withstands the scrutiny of clinical studies, it could replace Swan-Ganz catheters in many patients in whom pulmonary artery catheters are now used. It is less expensive than volumetric or CCO Swan-Ganz catheters and is less invasive. In comparison to Swan-Ganz catheters, the only data that esophageal Doppler sonography cannot obtain are mixed venous blood gases and the calculated variables, such as $VO_2$ or $AVDO_2$, that require data from mixed venous blood gases.

When preload has been optimized, if the endpoints in shock resuscitation have not been met, the next step is to assess afterload. Afterload may be assessed by calculating systemic vascular resistance (SVR):

$$\text{SVR} = \frac{(\text{MAP} - \text{CVP}) \times 80}{\text{CO}}$$

If systemic vascular resistance is high, $Do_2$ is increased by pharmacologic (e.g., nitroprusside) or mechanical (e.g., intra-aortic balloon pump) afterload reduction. If SVR is low, an inotropic agent to improve contractility should be added. Vasoconstrictors are virtually never indicated in the treatment of shock, and their use usually represents a failure to be sufficiently aggressive with preload optimization. Even patients with septic shock will rarely stop responding to fluid boluses and require vasoconstrictor drugs to maintain an MAP of more than the organ perfusion pressure ($\cong$ 50–60 mm Hg).

## RECOMMENDATIONS

Because no one test or device can be relied on to identify the presence of shock in all situations, the best "tool" is a well-trained clinician. Because chance favors the prepared mind, vigilance and an understanding of the pitfalls in recognizing the presence of shock are absolute requirements. Although clinical parameters may help to identify the presence of shock initially, they are clearly inadequate to judge the endpoint of resuscitation. Devices such as pulmonary artery catheters and esophageal Doppler sonography can supply objective information regarding the underlying cause of the shock state and its response to treatment but are of limited utility in determining resuscitation endpoints. The normalization of systemic acidosis, seen as elevated serum lactic acid or a base deficit generated by inadequate perfusion, is perhaps the most reliable perfusion marker available. It, too, is limited by its global sampling. The theoretic improved sensitivity of sampling local tissue beds for evidence of malperfusion, as with gastric tonometry or tissue oximetry, remains clinically unproven. Clinical judgment remains of paramount importance for determining when perfusion and oxygenation are sufficient.

## SUMMARY

Modern hemodynamic therapy is not only the recognition and treatment of hypotension but also the avoidance and treatment of shock in its broadest sense. The major issues include the recognition of hypoperfusion of the body as a whole or its individual tissues and organ systems and the determination of the best endpoints for the treatment of shock. Even if all of the commonly used clinical indicators of shock are "normal," shock on a cellular, tissue, or organ basis may still be present. Whether "organ-specific" assessments, such as gastric tonometry or tissue oxygen tension measurement, are the ultimate answer to this problem remains to be seen. The determination of adequate intravascular volume (preload) continues to present major difficulties in the care of critically ill or injured patients. Although PCWP is frequently helpful, it is not a gold standard. A bedside ultrasonic technique, such as esophageal Doppler sonography, may replace the Swan-Ganz catheter technique in many patients.


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