CHAPTER 2

The Pathophysiologic Foundations of Critical Care

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OBJECTIVES

This chapter will:

1. Help the reader understand the philosophy behind using dynamic real-time physiologic assessment in the management of the critically ill, by noting the dynamic interactions among disease process, physiologic reserve and therapy.
2. Categorize critically ill patients' disease processes into discrete categories that allow for a more focused diagnostic and therapeutic approach to care.

PRINCIPLES

Increasingly patients are admitted to the hospital only to receive emergency care of an acute condition, such as trauma, hollow viscus perforation, myocardial infarction, septic shock, and acute respiratory failure, or for a limited number of elective procedures, such as invasive diagnostic tests (angiograms), surgery, and high-risk therapies. Furthermore, the total hospitalization time and length of stay in an intensive care setting are decreasing, resulting in a greater degree of disease acuity in all centers of the hospital. Thus the principles of acute care medicine, which reflect issues of simultaneous global assessment and both nonspecific and personalized treatment of several related or modifying pathologic and adaptive processes, transcend any geographic area in the hospital. Furthermore, basic principles of management of patients with acute illness encompass triage, selection of appropriate diagnostic and therapeutic strategies by balancing risk-benefit issues and the patient care, and healthcare cost of knowledge. These decisions often cross numerous boundaries among medical and surgical specialties. The acute care physician, once relegated to serve in the intensive care unit, operating theater, or emergency department, now sees a greater role in the overall management of the acute hospitalized patient. The principles that underlie management of most conditions requiring acute treatments within the hospital setting, whether unexpected emergencies or the result of therapies such as cardiac surgery, organ transplantation, or bone marrow suppression, share a common basis of thought and action, which forms the central theme of acute care medicine.

Initial stabilization with the goal of sustaining tissue viability and preventing further organ injury, followed by a focused diagnostic and therapeutic effort to correct the key physiologic derangements, represent the primary initial goals of acute care medicine. However, to attain these goals it is necessary for the caregiver to have a broad knowledge base in the physiology, pathophysiology, and effect of therapies on all organ systems to provide effective care of the acutely ill patient. Furthermore, if efficient healthcare delivery is to be given to a population of acutely ill patients, realistic and appropriate guidelines must be developed in the hospital regarding scheduling of elective admissions, use of expensive and limited diagnostic and therapeutic resources, and a realistic method of continually monitoring their use to optimize patient care without excessive waste. By focusing diagnostic and treatment efforts on the most effective areas of investigation and management while limiting care to treatable and preventable causes, these efforts should result in efficient and effective use of limited healthcare resources and provide the greatest overall benefit to the patients and society we serve.

One of the fundamental pillars of this approach is the use of knowledge of the pathophysiologic processes causing disease in a specific patient and how to monitor disease severity and response to treatment and time.

APPLIED PHYSIOLOGY AT THE BEDSIDE

The body is an amazing organism that adapts to changes in external stress while maintaining adequate basal homeostasis within and among organs. The primary function of the cardiorespiratory unit is to deliver adequate amounts of oxygen (O_2) and nutrients to the tissues to allow normal organ-system function while removing metabolic waste and respiration-generated carbon dioxide (CO_2). Within this construct, the functionality of these systems has much metabolic reserve, because maximal metabolic demand rarely is required, and if maximal performance is required, then it is only for brief periods of time. For example, in healthy young subjects maximum voluntary ventilation, maximal negative inspiratory pressure, maximal cardiac output (CO), and maximal oxygen delivery (DO_2) exceed basal metabolic demands by 10- to 30-fold.

As baseline organ system function decreases because of either primary organ functional loss as a result of injury or age-related atrophy, the host can sustain basal function. Because increased work by less tissue to achieve the overall good is required, each organ system eventually will display performance characteristics approaching severe metabolic demands. For the cardiovascular system this manifests as first a greater increase in heart rate for minor exercise and then to resting tachycardia and increased vasomotor tone; for the respiratory system, tachypnea; for the kidneys, impaired concentration and salt wasting. Importantly, the phenotype observed at the bedside is not that of a primary pathologic process, such as hemorrhage, infection, or infarction, but the host's response to these pathologic processes to maintain homeostasis. This intrinsic homeostatic process, mediated through both systemic sympathetic response and local adaptive cellular mechanisms, is very good for the host, because it allows for survival as organ system dysfunction progresses. Without this self-correcting

internal system present, the host could not respond rapidly to external metabolic demands, such as increased exercise, eating, or environmental excess heat. Regrettably for the bedside clinician, such homeostatic mechanisms mask organ system dysfunction until it is advanced, because the body tends to sustain function as long as possible before deteriorating. Deterioration often reflects a terminal event. Thus waiting for deterioration to occur before treating a patient at risk for such deterioration is to wait too long, because organ failure reflects failure of host defense homeostasis.

Patients manifest unique signs and symptoms as a function of their baseline physiologic reserve and the magnitude of the stress; failure of these compensatory mechanisms results in external manifestations of organ failure. For the circulation, when sympathetic tone increase can no longer sustain adequate arterial pressure and hypotension develops, there must be associated decreases in vital organ blood flow. Thus hypotension represents a failure of host defense homeostasis and, if sustained even for short periods of time, will cause ischemia-related end organ injury and, if sustained, death. However, normotension does not equate to normal cardiovascular function. Thus an essential part of the assessment and management of critically ill patients is the continuous assessment and titration of support based upon their specific status and response.[1]

BASICS OF CARDIOVASCULAR PHYSIOLOGY

Because circulatory shock is a central aspect of most forms of critical illness, understanding basic principles of cardiovascular physiology is essential to the assessment and management of the critically ill patient. Clearly, all aspects of the patient, including neurologic control, gas exchange and ventilation, renal solute clearance, gut substrate absorption, hepatic and reticuloendothelial clearance, immune function and metabolic support, and appropriate endocrine function are essential vital components of body homeostasis. Still, in the resuscitation of the critically ill patient, if blood flow of oxygenated blood to the tissues at an adequate perfusion pressure is not achieved, then perfusion-associated organ injury will develop and all other measures will be meaningless. Thus a central tenet in acute resuscitation is reflected in restoring cardiovascular homeostasis. Indeed, basal organ system function and its reserve to meet increased metabolic demand define health and disease and the patient's ability to respond to therapy. The manner by which the bedside clinician infers the patient's physiologic state is by inspection, examination, and the use of various hemodynamic monitoring approaches that quantify specific physiologic parameters, such as blood pressure, cardiac output, and tissue perfusion.

The cardiovascular system is composed of blood vessels, circulating blood volume, and two hydraulic pumps that work collectively to meet the immediate metabolic demands of the body. Axiomatically, the heart can pump out only what blood it receives; thus the primary determinant of cardiac output is the rate of venous blood flow back to the heart, referred to as venous return. The left ventricle provides the hydraulic pressure necessary to sustain a high central arterial pressure essential to allow for the control of blood flow distribution among the various vascular beds and to supply in the steady state a higher mean systemic pressure than right atrial pressure to allow blood flow back to the right ventricle to be unimpeded. The total circulating blood volume remains relatively stable because the vascular endothelial lining, referred to as the glycocalyx, functions as an oncotic filter, whereas the tight junctions of the vascular endothelium function as the hydrostatic filters, allowing a dynamic equilibrium of blood volume to be created. All of these systems are innervated by autonomic sympathetic and parasympathetic efferent and afferent nerves that can locally or systemically alter tone and contractility. Increased sympathetic tone not only increases vasomotor tone and contractility but also causes tachycardia, a cardinal sign of circulatory stress.

The actual effective circulating blood volume, that amount needed to create an effective pressure gradient to sustain venous return despite markedly changing metabolic and physical demand, is highly variable and can change in seconds to meet those demands or induce cardiovascular collapse. The body regulates the effective circulating blood volume by altering blood flow distribution among various tissues with varying degrees of stressed and unstressed venous capacitance and varying degrees of resistance to venous return. For example, the mesenteric circulation (gut) has a high unstressed volume owing to the large potential capillary and venular space and a high output resistance as all blood must flow through a second organ, the liver, before reaching the right heart. Thus, for the same total blood volume, if more blood were shifted into the mesenteric circulation, all else being equal, the mean systemic pressure would decrease and the resistance to venous return would increase; thus for the same right atrial pressure, cardiac output would decrease. Similarly, by increasing sympathetic tone, thus diverting blood away from the gut while simultaneously increasing vascular tone and myocardial contractility, cardiac output will increase and right atrial pressure will decrease for the same blood volume.

Cardiac function has two primary roles. The first is to deliver all the blood each ventricle received with each heart beat so as not to allow filling pressure to raise while simultaneously sustaining an adequate enough output pressure to allow for blood flow autoregulation. Accordingly, because right atrial pressure is the back pressure to venous return, normal subjects have a right atrial pressure approximating zero to minimize any impediment to venous return. Heart failure, for its part, defines the filling pressure required to create a given stroke volume and their maximal limits. Furthermore, if severe pump failure develops, the left ventricle is no longer able to generate high systolic pressure while simultaneously requiring a higher filling pressure promoting hydrostatic pulmonary edema, the two hallmark signs of cardiogenic shock. The reason why humans have such a high mean arterial pressure is to force blood flow not into organs but to all those individual vascular beds to autoregulate their own local blood flow based on their own local metabolic demands. The arterial circuit is composed of a relatively stiff central capacitor comprising the aorta and the arteries serially linked to distal high resistant arteriole and their associated precapillary sphincters. With the exception of the kidney and lung, local metabolic demand defines local end-organ arterial tone. If metabolic demand increases, as with feeding/digestion, then the mesenteric arterioles dilate locally and inflow to those tissues increases. Arterial pressure is only relevant as it allows for blood flow regulation. Systemic hypotension abolishes autoregulation and is the primary rationale for the defense of blood pressure during the acute phase of resuscitation from circulatory shock. Thus right atrial pressure, effective circulating blood volume arterial tone, and cardiac contractility are intimately intertwined. These points can be described by two relations: (1) the relation between cardiac output and dynamic changes in right atrial pressure as blood volume and cardiac contractility vary

(Fig. 2.1) and (2) the relation between left ventricular stroke volume and mean arterial pressure as cardiac contractility varies (Fig. 2.2), arterial tone varies (Fig. 2.3) or end-diastolic volume varies (Fig. 2.4).

From this brief overview, we can come up with a few relevant conclusions (Box 2.1). First, tachycardia is a nonspecific sign of stress and should not be ignored, even if all other aspects of the patient seem adequate. What stress is causing the tachycardia must be discovered and, if the result of a pathologic process (e.g., hypovolemia, heart failure, vascular obstruction, reactive from hypovolemia), treated. Second, systemic arterial hypotension is a medical emergency because it reflects loss of normal homeostasis. Hypotension must be associated with loss of autoregulation of blood flow distribution, and this usually is associated with vital tissue (e.g., heart, kidney, and brain) hypoperfusion. Third, there is no "normal" cardiac output. Cardiac output is an adaptive hemodynamic value that varies as metabolic demand varies. Often significant changes in metabolic demand can occur without obvious external signs of change. Thus global blood flow values must be targeted to organ

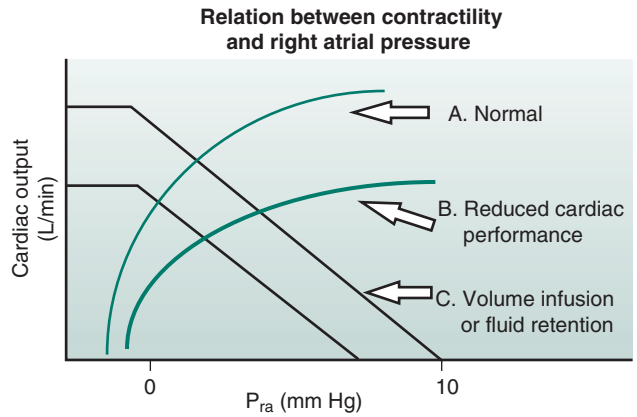

FIGURE 2.1 Theoretical relationship between steady state cardiac output and right atrial pressure (P_{ra}) across varying right atrial pressures as total blood volume increases and contractility decreases. Note that for any given blood volume and contractility, there exists only one right atrial pressure-cardiac output solution possible, referred to as the equilibrium point.

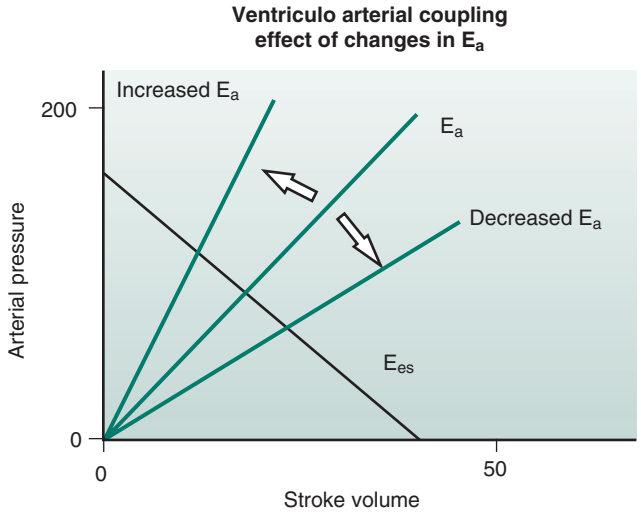

FIGURE 2.2 Theoretical relationship between mean arterial pressure and left ventricular stroke volume at a constant left ventricular end-diastolic volume, as left ventricular stroke volume is varied over varying levels of arterial vasomotor tone, quantified as arterial elastance (E_a). On the same diagram is the relationship between left ventricular stroke volume and mean arterial pressure as mean arterial pressure is varied. Increases in arterial tone result in greater increases in pressure for the same increase in stroke volume as seen when arterial tone is less. Note that as arterial tone increases (increased afterload), left ventricular stroke volume must decrease.

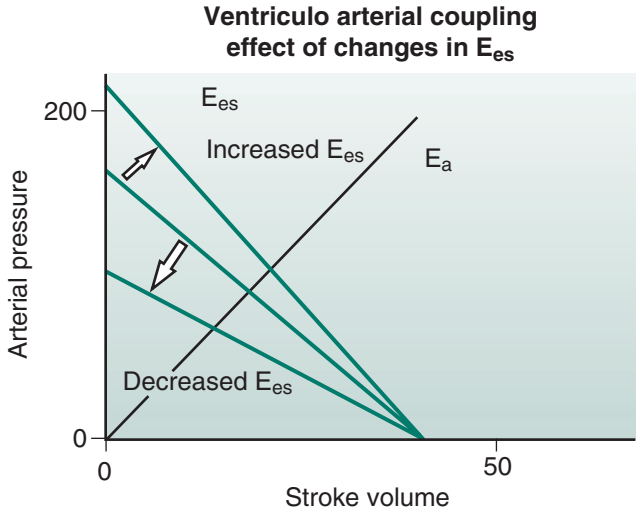

FIGURE 2.3 Theoretical relationship between mean arterial pressure and left ventricular stroke volume at a constant left ventricular end-diastolic volume, as left ventricular stroke volume is varied over varying levels of left ventricular contractility, quantified as end-systolic elastance (E_{es}). On the same diagram is the relationship between left ventricular stroke volume and mean arterial pressure as left ventricular stroke volume is varied. Increases in cardiac contractility result in greater increases in stroke volume for the same arterial tone. Note that as cardiac contractility increases, left ventricular stroke volume and mean arterial pressure must increase.

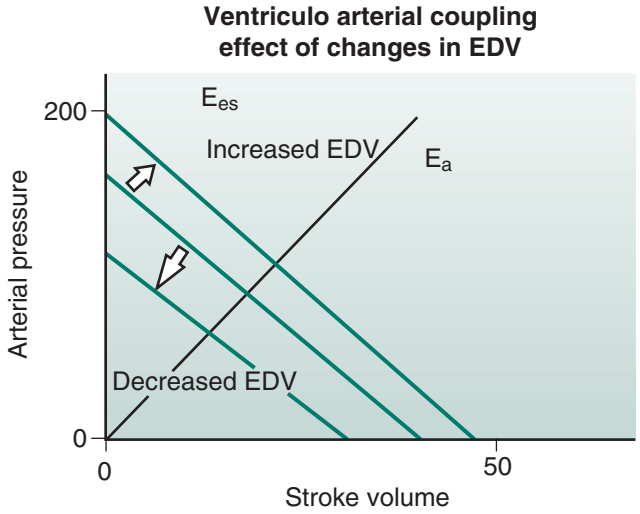

FIGURE 2.4 Theoretical relationship between mean arterial pressure and left ventricular stroke volume as left ventricular end-diastolic volume (EDV) is varied. On the same diagram is the relationship between left ventricular stroke volume and mean arterial pressure as mean arterial pressure is varied. Increases in left ventricular end-diastolic volume (preload) result in matched increases in mean arterial pressure and left ventricular stroke volume, similar to that seen by isolated increases in cardiac contractility.

BOX 2.1

Insights Into Cardiovascular Signs of Insufficiency

- Tachycardia
  - Nonspecific stress
- Arterial hypotension
  - Loss of vital homeostasis causing loss of blood flow regulation
- No normal cardiac output
  - Cardiac output is adaptive to changing metabolic demands
- Central venous pressure rises only in disease
  - Normally it is close to zero as to not limit venous return

perfusion metrics (e.g., blood lactate, venous O_2 saturation, venoarterial CO_2 gradient), not to some extrinsically defined value. Fourth, ventricular filling pressures, both right and left atrial pressure, estimated by central venous pressure and pulmonary artery occlusion pressure, respectively, do not reflect volume status but can be used to define contractility and the threat of further fluid resuscitation to cause compromise. Central venous pressure raises are a stopping rule for fluid infusion because they connote right ventricular failure and impending acute cor pulmonale. Similarly, pulmonary artery occlusion pressure rises are also a stopping rule for fluid infusion because they connote left ventricular failure and impending hydrostatic pulmonary edema. Finally, all responses to stress are by necessity a coordinated response across all appropriate parts of each organ system and the body as a whole. Thus, although hypotension may decrease total blood volume, effective circulating blood volume, cardiac output, and arterial pressure may remain unchanged because of the dynamic effects on contractility, blood flow distributions, and vasomotor tone listed above. It is the interaction of these different adaptive mechanisms and not each mechanism alone that defines the pathologic signatures of disease states.

CIRCULATORY SHOCK: RESUSCITATION GUIDELINES AND PROTOCOLS

Recently, several large prospective clinical trials on the emergency department treatment of circulatory shock, usually resulting from sepsis, have not been able to prove that protocol-based resuscitation is superior to aggressive resuscitation titrated to individual patient needs.[2] Although these findings should not surprise anyone, they do underscore the reality that resuscitation must be titrated based on known physiologic principles and then these physiologic principles must be applied in a continuous and titrated manner based on the patient's specific responses. The principles of critical care management have been presented as a play in four acts: salvage, optimization, stabilization, and deescalation.[3]

The first act is rescue, when the primary goal is merely to keep the patient alive long enough for other more definitive treatments to start to work while preventing further tissue ischemic injury, if possible. The focus here is on maintaining an adequate mean arterial pressure primarily to support cerebral and cardiac blood flows. Assuming that the critically ill patient initially is seen in either circulatory shock, acute respiratory failure, or a combination of both, initial resuscitation includes maintenance of a patent airway, adequate ventilation and oxygenation, intravascular fluid infusions if hypovolemia and decreased effective circulating blood volume are presumed, and if hypotension persists, adding vasopressors to support arterial pressure. Within this context, cardiac output is important only to sustain an adequate organ perfusion pressure. Although the threshold mean arterial pressure must be personalized, based on prior known values, especially if the patient has preexisting hypertension, an initial mean arterial pressure target of 65 mm Hg is reasonable. Similarly, respiratory efforts to keep arterial oxygen saturation above 88%, with adequate ventilation, is also indicated. Clearly, if there are any life-taking ongoing processes, such as massive hemorrhage, severe trauma, acute myocardial infarction, or acute intraabdominal processes, emergent plans must be made during this time to definitively address these individual processes. Realistically, these minimal goals should be established within the first 30 to 60 minutes of care.

Once patients have a viable blood pressure, they are essentially not dying from hypoperfusion of the heart and the brain, but resuscitation has only just begun. At this point, the focus turns to reversing the primary processes causing the initial cardiorespiratory insufficiency while simultaneously optimizing cardiac output to sustain adequate organ blood flow. This phase of care focuses on assessment of end-organ function and identifying and treating any reversible causes of shock. Because there is no "normal" cardiac output, knowing a specific value does little to aid in optimization interval unless its value is at the extremes of high or low. Changes in cardiac output in response to resuscitative therapies is as important as knowing the actual mean cardiac output value, because the goal is to reestablish end-organ perfusion. Thus the parameters monitored now are those assessing end organ blood flow and oxygenation. These include on the physical examination level of consciousness, urine output, skin mottling, capillary refill, and peripheral skin temperature. Metabolic markers such as blood lactate, venous blood oxygen saturation, and arterial to venous CO_2 gradients are useful but do not replace a careful and repeated physical examination. Also blood lactate levels are often problematic because failure to clear lactate, if elevated (i.e., >2 mmol/L) may reflect washout of tissue lactate by the newly increased organ blood flow, impaired liver extraction, or non–perfusion-associated elevations, as seen in severe sepsis. If lactate levels do decrease, they will do so over hours and must be monitored over time. The optimization phase often requires advanced hemodynamic monitoring to assess the impact of mechanical ventilatory support and vasoactive therapies. This phase of resuscitation should be completed within 4 to 6 hours of admission, if not sooner.

Once blood flow has been established, the care moves into the stabilization period, which can last from several hours to several days depending on the extent of end-organ injury and need for aggressive organ supportive measures, such as mechanical ventilation, hemodialysis, antibiotics, and specific surgeries as indicated. This is often the most difficult time in the management of the critically ill. Overzealous resuscitation extending beyond optimization phase can lead to massive fluid overload, interstitial edema, intraabdominal hypertension, and impaired oxygenation. Regrettably, no clear guidelines exist as to when to stop giving fluid therapy, but at a minimum, fluids should be withheld if the patient is not volume responsive and if they a rent displaying singed of tissue hypoperfusion. If patients have signs of tissue hypoperfusion, as listed earlier, and they are also not volume responsive, then the use of cardioactive therapies to augment cardiac function (e.g.,

dobutamine) and support organ perfusion pressure (e.g., norepinephrine) is indicated. During this time, if antibiotics are given, their specific dose and nature must be focused as narrowly as possible to minimize complications and the emergence of drug resistance. Similarly, homeopathic treatments (e.g., head of the bed elevation, stress ulcer and venous thrombosis prophylaxis) must be started and maintained as long as risk is present (e.g., intubated and mechanical ventilation).

It is not clear when deescalation of therapies should start. However, as a general principle, if a patient does not need a treatment to sustain normal homeostasis, it should be removed. This is the general principle for weaning from mechanical ventilation and also should be used for weaning from vasoactive drug therapies, intravascular fluid infusions, starting or increasing enteral feeding, and as third space fluid mobilizes postresuscitation, often diuretics to minimize edema and aid in diuresis. Patients with persistent renal insufficiency often need dialysis to remove this excess fluid, even if not otherwise requiring renal replacement therapy.

SEPSIS AND SEPTIC SHOCK

The most common process causing organ injury and death in the critically ill patient is sepsis resulting from infection.[4] Often this is an expected end point in the process of dying and only facilitates the dying process. However, sepsis occurs across all critically ill patients, many of whom would otherwise survive. Unlike other forms of circulatory shock, sepsis represents a protean systemic inflammatory process that encompasses altered immune responsiveness, metabolism, endocrine function, and peripheral vascular autoregulation. Although aggressive resuscitation and appropriate antibiotics are highly effective at reversing this process if started very early, often treatment is delayed. This delay may be due to delayed entry of the patient into the acute care system because the infectious process initially appeared benign or because of failure of the acute healthcare system to identify patients progressing into sepsis from simple flulike symptoms. Still, in the patient presenting with sepsis associated with hypotension and evidence of new end-organ injury, it is not clear if aggressive resuscitation alters outcome. This is because cellular injury and adaptation often develops with sustained systemic inflammation. It is unclear if resuscitation efforts will improve microcirculatory blood flow. Even if fluid and vasopressors restore organ perfusion pressure and microcirculatory flow, it is not clear that the cells being perfused will respond with increased metabolic activity and recovery, as seen in patients with primarily hypoperfusion-induced organ injury. In septic shock patients with evidence of new end organ injury, the goals of resuscitation are less clear and the potential for complications higher than with other forms of circulatory shock. At present, the clinical literature supports aggressive initial resuscitation to restore blood pressure, but after that most literature supports remaining in a stabilization period until the signs of infection abate.

SUMMARY

This introductory overview emphasized the complex processes, often with autonomic nervous system oversight, that interplay to maintain a relatively stable internal environment and outward signs of health. The signs of diminished organ system health reflect initially decreased metabolic reserve and then increased sympathetic tone at rest. Once organ failure becomes overtly obvious, the process has become far advanced. Potentially, the most effective way to identify impending organ system failure is to continually assess organ system reserve using functional physiologic monitoring tests. However, earlier identification of progressive organ injury may allow for earlier treatment of the initiating process, if a known treatment exists.

Key Points

1. Cardiovascular resuscitation from circulatory shock requires an understanding of the key processes that define cardiovascular homeostasis.
2. The primary determinant of oxygen delivery to the body that can be easily mediated is cardiac output.
3. Cardiac output is primarily determined by the interaction between the effective circulating blood volume, vasomotor tone, and cardiac performance.

A complete reference list can be found online at Expert-Consult.com.

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