Shock: An Overview

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Shock is one of the most frequently diagnosed, yet poorly understood clinical conditions encountered in the critically ill. The very definition of what constitutes "shock" remains controversial, largely due to its variable presentation and multifactorial etiology. Ongoing investigations have identified the origins and mechanisms of the various shock states to be complex and based within the cellular foundation of normal everyday existence. Despite advances in critical care management, patients who previously would have died from their initial physiologic insult are surviving, only to succumb to the late effects of shock. Although mortality from the shock states remains high, recent advances in hemodynamic monitoring technology have significantly enhanced a clinician's ability to improve patient outcome following the development of shock.

DEFINITION

Although early definitions of shock lack scientific terminology and reveal the inadequate understanding of pathophysiology prevalent at the time, they compensate for it in simplicity and accuracy. John Collins Warren described shock as "a momentary pause in the act of death" while Samuel Gross defined it as "a rude unhinging of the machinery of life." With improved understanding of cellular physiology and function, we now recognize Gross' "machinery of life" to be the delivery and utilization of oxygen at the cellular level. As a result, shock is currently best defined as a multifactorial syndrome resulting in inadequate tissue perfusion and cellular oxygenation affecting multiple organ systems.

The importance of regional blood flow to individual organ systems is the singular concept for recognizing both the obvious and subtler shock states. Perfusion may be decreased either systemically (as in hypotension) or limited to regional maldistribution (as in septic shock, where global perfusion is normal or even elevated). Regardless of etiology or severity, all forms of shock have the commonality of perfusion inadequate to meet metabolic demands at the cellular level. Decreased organ perfusion leads to tissue hypoxia, anaerobic metabolism, activation of an inflammatory cascade, and eventual vital organ dysfunction. The ultimate consequences of such malperfusion vary from patient to patient depending upon the degree and duration of hypoperfusion, the number of organ systems affected, and the presence of prior organ dysfunction. The challenge to the intensivist is identification of the hypoperfused state, quantification of its severity and prognosis, and rapid restoration of cellular perfusion to avoid organ dysfunction and failure. This chapter reviews the current methods for diagnosing, monitoring, and treating the various shock states.

PHYSIOLOGY

Over the past decade, significant progress has been made in elucidating the cellular basis for shock. Whereas hypoperfusion and cellular ischemia were previously thought to be sufficient to cause shock, they are now recognized as being solely the initiating triggers for a complex physiologic cascade. Cellular hypoxia predisposes tissues to "reperfusion injury" leading to local vasoconstriction, thrombosis, regional malperfusion, release of superoxide radicals, and direct cellular damage. Subsequent

activation of neutrophils and release of proinflammatory cytokines such as tumor necrosis factor (TNF), interleukin-1 (IL-1), and platelet activating factor result in cellular injury, organ dysfunction and failure, and frequently death.

Early diagnosis of cellular ischemia with prompt restoration of tissue perfusion and oxygenation is essential to preventing this inflammatory process and improving patient outcome from shock. The underlying etiology may be quite evident, as in the case of upper gastrointestinal hemorrhage, or may be occult, as in the case of intra-abdominal solid viscus injury from blunt trauma. Due to the significant morbidity and mortality associated with delayed shock resuscitation, the intensivist must commonly begin appropriate management before all clinical information or diagnostic studies are available. As a result, the intensivist must possess a solid understanding of the most likely shock states, their clinical presentation, and the necessary therapeutic interventions.

Recognition of shock may occur through basic physical findings and physiologic measurements. Although a normal systemic blood pressure cannot be used to rule out shock, an abnormally low blood pressure may be all that is needed to document hypoperfusion and explain a patient's shock state. The presence of shock is more likely to be occult, however, and to require more indepth investigation and utilization of advanced hemodynamic monitoring techniques. Assessment of regional tissue perfusion by review of end-organ function can help to document the presence of shock before

the late signs of systemic malperfusion are evident with their associated detrimental impact on patient outcome. Readily identifiable clinical changes in three vital organ systems may serve to identify the presence of shock: the brain, the heart, and the kidneys.

Decline in higher cortical function (mentation) may indicate diminished perfusion of the brain. This may be due to either decreased arterial blood pressure, the presence of flow-limiting lesions, or increased intracranial pressure. Although the brain can compensate to a certain degree for decreased perfusion, this ability appears to be lost when mean systemic arterial blood pressure falls below 60 to 70 mmHg (1). For patients used to higher systemic blood pressures or those with flow-limiting carotid lesions, the ability to compensate may be lost at even higher pressures.

Cardiac dysfunction due to shock may be one of the earliest signs of hypoperfusion. The heart plays a central role not only in early detection of hypoperfusion, but also in the perpetuation of shock. Depressed coronary perfusion as a consequence of systemic arterial hypotension or flow-limiting atherosclerotic stenoses leads to worsening cardiac dysfunction and a self-perpetuating progression of global hypoperfusion and pulmonary failure. Secondary cardiac dysrhythmias, a consequence of myocardial hypoxia, may further impair cardiac function and accelerate the process.

Renal compensation for reduced perfusion is well known. Although mild changes in arterial pressure may be tolerated, significant renal

hypoperfusion reduces glomerular filtration rate resulting in decreased hourly urinary output. As such, oliguria in the patient without prior renal insufficiency can be a valuable indirect indicator of shock that mandates close observation of urinary output in patients who are at risk for hypoperfusion.

CLASSIFICATION

Although the definition of shock is complex, clinicians require a conceptual framework for the purposes of communication and research on the topic. Hinshaw and Cox (proposed a classification of shock in 1972 that still holds merit (2). The four categories of shock included were: a) hypovolemic (shock as a consequence of inadequate circulating volume, as may be seen in hemorrhage), b) obstructive (shock caused by extracardiac obstruction of blood flow, as seen in cardiac tamponade), c) cardiogenic (shock caused by primary pump failure, as in decreased myocardial contractility after myocardial infarction), and d) distributive (shock associated with maldistribution of blood flow and volume, as in sepsis). Recently, this historical classification was supplemented with the category of e) endocrine (shock as a result of hormonal pathology, either through underproduction or overproduction), an entity whose importance has recently been increasingly recognized and diagnosed in the critically ill patient. Regardless of the classification into which the patient's shock state is placed, the intensivist must simultaneously resuscitate while searching for an inciting event to control.

Hypovolemic Shock

Hypovolemic shock is often the first consideration in the resuscitation of a patient with evidence of hypoperfusion. It is likely the most common form of shock, and almost all forms of shock include some component of hypovolemia, as a result of decreased preload. Physical findings include general systemic manifestations, such as cold, clammy skin from central nervous system stimulation (leading to sweat gland activation) and peripheral hypoperfusion (shunting blood volume centrally). These physical findings stem from the various compensatory mechanisms associated with the shock state. The sympathetic response includes arterial constriction, which diverts blood from the splanchnic viscera, skin, and skeletal muscle. Other sympathetic responses include venoconstriction to augment venous return to the right atrium and activation of the renin-angiotensin system. The latter results in the release of angiotensin II, which has a dual function as a vasoconstrictor and promoter of sodium and water retention. Vasopressin, released by the posterior pituitary, also acts as a vasoconstrictor and stimulus to sodium retention. A critical difference in the neurohumoral reaction to shock compared to the other reflexes is that their effects are delayed (10-60 minutes) while the cardiovascular responses are almost instantaneous (3).

Attention to objective data such as vital signs and urinary output are of value in categorizing the severity of shock. Hypovolemic shock is stratified into four classes based on the degree of circulating volume loss (TABLE I). It is important to recognize that significant blood volume may be

shed in the absence of any clinical signs. A patient who can compensate well for hypovolemia may display tachycardia as the only objective clinical abnormality even when faced with a circulating blood volume reduction of up to 30%.

Hypovolemic shock may be further subclassified as either hemorrhagic or non-hemorrhagic. Hemorrhagic shock may be visibly apparent (as in external blood loss from traumatic injury, operative bleeding, or gastrointestinal or vaginal bleeding) or occult (as with chronic gastrointestinal hemorrhage or ruptured aortic aneurysms). The intensivist should focus on arresting the hemorrhage with the same or greater fervor as with the resuscitation. Recent emphasis on controlling bleeding rather than simply providing volume replacement therapy is an essential difference in the current approach to hemorrhagic shock (4).

Non-hemorrhagic hypovolemic shock is seen in a number of pathologic states and can have as its cause both absolute loss of total body fluid volume and migration of acellular fluid from the intravascular to the extravascular or interstitial compartment (so-called "third spacing"). Total body fluid volume depletion occurs as a consequence of uncompensated gastrointestinal losses, urinary losses, evaporative losses, or transudation of fluid in response to shock and resuscitation. Gastrointestinal losses include fluids lost because of pathologic conditions such as high output fistulae or protracted vomiting, but also underrecognized losses from nasogastric tube suction. Although low urinary output is often the initial sign of an underperfused state, pathologic states of high urine output (e.g., diabetes insipidus, diabetic ketoacidosis, diuretic administration) may result in non-hemorrhagic hypovolemic shock. In these cases, urinary output may be a poor predictor of global tissue perfusion, as urinary output may remain normal or high despite intravascular hypovolemia. Evaporative losses from fever may reduce

TABLE I: CLASSIFICATION OF SHOCK (based on a 70 kg patient)

	CLASS I	**CLASS II**	**CLASS III**	**CLASS IV**
Blood Loss (mL)	up to 750	750-1500	1500-2000	2000 or more
Blood Loss (%BV)	up to 15%	15-30%	30-40%	40% or more
Pulse Rate	<100	>100	>120	140 or higher
Blood Pressure	Normal	Normal	Decreased	Decreased
Pulse Pressure	Normal/Increased	Decreased	Decreased	Decreased
Capillary Refill	Normal	Decreased	Decreased	Decreased
Respiratory Rate	14-20	20-30	30-40	>35
Urine Output (mL/hr)	30 or more	20-30	5-15	Negligible
CNS-Mental Status	Slightly anxious	Anxious	Anxious - confused	Confused -lethargic
Fluid Replacement	Crystalloid	Crystalloid	Crystalloid + blood	Crystalloid + blood

(Modified from: Committee on Trauma of the American College of Surgeons. Advanced Trauma Life Support for Doctors.

intravascular volume, but iatrogenic causes of evaporation, such as prolonged open body cavity surgery, are a greater cause of significant volume loss. Shock may still exist despite normal or increased total body fluid volume when such volume is not intravascular and capable of participating in end-organ perfusion. Transudation of fluid occurs predictably in severe illnesses such as trauma, pancreatitis, and small bowel obstruction. The absence of such fluid from the functional intravascular space as a result of shock-induced "capillary leak" must be recognized. Such is especially the case in the severely burned patient. Significant fluid sequestration occurs in both the burned and nonburned tissue. This is the result of both microcirculatory failure as well as the effect of inflammatory mediators such as interleukins, leukotrienes, serotonin, kinins and free radicals. It is imperative that the intensivist focus on resuscitation of the patient's intravascular volume as opposed to their total body volume. Failure to do so will uniformly result in underresuscitation, continued end-organ malperfusion, continued shock, and poor patient outcome.

Obstructive Shock

Obstructive forms of shock are those in which the underlying pathology is a mechanical obstruction to normal cardiac output and a subsequent diminution in systemic perfusion. As such, this form of shock could be considered a locally induced hypovolemic state. Cardiac tamponade is a common cause of obstructive shock. The distinction between a pericardial effusion and cardiac tamponade is open to some debate (5,6). The pericardium resists sudden stretching, and in acute tamponade the cardiac

silhouette may appear normal in size. As a result of the noncompliance of the pericardium, a small amount of fluid (usually less than 200 mL) is all that is necessary to produce tamponade. With chronic distention, however, large volumes of pericardial fluid may accumulate with little to no effect on cardiac physiology. The volume of the effusion alone, therefore, does not dictate the clinical course as much as the acuity of its development. Causes of acute pericardial effusion include trauma, ischemic myocardial rupture and aortic dissection.

Clinical signs of tamponade include jugular venous distention and a central venous pressure (CVP) waveform demonstrating a rapid X descent and a blunted Y descent because of the inability of the heart to fill in diastole. Pulsus paradoxus, an exaggerated fluctuation in arterial pressure from changes in intrathoracic pressure during respiration, may be present. Echocardiography may further support the diagnosis. Recent advances in the use of ultrasonography by non-cardiologists to determine the presence of pericardial fluid has demonstrated excellent sensitivity and rapid performance of the examination (7).

Pulmonary thromboembolus may occasionally present as profound circulatory collapse. Cardiac output is restricted either by mechanical obstruction of the pulmonary arterial tree or by pulmonary hypertension induced by the release of secondary mediators. This vascular obstruction results in a low cardiac output state with elevated CVP and pulmonary hypertension, but with a normal pulmonary artery occlusion pressure (PAOP).

Through similar mechanisms, venous air embolism can completely obstruct pulmonary arterial blood flow with ensuing cardiac arrest. Central hemodynamics are similar to those of thromboembolic disease. Although numerous causes exist, of greatest concern are placement of central venous access catheters and surgical procedures in which the operative site is greater than 5 cm above the right atrium (8,9). Venous air embolism is diagnosed clinically by auscultation of a characteristic "mill wheel" heart murmur. Immediate placement of the patient in a slightly head down, left lateral decubitus position is advocated as are attempts to aspirate air from the right ventricle through a central venous catheter.

Finally, venous obstruction leading to shock may be seen with tension pneumothorax. In this condition, elevated intrapleural pressure from an injury to the lung or airways collapses the intrathoracic great veins, resulting in inadequate venous filling and shock. Tension pneumothorax should be diagnosed by physical examination and not chest radiography. Needle decompression often restores venous filling sufficiently to reverse the shock state until a thoracostomy tube can be placed. In many patients, the length of some venous cannulas may be insufficient to reach the pleural space (10). If suspicion of the diagnosis is significant, a lack of response to needle decompression should prompt immediate tube thoracostomy.

Cardiogenic Shock

In cardiogenic shock, the underlying defect is primary pump failure, but this is not always due to myocardial dysfunction. The causes of pump failure include myocardial infarction with loss of myocardium, reduced contractility (cardiomyopathy), ventricular outflow obstruction (aortic valvular stenosis, aortic dissection), ventricular filling anomalies (atrial myxoma, mitral stenosis), acute valvular failure (aortic or mitral regurgitation), cardiac dysrhythmias and ventriculoseptal defects. Most often, cardiogenic shock is a direct or indirect consequence of acute myocardial infarction.

Cardiogenic shock due to left ventricular infarction suggests that more than 40% of the left ventricle is involved (11,12). Unless a lesion amenable to surgical correction is discovered (e.g., valvular dysfunction), associated mortality exceeds 75%. On physical examination, signs of peripheral vasoconstriction are evident and oliguria is common. The hemodynamic profile typical in this condition includes decreased cardiac output with elevated PAOP and systemic hypotension. When diastolic dysfunction exists, actual preload (end diastolic volume) may be decreased, although physical examination reveals findings of "volume overload" including pulmonary and peripheral edema, and hepatomegaly. This conundrum is explained by the fact that hydrostatic pressure does not reliably reflect intravascular volume status. Nevertheless, the pulmonary artery catheter may provide additional diagnostic information. A marked increase in oxygen saturation of blood from the right atrium versus the pulmonary artery in the face of cardiogenic shock and infarction strongly supports a diagnosis of ventricular septal rupture. Large V-waves seen while the catheter balloon is in occlusion suggests mitral regurgitation from papillary muscle rupture, which

may occur following inferoposterior myocardial infarction. Equalization of diastolic pressures is diagnostic for cardiac tamponade.

Right ventricular dysfunction as a consequence of inferior wall myocardial infarction carries a better prognosis than left-sided failure. Diagnosis may be suggested by a right ventricular diastolic pressure elevation in the face of a decreased pulmonary artery pressure (13). Hypotension caused by right-sided heart failure must be distinguished from left-sided failure because of significant differences in their management. Shock from right-sided failure is corrected with volume resuscitation to maintain right ventricular preload. If inotropes are indicated, agents that do not increase pulmonary vascular resistance should be chosen.

Cardiac dysrhythmias are another source of cardiogenic shock. In addition to malignant dysrhythmias such as ventricular fibrillation that have associated shock, other dysrhythmias may result in hypotension in patients with coexisting myocardial disease. Atrial dysrhythmias or the "pacemaker syndrome" (where the set rate of a ventricular pacemaker is set above the atrial rate) may make a previously normotensive patient with an abnormal ventricle become hypoperfused.

Distributive Shock

The classic hemodynamic profile of septic shock (high cardiac output and systemic hypotension) has prompted some clinicians to institute antimicrobial therapy and to search for an infectious source in any patient who exhibits these cardiac parameters. Such hyperdynamic patterns are seen in other conditions, however,

including acute injury, anaphylaxis, spinal cord injury, and severe liver dysfunction. The term distributive shock was introduced to account for these dissimilar diseases with a common clinical hemodynamic picture.

The management of septic shock (maldistribution of blood flow in the face of documented or suspected infection) remains a major challenge to the intensivist. The hemodynamic profile in septic shock is protean, and relates not only to preexisting cardiovascular pathology, but also to the point at which hemodynamic measurements are made. Early in its course, septic shock is manifest by decreased systemic vascular resistance, normal to low cardiac filling pressures, and increased cardiac output (14). Despite elevated cardiac output, abnormalities exist in tissue oxygen extraction. The exact cause of this maldistribution is unclear, but may relate to excessive blood flow to areas of normal metabolic demand and hypoperfusion of areas of increased demand (15). Despite elevated cardiac output, myocardial depression in sepsis may be demonstrated through decreased ejection fraction, right ventricular dysfunction, and left ventricular dilation. Cardiac function deteriorates further in later stages of septic shock, and the patient's hemodynamic status mimics that of cardiogenic shock (16,17).

The maldistribution of substrate delivery is complicated by conflicting clinical data. In most forms of shock, the initial illness leads to a low cardiac output state, and reduced SaO_2. In septic shock, both cardiac output and SaO_2 are elevated. Despite these data, evidence exists to support tissue oxygen deficit despite adequate

systemic oxygen delivery (18-20). Conflicting data suggest that tissue oxygenation in sepsis is not impaired (21). Additional data has come forth to explain the lactic acidosis and end-organ dysfunction seen in septic shock, suggesting that the substrate utilization derangement occurs at the cellular level, perhaps through disruption of normal mitochondrial metabolic pathways (22-24).

A complex immunologic sequence initiates septic shock. A variety of potentially inciting toxic stimuli are currently under investigation, especially the role of endotoxin, a lipopolysaccharide cell wall constituent of gram-negative bacteria. TNF and IL-1 are released in response to endotoxin, stimulating release of other mediators of acute inflammation. The combined effects of these mediators result in the complex hemodynamic pattern characteristic of septic shock.

In addition, a well-documented myocardial depression has been demonstrated, despite a cardiac output that would be considered elevated. More specific investigation has also noted that these patients have reduced left ventricular ejection fractions with increased end diastolic and end systolic volumes. Whether the reduced cardiac performance is related to direct myocardial depression or cardiac ischemia remains a matter of scientific debate (25-27).

Anaphylaxis represents another form of distributive shock that is seen following diagnostic studies, medication administration, and insect envenomation (28). Anaphylactic reactions severe enough to result in shock usually occur shortly after exposure to the offending agent. Physical findings associated with anaphylaxis include a dermatologic reaction (erythema, urticaria, etc.) and respiratory obstructive processes. Occasionally, reaction is severe enough to produce shock through myocardial depression. Hemodynamic parameters to support the diagnosis include low CVP and PAOP, an elevated hematocrit, and reduced cardiac output.

Neurogenic shock, another type of distributive shock, should be distinguished from spinal shock. Neurogenic shock results in autonomic dysfunction as a result of spinal cord injury above the upper thoracic level, with consequent hypotension, bradycardia and warm, dry skin. Spinal shock is a neurologic condition: a transient reflex depression below the level of spinal cord injury due to the abrupt withdrawal of descending excitatory influences from higher centers as well as persistent inhibition from below the injury. In the trauma patient, other sources of hemodynamic instability, such as occult hemorrhage, should be excluded before attributing shock to a neurogenic source (29,30).

The abnormal blood flow distribution in neurogenic shock stems from the fall in peripheral vascular tone. Although euvolemic, the patient has a relative expansion of the intravascular space through vasodilatation. Because initial volume status is normal, fluid resuscitation should proceed with caution. If hypotension does not respond to sequential volume infusions, it may be treated with alpha-adrenergic agents, and concomitant bradycardia may be corrected with atropine to block the

predominant parasympathetic influences. In most cases of neurogenic shock, hypotension resolves within 24 to 48 hours.

Endocrine Shock

In the outpatient setting, patients with hypothyroidism demonstrable by laboratory testing may have mild systemic symptoms. In the intensive care environment, however, these patients may manifest respiratory and cardiovascular symptoms that can impact on both their management and possibly survival. Cardiac effects of hypothyroidism include diminished cardiac output as a result of lower inotropic activity in association with bradycardia. Although hypotension may be seen, more commonly hypertension as a consequence of increased vascular resistance is encountered (31). The hypothyroid patient has a decreased ventilatory drive in response to hypoxemia and hypercapnia that may result in difficult ventilatory weaning (32). Drug metabolism is generally slowed in hypothyroidism and accelerated in hyperthyroidism (33).

Diagnosis of hypothyroidism may be made by demonstration of an elevated serum thyroid stimulating hormone level. In borderline cases, the free thyroxine index may also be measured. A depressed free thyroxine index may be seen despite normal thyroid stimulating hormone in patients with hypothalamic disease. In such patients, consideration of panhypopituitarism should be given. This is especially important since rapid thyroid replacement in patients with adrenal insufficiency may lead to Addisonian crisis. If the possibility of a panhypopituitary state exists, concomitant empiric treatment with glucocorticoids should be instituted along with thyroid hormone replacement. Secondary hypothyroidism may be further supported by evidence of hypogonadism.

Myxedema coma is an uncommon presentation of the hypothyroid state that may include hypotension. The cardiovascular picture of this disease is of a flabby, enlarged heart with global hypokinesia. Pericardial effusion may be present, and may be of such degree as to cause tamponade. Sinus bradycardia may also be seen (34). Appropriate therapy for patients with myxedema coma who present in shock includes isotonic volume resuscitation, rewarming, and thyroid hormone replacement.

Paradoxically, patients with thyrotoxicosis may also present with shock. The cardiomyopathy of hyperthyroidism is often a reversible condition. High output heart failure may be of particular concern, however, in the older patient who may have preexisting cardiac or coronary artery disease, increased heart rate, ejection fraction and cardiac output can lead to myocardial ischemia. Tachycardia may not always be present, as other indications for beta-blockade may have led to masking of this clinical sign. Tachyarrhythmias, including atrial fibrillation and supraventricular tachycardia, may be seen and should be treated appropriately. In patients with hyperthyroidism whose clinical picture includes congestive heart failure, beta-blockade may worsen their condition.

The development of relative adrenal insufficiency in response to certain pathophysiologic states has received increased

attention recently (35,36). Unrecognized adrenal insufficiency in the critically ill patient whose adrenal response fails to meet their physiologic needs may contribute to the need for prolonged mechanical ventilation and ICU length of stay. A lower threshold for testing of adrenal insufficiency and administration of titrated levels of corticosteroid therapy to achieve a "euthyroid state" has been advocated (35,36).

PHYSIOLOGIC MONITORING

Perhaps more than for any other disease process in the intensive care unit, physiologic monitoring is essential to the accurate diagnosis and appropriate management of the patient presenting with shock. Such monitoring typically begins with use of common "vital signs", but rapidly progresses to application of advanced and frequently invasive monitoring devices such as: indwelling arterial, central venous, intracranial, and intravesicular pressure catheters; pulse oximeters; end-tidal carbon dioxide monitors; respiratory function monitors; and pulmonary artery catheters.

<u>VITAL SIGNS</u>

The diagnosis of shock was originally based on abnormalities in a patient's physiologic variables or "vital signs" (i.e., heart rate, blood pressure, temperature, urinary output, and, more recently, pulse oximetry). Until the late 1960s, the presence of tachycardia and hypotension was considered synonymous with shock. As clinicians gained more experience in treating critically ill patients it became apparent that normalization of heart rate, blood pressure, temperature, and urinary output was not necessarily sufficient to reverse a patient's shock

state. Critically ill patients continued to have a high incidence of multiple organ failure and mortality despite seemingly adequate resuscitation based upon restoration of vital signs to "normal" ranges.

Vital signs alone are not sufficient to diagnose the presence of shock. Shock is defined by the adequacy of end-organ function rather than derangements in global vital signs. Nevertheless, vital signs remain the foundation for screening for shock, and completely normal vital signs in the absence of confounding factors eliminate shock from the differential diagnosis.

<u>Heart Rate</u>

Alterations in heart rate are common in patients in shock. Tachycardia is most commonly encountered, and is predominantly a direct effect of intravascular volume loss, as in hypovolemic or distributive shock, where heart rate increases to maintain adequate cardiac output and oxygen delivery to injured tissues. These increases may become pathologic, however, when heart rate exceeds 120-130 beats per minute (37). Above this rate, diastolic filling time decreases to the point that insufficient ventricular filling decreases stroke volume. The presence of tachycardia can be used to predict the presence of intravascular volume depletion and its resolution to suggest the adequacy of volume resuscitation (38). A decrease in heart rate in response to a rapidly administered volume challenge can be a simple and useful test for diagnosing hypovolemia.

Bradycardia is usually representative of severe physiologic derangement and impending cardiovascular collapse. Its presence in a

critically ill patient demands immediate attention. Bradycardia may also be encountered in patients with neurogenic shock as a result of injury to the sympathetic cardioacceleratory fibers arising from the upper thoracic region of the spinal cord. Elderly patients, those receiving beta-blocker therapy, high spinal cord injuries, and patients with transvenous pacemakers may not be able to increase heart rate in response to shock. Patients with an inappropriately low heart rate and inadequate cardiac output will benefit from increasing heart rate by withholding beta-blocker therapy, use of chronotropic medications, or reprogramming of their transvenous pacemaker to a higher rate.

Blood Pressure

Hypertension is an uncommon finding in shock. Patients are typically hypotensive due to hypovolemia, decreased cardiac contractility, or systemic vasodilatation. Hypotension results in inadequate tissue perfusion and promotes the development of anaerobic metabolism and ongoing shock. Normotension should be restored as soon as possible to improve tissue perfusion.

Blood pressure may be measured noninvasively by sphygmomanometry or invasively by indwelling arterial catheter. Both techniques are subject to mechanical and physiologic measurement errors, or "dynamic response artifacts", that can be misleading and result in inappropriate therapy. (39) Due to these intrinsic monitoring errors, systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements may vary widely from one measurement technique to another. The mean arterial pressure (MAP), however, will remain fairly consistent regardless of the measurement method and any artifact present. Because of its increased reliability, MAP should be used to titrate cardioactive infusions and other resuscitative therapies. MAP is calculated as:

$$MAP = (SBP + 2(DBP))/3$$

Temperature

Patient temperature, although not indicative of either the presence or absence of shock, may help define the etiology and can have significant prognostic value. (40-42) Temperature is most accurately measured by an intravascular thermistor (i.e., from a pulmonary artery catheter), although tympanic, esophageal, oral, and rectal measurements may be acceptable in appropriate patients. Axillary temperatures should not be utilized due to their poor accuracy (43).

The presence of hypothermia (core temperature < 96.8° F or 36.0° C) is of significant importance in the definition and treatment of shock as it suggests severe physiologic derangement and has a significant impact on patient survival (40-42,44,45). Hypothermia places the patient at risk for cardiac dysrhythmias, acute renal failure, and refractory coagulopathy (44,45). When hypothermia is not rapidly corrected, mortality is extremely high (41,42). While hypothermia reduces metabolic activity of the body, rewarming significantly increases global metabolic demands and oxygen consumption. Such demands may exceed the patient's oxygen delivery capacity resulting in an oxygen transport imbalance. Care must be taken

to ensure adequate oxygen delivery and tissue perfusion during the rewarming process. Because of its significant morbidity and mortality, hypothermia should be avoided or rapidly corrected in critically ill patients.

Hyperthermia (core temperature > 101.0° F or 38.3° C) represents the body's response to injury, inflammation, and infection. It may suggest the presence of an infectious process as the etiology for shock (i.e., septic shock). Hyperthermia should result in a careful clinical assessment and physical examination of the patient rather than automatic orders for costly radiologic and laboratory tests commonly associated with a low diagnostic yield. Empiric antibiotic therapy may be warranted based upon the patient's condition. It must be kept in mind, however, that there are many causes of fever in the critically ill patient and that an elevated temperature alone does not define the presence of infection.

Urine Output

Renal function is an important predictor of the presence of shock. Inadequate renal blood flow results in decreased urine output. Of the four traditional vital signs, oliguria is one of the earliest signs of inadequate perfusion at the tissue level. Decreases in urine output as a result of hypovolemia are seen before changes in heart rate or blood pressure (TABLE I). Reponses of urine output to therapeutic interventions can guide shock resuscitation as long as confounding factors are not present (i.e., diabetes insipidus, diabetic ketoacidosis, diuretic therapy, renal tubular dysfunction).

Pulse Oximetry

Technological advances in the 1970s and 1980s led to the introduction of what some have coined the "fifth vital sign" (46). Pulse oximetry is now widely utilized as a noninvasive and cost-effective method of continuously monitoring arterial oxygen saturation in both the intensive care unit and operating room settings. Based on the principles of spectrophotometry and plethysmography, this technique uses the differential light absorption characteristics of oxy- and deoxyhemoglobin to calculate the percentage of hemoglobin in the blood which is saturated with oxygen. This addition to the traditional four vital signs serves two purposes. First, it provides an early warning of hypoxemia allowing corrective interventions to be made. Second, it can be used as an endpoint in the resuscitation of patients in shock and in the assessment of oxygen transport balance. For these reasons, continuous pulse oximetry should be considered the standard of care in any intensive care setting (47,48).

INVASIVE HEMODYNAMIC MONITORING

In 1970, Swan and Ganz introduced the flow-directed pulmonary artery catheter allowing clinicians to measure pulmonary artery pressures at the bedside (49). In 1972, addition of a thermistor near the tip of the catheter provided the ability to calculate cardiac output using the thermodilution technique. This revolutionary advance in physiologic monitoring became the standard of care by the late 1970s in patients with multisystem organ dysfunction or refractory shock. In the 1980s, continuous mixed venous oximetry capability was added as the importance

of oxygen delivery, oxygen consumption, and oxygen transport balance in the diagnosis and management of shock states became clear. In the early 1990s, catheters capable of calculating right ventricular volumes became available further improving preload assessment in the critically ill. Recently, "fourth-generation" pulmonary artery catheters designed to continuously assess hemodynamic function and oxygen transport have become commonplace in the intensive care unit setting. Although a variety of other hemodynamic monitoring techniques have been developed over the years (including bioimpedance, pressure-wave contour analysis, esophageal Doppler, and transesophageal echocardiography), pulmonary artery catheterization remains the "gold standard" for bedside hemodynamic monitoring of the patient in shock.

The circulatory system consists of two circuits

connected in series: the systemic and pulmonary vasculature. Two pressures are present in each circuit, generated by either the left or right ventricle; an "outgoing pressure" (MAP or MPAP) and an "incoming pressure" or estimate of "preload" (PAOP or CVP) (FIGURE 1). These pressures can be used to calculate the resistance or "afterload" of each circuit (SVRI or PVRI) as well as the work (LVSWI or RVSWI) done for each circuit. The pulmonary artery catheter thus provides three different types of variables: pressure, volume, and flow. Combining these variables in various calculations provides a wealth of physiologic data that can be utilized to diagnose a patient's shock state and guide appropriate resuscitative therapy. These calculated parameters play an integral role in the assessment and treatment of all critically ill patients. (TABLE II).
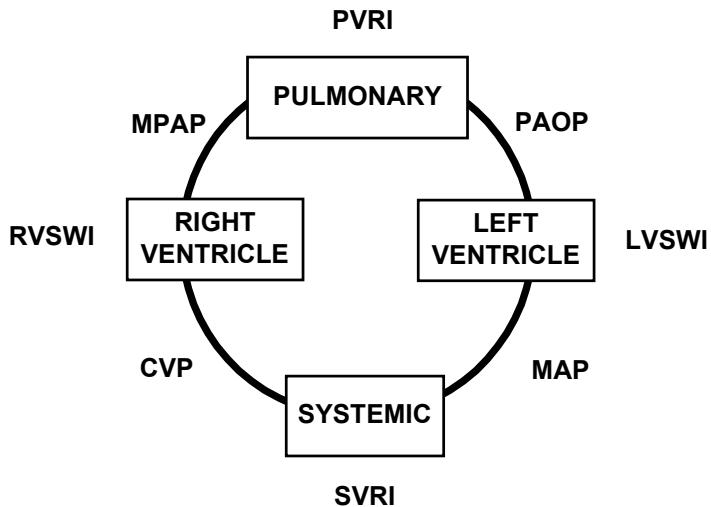

FIGURE 1: Measured and calculated hemodynamic variables in the assessment of vascular resistance and cardiac work. MAP - mean arterial pressure; MPAP - mean pulmonary artery pressure; PAOP - pulmonary artery occlusion pressure; CVP - central venous pressure; SVRI - systemic vascular resistance index; PVRI - pulmonary vascular resistance index; LVSWI - left ventricular stroke work index; RVSWI - right ventricular stroke work index

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TABLE II: HEMODYNAMIC VARIABLES

Measured Variables

Variable (abbreviation)	Unit	Normal Range
Systolic Blood Pressure (SBP)	Torr	90-140
Diastolic Blood Pressure (DBP)	Torr	60-90
Systolic Pulmonary Artery Pressure (PAS)	Torr	15-30
Diastolic Pulmonary Artery Pressure (PAD)	Torr	4-12
Pulmonary Artery Occlusion Pressure (PAOP)	Torr	2-12
Central Venous Pressure (CVP)	Torr	0-8
Heart Rate (HR)	beats/min	(varies by patient)
Cardiac Output (CO)	L/min	(varies by patient)
Right Ventricular Ejection Fraction (RVEF)	(fraction)	0.40-0.60

Calculated Variables

Variable (abbreviation)	Unit	Normal Range
Mean Arterial Pressure (MAP)	Torr	70-105
Mean Pulmonary Artery Pressure (MPAP)	Torr	9-16
Cardiac Index (CI)	L/min/m^2	2.8-4.2
Stroke Volume (SV)	mL/beat	(varies by patient)
Stroke Volume Index (SVI)	mL/beat/m^2	30-65
Systemic Vascular Resistance Index (SVRI)	dyne·sec·cm^{-5}	1600-2400
Pulmonary Vascular Resistance Index (PVRI)	dyne·sec·cm^{-5}	250-340
Left Ventricular Stroke Work Index (LVSWI)	gm·m/m^2	43-62
Right Ventricular Stroke Work Index (RVSWI)	gm·m/m^2	7-12
Coronary Perfusion Pressure (Coronary PP)	Torr	>60
Cerebral Perfusion Pressure (Cerebral PP)	Torr	>60
Abdominal Perfusion Pressure (Abdominal PP)	Torr	>50
Right Ventricular End-Diastolic Volume Index (RVEDVI)	mL/m^2	60-100
Body Surface Area (BSA)	m^2	(varies by patient)

Pressure and Pressure-Derived Variables

Pressure variables form the foundation for physiologic monitoring in the assessment of shock. Typically, however, the absolute value of any single pressure variable is not as important as the trend, calculated variables, and perfusion pressures that can be identified using this pressure.

Mean Arterial and Mean Pulmonary Arterial Pressure

Mean arterial pressure (MAP) has been discussed previously as the calculated average of SBP and DBP. Mean pulmonary arterial pressure (MPAP) is the equivalent pressure for the pulmonary circuit and is calculated using pulmonary arterial systolic (PAS) and diastolic (PAD) pressure:

$$MPAP = (PAS + 2(PAD))/3$$

Mean pressures should be utilized to guide decision making and resuscitative therapy whenever possible as they are less subject to monitoring artifacts (39). They are also essential components to calculate vascular resistance and cardiac work.

Pulmonary Artery Occlusion and Central Venous Pressures

Intracardiac filling pressure measurements such as PAOP or "wedge" and CVP are commonly used to estimate intravascular volume or "preload". Preload augmentation is an essential element in the initial resuscitation of all forms of shock. Preload, by the Frank-Starling Law, is defined in terms of myocardial fibril length at end-diastole. Because this is clinically unmeasurable, several assumptions are made to utilize PAOP to clinically assess the preload status of the left ventricle (FIGURE 2). First, for a given geometric shape, left ventricular end-diastolic volume (LVEDV) is assumed to be proportional to myofibril length. Second, in the absence of changing ventricular compliance end-diastolic volume is proportional to end-diastolic pressure. Third, in the absence of mitral valve disease, left ventricular end-diastolic pressure (LVEDP) is equal to mean left atrial pressure

(LAP). Fourth, properly transduced PAOP is equal to LAP. Similar assumptions must be made with the use of CVP in estimating preload status of the right ventricle.

If each of the above assumptions is valid, transmural PAOP will reflect left ventricular preload status. Unfortunately, these assumptions are frequently invalid in critically ill patients due to changing ventricular compliance caused by shock, myocardial ischemia, changing ventricular afterload and intravascular volume, changes in contractile state caused by inotropes, vasopressors, and vasodilators, changes in intrathoracic pressure caused by mechanical ventilation, changes in intra-abdominal pressure due to edema, blood, and space occupying lesions, and changes in lung and chest wall compliance and airway resistance. PAOP measurements, therefore, cannot be assumed to accurately reflect a critically ill patient's
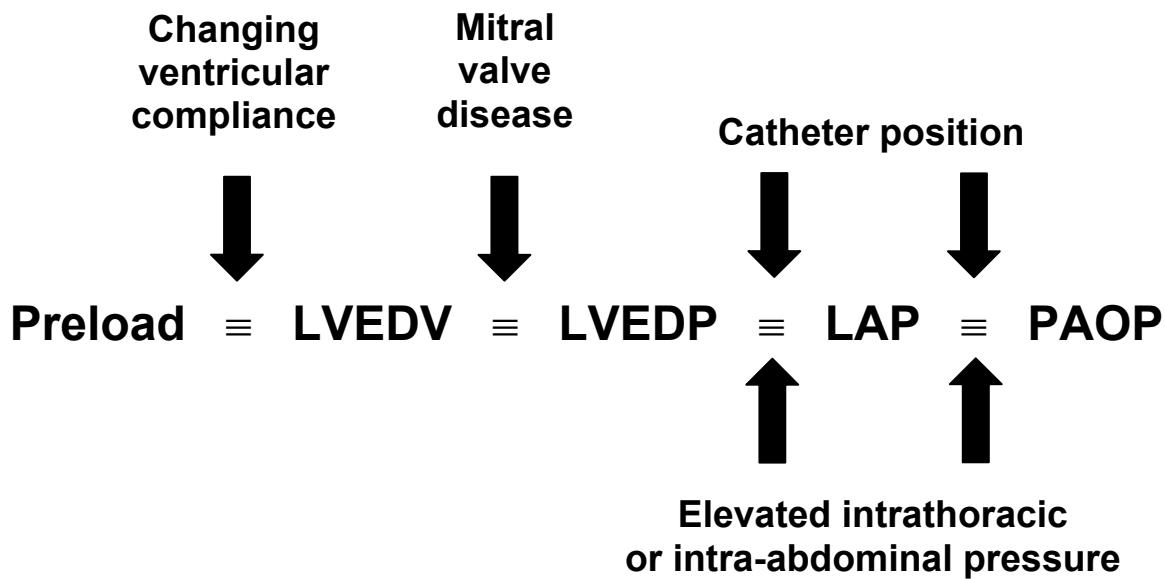

FIGURE 2: POTENTIAL CAUSES FOR ERROR IN PAOP MEASUREMENTS
LVEDV - left ventricular end-diastolic volume, LVEDP - left ventricular end-diastolic pressure, LAP - left atrial pressure, PAOP - pulmonary artery occlusion pressure

intravascular volume (50-54). In fact, reliance upon PAOP measurements for preload assessment in the critically ill may lead to inappropriate interventions in over 50% of patients (55). The *trend*, rather than absolute value, of such measurements in response to therapeutic interventions is of greater value. The optimal PAOP is that value which, through careful evaluation of the patient's hemodynamic status, is determined to maximize cardiac output, oxygen delivery, and oxygen consumption.

CVP is frequently misused as an estimate of left ventricular preload and overall intravascular volume status. For similar reasons to those just described, absolute CVP measurements do not accurately portray left ventricular volume status or ventricular function (50,53,54). As with PAOP, the trend of CVP measurements in response to therapeutic measures may be of value.

Coronary Perfusion Pressure

Maintaining adequate coronary perfusion should be a primary goal in resuscitation of any patient in shock. Patients with preexisting coronary artery disease who may have marginal myocardial blood flow can develop ischemia or infarction if coronary perfusion pressure falls below a critical threshold. Coronary perfusion pressure is calculated as the pressure change across the coronary artery during maximal blood flow (diastole). DBP, and not SBP, is the most important determinant in maintaining adequate myocardial perfusion. PAOP estimates myocardial wall tension and resistance to perfusion by approximating the end-diastolic pressure in the left ventricle (LVEDP).

Coronary perfusion pressure = DBP - PAOP

Coronary perfusion pressure should be maintained above 50 mm Hg. Below this critical value, the myocardium may not receive adequate blood flow and the risk for myocardial ischemia and infarction increases (37). Thus, every attempt should be made to maintain an adequate DBP during resuscitation of shock. Vasodilators with a primary effect on the venous vasculature must always be used with caution to avoid decreasing DBP to the point that myocardial perfusion is compromised.

Cerebral Perfusion Pressure

Monitoring of cerebral perfusion pressure is important in the head-injured patient with increased ICP. Because the brain is enclosed within the skull with little room for expansion, cerebral edema and pathologic masses (such as hematomas and tumors) can increase ICP, causing significant and detrimental effects on cerebral blood flow and oxygenation. Monitoring of ICP is an important component of the hemodynamic monitoring of patients with brain injury and shock. Cerebral perfusion pressure is calculated as the pressure change across the brain:

Cerebral perfusion pressure = MAP - ICP
(or CVP, whichever is higher)

The goal is to maintain a cerebral perfusion pressure greater than 60 to 70 mm Hg (56). This may be accomplished by either increasing MAP (using vasopressors such as the alpha-agonists neosynephrine or norepineprhine) or decreasing intracerebral volume (through the use of mannitol and hypertonic fluids) thereby decreasing ICP.

Blood Flow and Flow-Derived Variables

The pulmonary artery catheter is also used to calculate blood flow-related variables such as cardiac output and stroke volume to diagnose and treat shock more accurately. Flow-related variables are used with pressure variables to calculate vascular resistance and estimate the work performed by the left and right ventricles.

Interpatient variability makes it difficult to assign a "normal" range to flow-derived variables. What might be an adequate cardiac *output* for a 50-kg woman is inadequate for a 150-kg man. To normalize these measurements and allow comparison from patient to patient, flow-derived variables are indexed to body surface area (BSA) obtained from a nomogram. Indexed variables, such as cardiac *index* and stroke volume *index*, are more meaningful since normal ranges aid in interpretation. All flow-derived hemodynamics should be indexed to facilitate comparison with accepted normal ranges.

Cardiac Index and Stroke Volume Index

Cardiac index (CI) is the total blood flow from the heart (in liters per minute) divided by BSA. Stroke volume index (SVI) is the volume of blood ejected from the heart per beat divided by BSA:

CI = Cardiac output / BSA

SVI = CI / heart rate

Most shock states have a decreased CI as a result of intravascular volume depletion or increased vascular resistance. In order to maintain cardiac output, tachycardia is the usual response to a low stroke volume. Therapy is to restore intravascular volume and increase SVI, thus improving CI. An increased CI may be seen

in early septic shock, but may also be seen with other non-shock hyperdynamic states such as cirrhosis, pregnancy, and in high performance athletes.

Systemic vascular resistance index

According to Ohm's law, the resistance of an electrical circuit is equal to the voltage difference across the circuit divided by the current. A simplified view of the circulatory system is likened to an electrical circuit in which the resistance across the systemic or pulmonary vascular beds can be calculated using Ohm's law (FIGURE 1):

Resistance = Voltage difference / current

Vascular resistance =

Pressure change / total blood flow

Systemic Vascular Resistance Index (SVRI) =
   Change in pressure across the systemic circuit
      (mm Hg) / total blood flow L/min/m^2)

SVRI (in dynes•sec•cm^{-5}) =

(MAP-CVP)(79.9)/CI

Pulmonary Vascular Resistance Index (PVRI) =
   Change in pressure across the pulmonary circuit
      (mm Hg)/ total blood flow (L/min/m^2)

PVRI (in dynes•sec•cm^{-5}) =

(MPAP-PAOP)(79.9)/CI

The constant, 79.9, is used to convert mm Hg•L/min to the more physiologic units of dyne•seconds•cm^{-5}.

Increased SVRI is commonly seen in obstructive, hypovolemic, late septic, and cardiogenic shock. Systemic resistance may also rise in non-shock states such as pheochromocytoma (secondary to increased endogenous catecholamine output). Decreased SVRI is common in distributive shock states (neurogenic or early septic shock). Vasodilators such as sodium nitroprusside, nitroglycerin, and other antihypertensives reduce SVRI. Increased PVRI (pulmonary hypertension) is encountered in patients with acute respiratory distress syndrome (ARDS), increased intra-abdominal pressure (intra-abdominal hypertension), mitral stenosis, or aortic stenosis.

Perfusion pressure and vascular resistance determine total blood flow to an organ, but absolute values of these determining factors do not define the shock state. For example, a high vascular resistance is commonly compensatory for reduced systemic perfusion pressure. The same numeric value of high resistance may contribute to organ dysfunction when it is so high that perfusion pressure cannot overcome it. When organ blood flow is maldistributed, as in septic shock, multiple organ dysfunction may occur despite normal systemic perfusion pressure.

Ventricular Stroke Work Indices

The ventricular stroke work indices describe how much work the ventricles perform and can identify patients with poor cardiac function. They are useful to construct ventricular function curves to assess a patient's response to therapy. As with the vascular resistances, the work performed by the heart can also be calculated using the laws of physics. Work is calculated as the force generated multiplied by the distance over which the work is performed. Clinically, the force generated (per area) by each ventricle is the change in pressure it creates. The distance (per area) is the volume of blood ejected with each beat (stroke volume).

Ventricular Stroke Work Index =

Change in pressure x change in volume

LVSWI = (MAP-PAOP)(SVI)(0.0136)   (g•m/m^2)

RVSWI = (MPAP-CVP)(SVI)(0.0136)   (g•m/m^2)

The constant (0.0136) converts mm Hg-liters/beat-m^2 to g•m/m^2.

Causes of increased left and right ventricular stroke work index include ventricular hypertrophy and physiologic conditioning (as in athletes). More commonly encountered is a decreased ventricular stroke work index as occurs in various shock states, heart failure, aortic or mitral stenosis, myocardial depression/ischemia/infarction, pulmonary hypertension, and advanced age. When evaluating decreased ventricular stroke work it is important to keep in mind that the decreased function may be due to decreased intravascular volume (decreased SVI), changes in vascular resistance (increased MAP or MPAP) or decreased contractility. If preload and afterload remain constant, decreases in stroke work indicate decreases in ventricular contractility (57).

Volumetric Variables

In the 1980s, improvements in technology led to the introduction of a new generation of pulmonary artery catheters known as "volumetric" catheters (38,55,58-73). A combination of physical changes to the catheter and a specialized cardiac output computer allow measurement of the right ventricular ejection fraction (RVEF), providing an online measurement of right ventricular contractility and afterload. The RVEF can be used to calculate the right ventricular end-diastolic volume index (RVEDVI) providing a volumetric, as opposed to pressure-based, estimate of intravascular volume status.

$$RVEDVI = SVI / RVEF$$

RVEDVI is an accurate indicator of right ventricular preload and "preload recruitable" increases in cardiac index in a wide range of patient populations including general surgery, major trauma, respiratory failure, pulmonary hypertension, and sepsis (38,55,64-73). Each of these studies has demonstrated that volumetric assessment of cardiac preload using RVEDVI is significantly more accurate than reliance upon pressure-based variables such as PAOP or CVP. Further, both Miller et al. and Cheatham et al. have demonstrated a significant decrease in the incidence of both multiple organ system failure and mortality in surgical patients where RVEDVI was used as the end-point of resuscitation (70,71). Volumetric pulmonary artery catheters are particularly useful in patients receiving mechanical ventilation with positive end-expiratory pressure (PEEP) and those with increased intraabdominal pressure where

increases in intrathoracic pressure may artifactually increase PAOP and CVP measurements (71-73).

With recognition of the limitations of pressure-based estimates of cardiac preload and concern over the safety of right heart catheterization, several additional methods of volumetric preload assessment have been developed. Pulse contour analysis measures cardiac output by integration of the area beneath the arterial pressure waveform. It requires only an indwelling arterial pressure catheter and central venous catheter, thus avoiding the need for pulmonary artery catheterization. This monitoring technique allows calculation of global end-diastolic volume (GEDV), an estimate of right and left end-diastolic volumes, as well as intrathoracic blood volume (ITBV). This technology has been demonstrated to correlate well with hemodynamic measurements obtained via pulmonary artery catheter (74). The disadvantage of this technique is that a manual thermodilution bolus injection is required for each volume measurement, a requirement made obsolete by the new volumetric continuous cardiac output pulmonary artery catheters. Esophageal Doppler ultrasonography and transesophageal echocardiography (TEE) have also been advocated for hemodynamic assessment and monitoring of cardiac preload status in the critically ill (75). Although comparable accuracy with pulmonary artery catheter-derived measurements of hemodynamic function has been demonstrated, neither of these techniques has been found to be more efficacious nor do they allow continuous

assessment of cardiopulmonary function as discussed below.

Oxygen Transport

With the recognition of the importance of oxygen delivery and consumption in the treatment of the various shock states, monitoring of a patient's oxygen transport balance has become commonplace. The foremost question in critical care is whether oxygen transport to the tissues is sufficient to meet the demand for oxygen at the cellular level. Oxygen transport represents the balance between "supply" (oxygen delivery) and "demand" (oxygen consumption). When shock-induced systemic or regional malperfusion exists, oxygen demand exceeds oxygen supply and anaerobic metabolism, lactic acidosis, and cellular death result. Left unchecked, this imbalance in oxygen transport will lead to organ dysfunction and failure. The intensivist's role is to recognize the presence of such an imbalance in oxygen supply at the cellular level and initiate therapeutic interventions aimed to increase oxygen delivery, prevent further organ dysfunction, and improve patient outcome from shock. Since it is difficult to control tissue oxygen demand, most clinical efforts have focused on augmenting oxygen delivery to the tissue.

Any assessment of oxygen transport begins with calculation of the oxygen content of blood (FIGURE 3). Oxygen exists in blood in one of two forms. The majority of oxygen (>98%) is bound to hemoglobin with each gram being capable of binding 1.34 mL of oxygen. Due to oxygen's low solubility coefficient (0.003), a significantly smaller amount of oxygen (< 2%) is dissolved in plasma. Delivery of oxygen to the tissues of the body is highly dependent upon the hemoglobin concentration. By calculating cardiac index, arterial oxygen content (CaO_2), and mixed venous oxygen content (CvO_2), oxygen delivery (DO_2) and oxygen consumption (VO_2) can be calculated and used to both monitor and treat
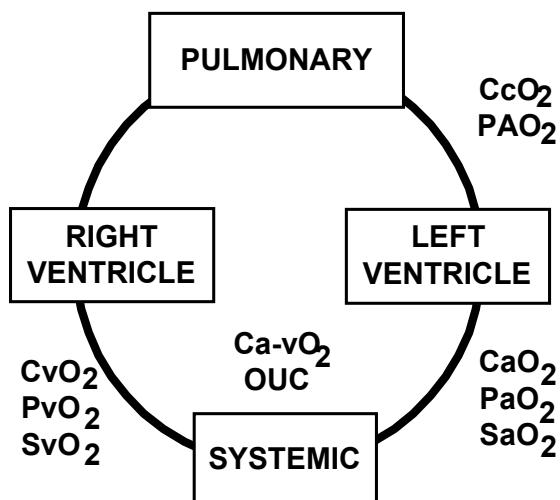

FIGURE 3: The vascular circuit of the body: oxygen content, tension, and saturation can be defined at any point in the body. $Cc'O_2$ - pulmonary capillary oxygen content; CaO_2 - arterial oxygen content; CvO_2 - venous oxygen content; Ca-vO_2 - arterio-venous oxygen content difference; P_AO_2 - alveolar oxygen tension; PaO_2 - arterial oxygen tension; PvO_2 - venous oxygen tension; SaO_2 - arterial oxygen saturation; SvO_2 - mixed venous oxygen saturation; OUC - oxygen utilization coefficient.

oxygen transport imbalances.

The oxygen content in the pulmonary end-capillary (CcO_2) is the highest content possible as none of the oxygen has been consumed by the tissues or diluted by unsaturated blood. With rare exception, the oxygen saturation of hemoglobin in the pulmonary end-capillary can be assumed to be 100% if the patient is receiving an oxygen fraction (FiO_2) > 0.30. The alveolar oxygen tension (P_AO_2) can be calculated using Dalton's law:

P_AO_2 = alveolar oxygen tension =

$$FiO_2(P_B - P_{H_2}0) - (PaCO_2/RQ)$$

where:

P_B = barometric pressure ($\cong$ 760 mm Hg)

P_{H_2O} = water vapor pressure ($\cong$ 47 mm Hg at 37° C)

RQ = respiratory quotient ($\cong$ 0.8)

Assuming a normal hemoglobin of 15 g/dL, the pulmonary end-capillary oxygen content is then calculated as follows:

CcO_2 = pulmonary end-capillary oxygen content
   = oxygen bound to pulmonary end-capillary Hgb + oxygen dissolved in plasma
   = (1.34 x Hgb x 1.0) + (P_AO_2 x 0.003)
   $\cong$ 20.4 mL O_2/dL blood

The oxygen content of blood as it leaves the heart is not the same as in pulmonary end-capillary blood due to the introduction of desaturated blood from three sources. The first is bronchial blood, which, after supplying the bronchi, empties into the pulmonary veins. The second is intrapulmonary shunt (Qs/Qt) which is that percentage of blood that travels through the pulmonary circulation without being exposed to aerated alveoli. In a normal patient, intrapulmonary shunt is 2-5%, but this value can be significantly higher in patients who have pulmonary dysfunction or are in shock. The third source of desaturated blood is the Thebesian veins, which, after supplying the myocardium, drain directly into the left ventricle. The CaO_2 can therefore be calculated as:

CaO_2 = oxygen bound to arterial Hgb + oxygen dissolved in arterial plasma
   = (1.34 x Hgb x SaO_2) + (PaO_2 x 0.003)
   $\cong$ 20.1 mL O_2/dL blood

For most purposes, the contribution of dissolved oxygen is so small as to be clinically insignificant and is often disregarded.

Following extraction of oxygen by the tissues and organs of the body, the blood is returned to the heart (FIGURE 3). The partial pressure of venous oxygen (PvO_2) can be measured by a venous blood gas or can be estimated (with little effect on derived variables) as 35 mm Hg (within the normal range) due to the small effect it has on the total oxygen content (76,77). The venous oxygen content of blood as it returns to the heart (CvO_2) is therefore calculated as:

CvO_2 = mixed venous oxygen content as blood returns to the heart
   = oxygen bound to venous Hgb + oxygen dissolved in venous plasma
   = (1.34 x Hgb x SvO_2) + (PvO_2 x 0.0031)
   $\cong$ 15 mL O_2/dL blood

The arterial-venous oxygen content difference ($Ca\text{-}vO_2$) represents the amount of oxygen extracted by the tissues and organs of the body. It is frequently elevated in shock due to the increased oxygen demands of injured tissue. The $Ca\text{-}vO_2$ is calculated as:

$Ca\text{-}vO_2$ = arterial-venous oxygen content
   difference
   = CaO_2 - CvO_2
   $\cong$ 5 mL O_2/dL blood

$Ca\text{-}vO_2$ is an important indicator of the relative balance between cardiac output and oxygen consumption (VO_2). A $Ca\text{-}vO_2$ in excess of 5.5 mL O_2/dL suggests that cardiac output is inadequate to meet cellular oxygen demands and that anaerobic metabolism and lactic acidosis may result. Maneuvers to improve cardiac output and oxygen delivery should be performed with the goal of meeting cellular oxygen demand and reducing $Ca\text{-}vO_2$ to a normal range (76).

The volume of oxygen delivered from the left ventricle (DO_2) and the amount of oxygen consumed by the tissues (VO_2) provide the clinician with vital information by which to assess the patient's overall oxygen transport balance. DO_2 is determined by two factors: the volume of oxygen in blood (CaO_2) and the blood flow delivered (cardiac output). Values indexed to body surface area allow comparison across patients of differing body habitus, so that:

DO_2 = oxygen delivery index
   = volume of oxygen pumped from the left
   ventricle per min per m^2
   = (CaO_2)(CI)(10 dL/L)

$\cong$ 600 mL O_2/min/m^2

VO_2 is calculated similarly utilizing $Ca\text{-}vO_2$ to account for the oxygen consumed by the body:

VO_2 = oxygen consumption index
   = volume of oxygen consumed by the body
   per min per m^2
   = volume of oxygen delivered - volume of
   oxygen returned per min per m^2
   = ($Ca\text{-}vO_2$)(CI)(10 dL/L)
   $\cong$ 150 mL O_2/min/m^2

One of the most important determinants of tissue oxygen delivery is hemoglobin concentration. The optimal hemoglobin concentration to maximize tissue oxygen delivery has traditionally been thought to be 10-13 g/dL. Several recent studies, however, have suggested that transfusion to such levels in critically ill patients provides no survival benefit in the absence of recent acute myocardial infarction, unstable angina, or acute blood loss (78,79). These studies have advocated maintenance of a hemoglobin concentration of 7.0-9.0 g/dL in the critically ill. Although a subject of continued controversy, the optimal hemoglobin concentration can be appropriately considered to be the concentration that maximizes oxygen delivery and restores a patient's oxygen transport balance while minimizing the potentially detrimental infectious and immunosuppressive effects of allogeneic blood. Since the oxygen affinity of hemoglobin is high, even subnormal hemoglobin concentrations may be capable of carrying adequate volumes of oxygen to the tissues, especially if attention is turned to factors that will aid in the unloading of oxygen from

hemoglobin at the cellular level. Judicious amounts of acidemia, hypercarbia, and fever all produce a right shift in the oxyhemoglobin association curve which may improve tissue unloading of oxygen.

Two additional oxygenation variables characterize the relative balance between oxygen delivery and oxygen consumption ("supply" versus "demand"): the oxygen utilization coefficient (OUC) and the mixed venous oxygen saturation (SvO_2) (discussed below). The OUC, also known as the oxygen extraction ratio (O_2ER), is the fraction of delivered oxygen that is consumed by the body and is calculated as follows:

OUC = oxygen utilization coefficient

   $= VO_2 / DO_2$

   $\cong 0.25$

If the arterial oxygen saturation (SaO_2) is

maintained at a high level, the OUC can be approximated as 1- SvO_2. SvO_2 and OUC quantitate the global oxygen transport balance of perfused tissues.

Once these variables have been derived, various calculations can be performed which provide important physiologic data that can be utilized to diagnose a patient's the severity of the patient's shock state and ensure that oxygen delivery can be optimized (TABLE III).

Intermittent vs. Continuous Monitoring

In the early 1990s, continuous cardiac output pulmonary artery catheters were introduced. Instead of using cold injectate boluses, these catheters have heating coils on their surface that allow precise pulses of thermal energy to be transferred to pulmonary artery blood. A dedicated computer system measures the resulting blood temperature changes and correlates the applied thermal energy pulses to

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TABLE III: OXYGENATION VARIABLES

Measured Variables

Variable (abbreviation)	Unit	Normal Range
Arterial oxygen tension (PaO_2)	Torr	70-100
Arterial carbon dioxide tension ($PaCO_2$)	Torr	35-50
Arterial oxygen saturation (SaO_2 or SpO_2)	(fraction)	0.93-0.98
Mixed venous oxygen saturation (SvO_2)	(fraction)	0.70-0.78
Mixed venous oxygen tension (PvO_2)	Torr	36-42
Hemoglobin (Hgb)	gm	13-17

Calculated Variables

Variable (abbreviation)	Unit	Normal Range
Oxygen delivery index (DO_2)	mL/min/m^2	500-650
Oxygen consumption index (VO_2)	mL/min/m^2	110-150
Arterial oxygen content (CaO_2)	mL O_2/dL blood	16-22
Mixed venous oxygen content (CvO_2)	mL O_2/dL blood	12-17
Arterial-venous oxygen content difference (Ca-vO_2)	mL O_2/dL blood	3.5-5.5
Oxygen utilization coefficient (OUC)	(fraction)	0.22-0.30
Respiratory quotient (RQ)	(fraction)	0.7-1.0
Intrapulmonary shunt (Qsp/Qt)	(fraction)	0.03-0.08

calculate cardiac output. Continuous cardiac output measurements have been shown to be equal in accuracy to intermittent cold indicator injections as well as indocyanine green dye dilution techniques (80-83).

Continuous cardiac output technology has several advantages over previous cardiopulmonary assessment techniques. First, many of the factors which may alter the accuracy of intermittent thermodilution measurements (such as injectate volume and temperature, injection technique, and injectate timing with regards to ventilation) do not play a role in the determination of continuous cardiac output measurements. Thus, continuous cardiac output techniques may be more accurate than standard thermodilution methods (84). Second, measurement of cardiac output is possible without the potentially significant volume load incurred by thermodilution fluid injection methods

(80,81). Third, continuous assessment of cardiac output allows a near real-time indication of a patient's response to hemodynamic interventions, which is not possible with intermittent techniques. Such monitoring advances have identified that the critically ill patient exhibits significant physiologic variability not previously recognized with existing monitoring techniques (73) (FIGURE 4). In addition to cardiac output, these catheters are able to continuously measure volumetric variables such as RVEF and RVEDVI. With the addition of continuous arterial pulse oximetry and mixed venous oximetry, these catheters provide the intensivist with a minute-to-minute assessment of hemodynamic function and oxygen transport balance not previously available. These capabilities allow earlier identification of potentially untoward changes in cardiopulmonary function, allowing appropriate interventions to be made before potentially
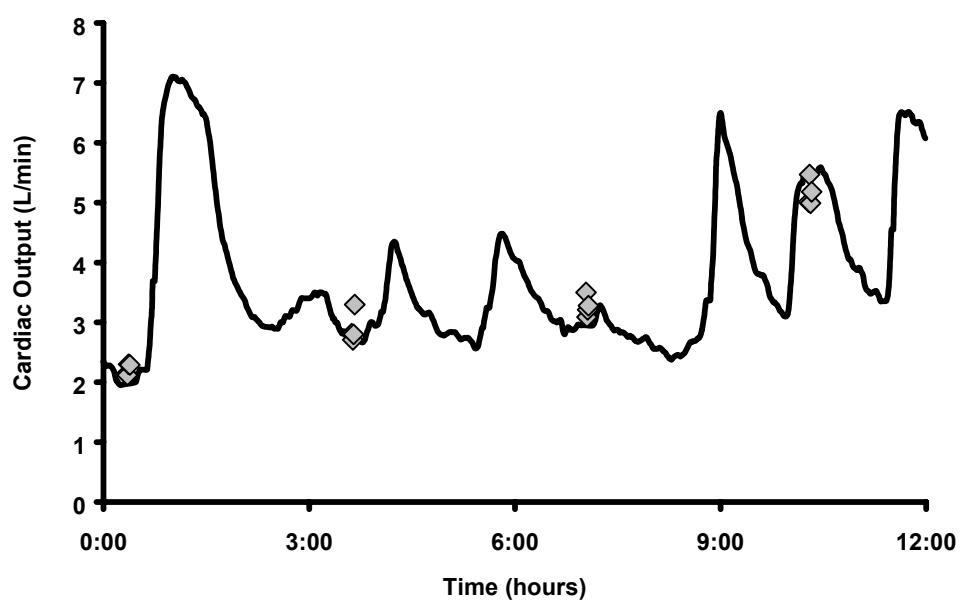

FIGURE 4: Continuous cardiac output monitoring allows detection of hemodynamic changes missed by use of conventional intermittent cardiac output techniques (diamonds).

devastating events can occur.

SHOCK RESUSCITATION ADEQUACY

Resuscitation of the critically ill patient who has developed one of the shock states is an ongoing process. It requires constant assessment of patient response to therapy administered. In the patient whose shock state and oxygen transport balance fails to improve, these interventions must be reconsidered and adjusted as necessary to achieve the desired result. To guide this dynamic resuscitation, a variety of "resuscitation adequacy" endpoints may be utilized.

Mixed Venous Oximetry

In 1980, fiberoptic technology was introduced to the pulmonary artery catheter allowing continuous measurement of SvO_2 using the technique of reflectance spectrophotometry. Continuously measured SvO_2 correlates well with oxygen extraction ratios calculated by laboratory measurements of arterial and mixed venous oxygen saturation and tension, hemoglobin concentration, and cardiac output (85). The four factors affecting SvO_2 are: SaO_2, hemoglobin concentration, cardiac output, and VO_2. Increases in any of the three variables affecting oxygen delivery (SaO_2, hemoglobin concentration, and cardiac output) result in an increase in SvO_2 while uncompensated increases in VO_2 result in a decrease in SvO_2. The SvO_2 measured in the proximal pulmonary artery is a flow-weighted average of the effluent blood from all perfused vascular beds. SvO_2 does not reflect the oxygen transport adequacy of non-perfused vascular beds nor does a normal SvO_2 mean that all tissues are adequately oxygenated. SvO_2 is a global indicator of oxygen supply - demand balance, but does not yield information about the adequacy of perfusion of any individual vascular bed.

A low SvO_2 (< 0.65) virtually always indicates an unfavorable disturbance in the normal balance between the delivery and consumption of oxygen. Normal or high values of SvO_2 are more difficult to interpret. A normal SvO_2 in a patient with otherwise normal hemodynamics generally indicates a stable condition with a satisfactory oxygen supply - demand balance. A high SvO_2 (> 0.78) is difficult to interpret and implies a maldistribution of peripheral blood flow, providing some vascular beds with oxygen delivery in excess of consumption. This state of vasoderegulation is often associated with high flow states such as cirrhosis, sepsis, pregnancy, and inflammation.

There are two common sources of error in venous oximetry measurements. Continuous venous oximetry relies upon the reflectance of infrared light from passing red blood cells. If the catheter is not properly calibrated via either an *in vitro* calibration prior to catheter insertion or an *in vivo* calibration via a mixed venous blood gas analysis, the SvO_2 values obtained may not accurately reflect the true SvO_2. Careful attention should be given to catheter calibration to prevent such errors. The second source of error is catheter malposition. If the catheter tip is against the wall of the pulmonary artery, the additional light reflected back to the catheter will artificially increase the SvO_2 measurement. Proper catheter positioning is essential to obtaining reliable SvO_2 values.

In intensive care units where pulmonary artery catheter derived hemodynamic and oxygenation variables are used in the minute-to-minute management of patients, continuous SvO_2 monitoring is cost effective (85-88). Although not a <u>specific</u> indicator of the cause of hemodynamic and oxygen transport compromise, continuous SvO_2 is a <u>sensitive</u> "on-line" monitor of the adequacy of oxygen transport balance and can be used to: a) provide an "early warning signal" to detect the onset of oxygen transport imbalance before physiologic deterioration is clinically apparent; b) evaluate the efficacy of therapeutic interventions directed towards improving oxygen transport balance such that physiologic end-points are reached more quickly; and c) identify potentially detrimental consequences of "patient care" (suctioning, positioning, etc.) that might otherwise go unnoticed.

"Supranormalization" of Oxygen Delivery and Oxygen Consumption

In 1977, Shoemaker et al. retrospectively reviewed the hemodynamic and oxygen transport variables of patients felt to be at high risk for post-operative complications (89). They discovered that patients who survived such operations had higher cardiac indices, oxygen delivery, and oxygen consumption than did non-survivors (90). They hypothesized that increasing CI,, DO_2, and VO_2 would lead to improved survival. This hypothesis was tested in 1988 in a prospective, randomized trial of high-risk surgical patients (91). Study patients were treated with fluid infusions, blood products, and inotropes with the goal of increasing CI to 4.5 $L/min/m^2$, DO_2 to 600 $mL/min/m^2$, and VO_2 to 170 $mL/min/m^2$. Control patients were treated

identically, but with the goal of simply normalizing their CI, DO_2, and VO_2. Patients treated to these "supranormal" goals had a significantly lower mortality rate (4% vs. 33%), fewer complications, fewer days of mechanical ventilation, lower intensive care unit length of stay, and decreased hospital charges (91).

These findings generated significant interest and controversy. Edwards et al. confirmed in a non-randomized study of septic shock patients that supranormal levels of oxygen transport could be achieved with an acceptable mortality rate using a goal-directed protocol (92). Tuschschmidt et al. performed a prospective, randomized study of supranormal oxygen transport in septic shock patients and confirmed many of Shoemaker's findings including a decreased mortality rate and intensive care unit length of stay (93). Yu et al. performed a prospective, randomized trial of supranormalization in a combined surgical/medical patient population and further confirmed that patients with higher cardiac indices and oxygen transport variables had a lower mortality rate (94). Both Yu and Tuschschmidt recognized that some patients cannot be "optimized", and despite all interventions are never able to achieve supranormal levels of oxygen transport. These patients have a higher mortality rate. Similarly, some patients spontaneously achieve supranormal values without any intervention being applied. These patients, like those who are optimized, have a better prognosis. This has led some to argue that a patient's ability to achieve supranormal levels of oxygen transport simply indicates a larger physiologic reserve and

improved ability to survive their injuries rather than a benefit from an applied intervention (95-97). This is supported by a recent prospective, randomized study from Shoemaker's group which identified that the patient's ability to achieve supranormal levels of DO_2 and VO_2 was prognostic of survival whereas the resuscitation strategy applied was not (98). Thus, although DO_2 and VO_2 should not be considered to be resuscitation endpoints *per se*, they are prognostic indicators for improved survival from critical illness.

Arterial Lactate

Shock is hypoperfusion resulting in inadequate oxygen delivery to meet tissue oxygen demand at the cellular level. The resulting oxygen debt forces cells to switch to anaerobic metabolism to make adenosine triphosphate (ATP), albeit by the grossly inefficient method of glycolysis. The by-products of glycolysis are hydrogen ion, pyruvate, and lactate. If aerobic metabolism is restored through resuscitation and improved tissue oxygen delivery, the excess hydrogen ion is buffered and pyruvate and lactate are both metabolized to yield ATP, carbon dioxide, and water. Under continued anaerobic conditions, however, hydrogen ion and lactate accumulate resulting in acidosis, injury, and cellular death. Serum lactate levels provide the clinician with an excellent laboratory marker of resuscitation adequacy.

Elevated serum lactate concentrations occur as a result of any combination of four processes. First, excess production of lactate may be due to the presence of ongoing anaerobic metabolism. Second, decreased lactate metabolism may result from hypoperfusion or dysfunction of the liver and/or kidneys. Third, lactate may accumulate in tissues during periods of hypoperfusion and wash out into the central circulation when perfusion to these relatively hypoxic tissues is restored. Fourth, excessive lactate production may occur in tissues that depend primarily upon aerobic glycolysis for energy production (such as the brain), giving the false impression of perfusion inadequacy. Severe elevations in serum lactate concentration may occur when any of these four processes are combined (i.e., shock resulting in hepatic hypoperfusion).

While serum lactate levels identify the presence of anaerobic metabolism, they are not specific in detecting abnormal regional perfusion. Profound hypoperfusion can exist with normal lactate levels when there is inadequate blood flow from ischemic tissue. Some septic patients have increased serum lactate levels in the absence of hypoperfusion as a result of increased aerobic glycolysis. In this situation, the elevated lactate continues to be significant despite resuscitation and is an indicator of a potentially severe pathologic process.

Elevated lactate concentrations predict an increased mortality rate (99-102). Abramson et al. demonstrated a low mortality rate in patients whose lactate level normalized within 24 hours, but mortality rates of 25 and 86 percent if lactate had not normalized by 24 and 48 hours respectively (100). The magnitude of the elevation correlates with mortality and reversal of hyperlactatemia suggests a better prognosis (99-101). While elevated lactate concentration is

strongly suggestive of a period of hypoperfusion, severe hypoxemia, or reduced oxygen delivery, correction of lactic acidosis *per se* will not improve patient outcome. The treatment of patients with elevated lactate concentrations should be directed at restoring perfusion and allowing spontaneous resolution of hyperlactatemia and normalization of arterial pH. Serial measurements of lactate during resuscitation from circulatory shock correlate with the effectiveness of the resuscitation. Worsening lactic acidosis occurring during aggressive therapy is generally associated with a poor prognosis whereas an improvement in lactate concentration with therapy is associated with a better prognosis (100-102).

Normal lactate clearance is a subject of considerable controversy. It is believed that the half-life of lactate in patients with normal hepatic and renal function is between two and four hours. The half-life of lactate in the presence of shock, ongoing anaerobic metabolism, and inadequate tissue perfusion may be significantly longer (103). Often following aggressive restoration of peripheral perfusion, there will be a slight increase in the lactate concentration due to peripheral washout. This generally corrects in a short period of time and the observed trend in lactate levels in adequately resuscitated patients should show a steady decrease. Only arterial or central venous lactate levels should be measured, as peripheral venous lactate levels may be reflective of regional malperfusion and not global resuscitation adequacy.

Base Deficit

Base deficit is the amount of base, in millimoles/liter, required to titrate whole blood to normal pH at normal physiologic values of temperature, $PaCO_2$, and PaO_2. The normal range for base deficit is +3 to -3 mmol/L. The presence of an elevated base deficit correlates with the presence and severity of shock (104,105). It predicts fluid resuscitation requirements and is a rapidly obtainable monitor of resuscitation adequacy (104). Further, it normalizes rapidly with restoration of aerobic metabolism making it a useful physiologic marker by which to guide resuscitation. Base deficit must be interpreted with caution in the patient who has received exogenous sodium bicarbonate as it will no longer be useful as a predictor of resuscitation adequacy.

Several authors have documented the usefulness of base deficit as a predictor of morbidity and mortality in trauma patients (104,105). Rutherford et al. identified that young patients (< 55 years of age) without a head injury who demonstrate a base deficit of -15 mmol/L have a 25% mortality rate (105). Patients with a head injury or patients > 55 years without a head injury have a 25% mortality at a base deficit of -8 mmol/L. Rutherford recommended that base deficit could be used to identify patients in severe shock who might benefit from having operative procedures terminated early (so-called "damage control" laparotomy) to facilitate resuscitation in the ICU. Davis et al. has demonstrated a significant correlation between an increasing (more negative) base deficit and the presence of ongoing hemorrhage (104).

Intramucosal pH Monitoring (pHi)

Because shock is defined at the cellular level, global measurements of oxygen delivery do not always detect regional blood flow abnormalities. Measurements of SvO_2, base deficit, and arterial lactate reflect global oxygen supply - demand balance, and are not specific for malperfusion at the cellular level. Interest in monitoring individual tissue beds as a method of detecting inadequate tissue perfusion has therefore become widespread.

The splanchnic circulation appears to be affected early in any of the shock states. Blood flow is redistributed to vital organs such as the brain and heart at the expense of the gastrointestinal tract. In states of severe shock, this survival mechanism may lead to intestinal ischemia and infarction. Ischemic intestine, and especially the highly sensitive mucosa, may be a source of infection, sepsis, and multiple system organ failure (106).

Although originally developed in the 1950s, gastrointestinal tonometry has recently been applied to measure malperfusion of the splanchnic circulation affording clinicians with information regarding a single vascular bed. Tonometry utilizes a tissue's high permeability to carbon dioxide (CO_2) and the rapid equilibration of intraluminal fluid CO_2 with that of tissue fluid to predict the "intramucosal pH" or pHi of the adjacent tissues (107,108). Intramucosal acidosis, as determined via tonometry, appears to predict inadequate oxygen delivery to the intestinal mucosa and has been advocated as an endpoint by which to guide resuscitation (109-114).

Several early studies demonstrated that a pHi <7.32 correlated with mortality and the development of multiple system organ failure (109,115,116) In recent years, emphasis has been placed on the gastric mucosal-arterial PCO_2 gradient or "PCO_2 gap", although the clinical value of this endpoint, like that of pHi, remains unclear (117). The difficulty of the technology and interpretation of the data have resulted in less than widespread utilization of gastric tonometry. As a monitoring technology, however, gastric tonometry represents a first step toward monitoring tissue perfusion at the cellular level. Further studies are needed to prove the usefulness of gastric tonometry in resuscitation of shock.

Abdominal Perfusion Pressure

In recent years, the prevalence and impact of elevated intra-abdominal pressures in the critically ill has been increasingly recognized (118). The high mortality associated with so-called "intra-abdominal hypertension" and "abdominal compartment syndrome" has been well-documented (71,73,118). The significant reduction in patient morbidity and mortality afforded through use of abdominal decompression and temporary abdominal closure techniques is now widely recognized and practiced (71,118).

Interest in assessment of regional perfusion inadequacy in the patient with intra-abdominal hypertension has led to the development of "abdominal perfusion pressure" (APP) as a resuscitation endpoint (73). Calculated as the perfusion pressure across the abdominal viscera (MAP minus intra-abdominal pressure), APP has

been found to significantly correlate with survival in patients with elevated intra-abdominal pressures as a result of intra-abdominal hemorrhage, visceral edema, or space-occupying lesions such as intra-abdominal tumors or ascites (73). Maintenance of an APP greater than 50 mmHg through use of abdominal decompression techniques and administration of vasoactive medications has been demonstrated to improve mortality in surgical and trauma patients. Although further investigation is necessary to completely validate this parameter, APP appears to be a useful endpoint in guiding the resuscitation of patients with elevated intra-abdominal pressures.

TREATMENT PRINCIPLES

Patient morbidity and mortality following development of one of the shock syndromes correlates directly with the duration and severity of malperfusion. The intensivist has three goals in treating the patient in shock. First, to promptly diagnose the presence and etiology of shock. Second, to rapidly restore systemic and regional perfusion in order to prevent ongoing shock and cellular injury. Third, to prevent the development of end-organ failure. In reality, the intensivist must often begin resuscitation prior to identifying the etiology of shock. For this reason, the intensivist must command a strong understanding of the various therapeutic options for each of the shock states. Utilizing the hemodynamic variables and calculations described above, shock resuscitation should focus on assessment of each individual patient's preload, contractility, afterload, and oxygen transport balance with the intent to optimize the patient's end-organ perfusion and cellular oxygenation.

Preload

In almost all shock states, a component of diminished preload, either relative or absolute, exists. Therefore, the initial therapeutic intervention for almost all patients in shock should be administration of an intravenous balanced salt solution. The amount of fluid necessary to fully resuscitate a patient varies, but an initial bolus of 20 mL/kg is reasonable in profound hypotension. Additional crystalloid infusions should be guided by monitoring the patient for signs of improved organ perfusion: reduction in tachycardia, restoration of normotension, maintenance of adequate urine output, return of normal mentation, and improvement in oxygen transport variables. Invasive hemodynamic monitoring may be of significant value in achieving these goals.

Appropriate venous access is essential for rapid volume replacement. Optimal access is through short, thin-walled large-bore intravenous catheters. Since resistance is inversely proportional to the radius to the fourth power, even small increments in catheter diameter will significantly reduce resistance to flow of crystalloid and blood infusions. When peripheral sites are unavailable, central venous catheterization of either the internal jugular or subclavian veins via the Seldinger can be utilized. Enthusiasm for femoral vein catheterization should be tempered by the increased rate of deep venous thrombosis seen on the side of catheter placement as compared to the contralateral vein (119).

The crystalloid versus colloid debate continues to be waged despite abundant

research demonstrating minimal differences in patient outcome (120-123). Advocates of colloid resuscitation point to studies that document the lower volumes of colloid necessary to achieve the same therapeutic end-point. Recent meta-analyses of the numerous prospective, clinical trials in this area have consistently supported the use of crystalloid infusions during resuscitation with colloids being restricted to specific indications (120-122). No survival benefit is associated with colloid resuscitation, and the meta-analyses have suggested a consistent survival advantage of crystalloid over colloid (120-122). Given the increased costs of colloid administration and the lack of data supporting its use, crystalloid resuscitation is preferred (120-123). Miller et al investigated the use of large volume crystalloid resuscitation versus a more moderate fluid resuscitation in combination with inotropic medications in surgical and trauma patients (124). Large volume crystalloid resuscitation alone was found to significantly improve patient survival and organ failure.

During large volume resuscitation, the patient is at risk for iatrogenic hypothermia. Consequences of significant hypothermia (<35° C) include delayed drug metabolism and a reversible platelet dysfunction that is of particular concern in the postoperative patient (125). Cardiac dysrhythmias may present with progressive hypothermia that are refractory to chemical correction until the patient is made normothermic. Compensatory thermogenesis by shivering increases oxygen consumption and adds to metabolic acidosis, thereby complicating resuscitation from shock. Prevention of hypothermia is more easily accomplished than

correction. Warmed intravenous fluids, warming blankets and a warm ambient environment may prevent shock-induced hypothermia.

Use of the Trendelenburg position was historically touted to treat shock prior to establishment of venous access. The theory was to divert blood from the venous capacitance to the central circulation, improving cardiac filling and augmenting cardiac output. Recently, this technique has fallen into disfavor, because studies fail to demonstrate consistent redistribution of blood volume to the central circulation (126). The Trendelenburg position also may cause respiratory embarrassment, impaired gas exchange, and complicate the management of shock. This effect may be even more pronounced in the morbidly obese.

Contractility

Resuscitative therapy aimed to alter contractility should begin with optimization of the patient's heart rate. While tachycardia may partially compensate for low perfusion, further increases in heart rate may only diminish diastolic filling of the heart and reduce cardiac output. Treatment of pain and anxiety as well as control of supraventricular tachyarrhythmias in the volume resuscitated patient can improve cardiac output. In bradycardia from neurogenic shock, atropine induced blockage of parasympathetic stimulation may help ameliorate the hypoperfusion by raising heart rate and cardiac output. Patients on beta-blockers who have an inappropriately low heart rate may benefit from administration of both calcium and glucagon. Patients with pacemakers who are unable to raise their own heart rate in response to shock

will frequently benefit from resetting their pacemaker to a higher rate.

Contractility agents should be considered only after adequate attempts to improve preload and afterload (where appropriate) have been made. Dopamine, a naturally occurring catecholamine that is the immediate precursor of norepinephrine, is a widely used agent with a variable response based on dosing. Classically, low rates of infusion (0-3 mcg/kg/min) have been considered "renal dose" in that dopamine increases glomerular filtration rate (GFR) and renal blood flow in healthy volunteers. However, the clinical effects on improved GFR and urine output in the critically ill have been questioned (127,128) In addition, systemic hemodynamic effects have been observed in patients with doses in this low range. (129) In modest doses (5-10 mcg/kg/min), cardiac contractility and heart rate are increased through stimulation of cardiac beta receptors. High dose therapy (10 mcg/kg/min and higher) results in increasing stimulation of alpha adrenergic receptors and elevations in systemic blood pressure. Although a valuable tool in improving cardiac performance, dopamine should be used with caution in patients with coronary artery stenosis because of the potential side effect of tachycardia and overall increases in myocardial oxygen demand.

Dobutamine is a synthetic catecholamine that also acts on beta-1 receptors, but unlike dopamine, does not directly release norepinephrine. When its chronotropic effects are minimal and heart rate does not increase, the primary inotropic effects of dobutamine have little effect on myocardial oxygen demand (130). This may be due to the systemic vasodilation that accompanies dobutamine therapy. This afterload reduction may increase cardiac output in the weakened heart, but may also decrease blood pressure leading to reduced systemic perfusion overall. Dobutamine should therefore be used with caution in hypovolemic, vasodilated states.

Norepinephrine is a naturally occurring catecholamine with both alpha and beta adrenergic activity. As a potent vasoconstrictor, there is some reluctance to use this agent because of its possible effects on mesenteric and renal blood flow. However, in the setting of an appropriately volume repleted patient who remains hypotensive, norepinephrine has been shown to be effective and safe and may have *beneficial* effects on renal function (129,131,132).

Amrinone is a noncatecholamine intravenous inotrope that, like dobutamine, has vasodilatory effects. Its mechanism of action is as a phosphodiesterase III inhibitor, raising intracellular cyclic AMP. In patients with congestive heart failure, amrinone increases stroke volume without an effect on heart rate (133). In some patients, its vasodilatory properties preclude its use because of dramatic hypotension.

Afterload

Once preload is optimized and hemodynamic goals have still not been met, afterload should be assessed and corrected as needed. The persistently hypotensive patient cannot be considered a candidate for afterload reduction. In patients with hypertension or even normotension, however, afterload reduction may allow for

improved cardiac output and hence improved resuscitation, especially in patients with decreased contractility.

Sodium nitroprusside is a commonly used agent with advantages of rapid onset and short duration, making it ideal for titration in the hemodynamically labile patient. Nitroprusside acts as both a venous and arterial vasodilator in essentially equal amounts. However, it should be used with caution in patients with coronary artery disease where concerns of coronary steal and myocardial ischemia exist. Alternatively, intravenous nitroglycerin may be used. Although primarily affecting venous capacitance, nitroglycerin also decreases arterial resistance and may improve cardiac output. Angiotensin converting enzyme (ACE) inhibiting agents may also be of significant value in reducing afterload in the normovolemic patient with poor cardiac function.

Afterload may also be reduced mechanically using a percutaneously placed intra-aortic balloon counterpulsation pump (IABP) (134). IABP is commonly used in myocardial infarction and in the immediate postoperative period after coronary artery bypass. IABP both provides mechanical afterload reduction and improves coronary artery perfusion. IABP demonstrates survival benefit primarily in myocardial infarction patients who have reversible pathology and has been used successfully in high risk patients undergoing noncardiac surgery (135).

Although afterload reduction may be beneficial in improving cardiac performance, the patient with aortic stenosis leading to shock may be harmed by use of these agents. In this disease, left ventricular wall tension remains high, and afterload reduction only serves to reduce coronary perfusion by reducing coronary perfusion pressure.

Oxygen Transport

Optimizing oxygen carrying capacity, arterial oxygenation, heart rate and increasing stroke volume will all improve oxygen delivery from the left ventricle. The goal of shock resuscitation is to improve tissue oxygenation so that oxygen consumption can increase to meet the oxygen demand of the cells to function aerobically. Normalization of anaerobic markers such as base deficit and excess arterial lactate should be one of the goals of shock resuscitation. Further increases in therapy to avoid "flow-dependence" of oxygen consumption would seem to be a minimal therapeutic goal.

Restitution of adequate levels of hemoglobin increases oxygen carrying capacity and expands intravascular volume (preload). The arguments for optimization of hemoglobin consider the relative benefits of increasing oxygen delivery weighed against the hazards of allogeneic blood transfusion. Transfusion of red blood cells can significantly improve oxygen transport. Increasing hemoglobin concentration from 8 g/dL to 12 g/dL will increase oxygen delivery by 50%, if cardiac output and gas exchange remain unchanged. Similar improvements in oxygen delivery by increasing myocardial contractility alone would require increases in cardiac output that would be challenging to produce with pharmacologic interventions. Transfusion of red blood cells to increase oxygen delivery is limited

by increases in blood viscosity that adversely affect tissue oxygenation. When hemoglobin concentration exceeds about 16 g/dL, cardiac output can decrease countering the beneficial effects of increased oxygen carrying capacity. Sludging of blood at high hematocrit in the capillaries may further decrease tissue oxygenation. Further compounding the controversy are studies that demonstrate the failure of blood transfusion to improve outcome in critically ill patients (78,79). Such studies, however, have tended to exclude certain populations of patients and further study is necessary to identify which subpopulations of the critically ill may benefit from maintenance of higher hemoglobin levels.

SUMMARY

Shock is a common and highly lethal condition that is being increasingly encountered in the critically ill. Its etiology is varied and complex. It may present in a spectrum from subclinical laboratory abnormalities to complete cardiovascular collapse. A high degree of clinical suspicion and thorough evaluation is essential to both making the diagnosis and initiating timely resuscitative therapy. Inadequate tissue perfusion that is unresponsive to initial treatment should lead to aggressive, goal-directed therapy. Correction of abnormalities in ventricular preload, contractility, afterload, and systemic oxygenation are the first steps to breaking the cycle of cellular injury and microcirculatory failure. Correction of the precipitating, underlying condition is essential for patient survival. Early treatment to predefined physiologic endpoints reduces the potentially devastating complication of end-organ dysfunction and failure.

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