Cardiovascular insufficiency commonly occurs in critically ill patients and may be the reason for intensive care unit (ICU) admission or a complication of treatment or disease during ICU stay. If cardiovascular insufficiency is associated with inadequate O2 delivery to the tissues, then the patient is said to be in shock. The management of shock-like states depends on both the etiology of the condition and attaining certain cardiovascular targets of blood flow, O2 delivery and perfusion pressure. Thus, the physician caring for such individuals needs to have a rational approach to both the diagnosis of shock and its resuscitative therapy.

Shock is a circulatory state characterized by inadequate delivery of nutrients and O2 delivery to meet the metabolic requirements of the tissues. Shock etiologies have been traditionally divided into four broad categories based on pathophysiologic mechanisms: hypovolemic, cardiogenic, distributive, and obstructive.

Although resuscitation of patients in shock may restore adequate global O2 transport, it may not restore blood flow to damaged vascular beds due to the associated alterations in auto-regulation and microvascular blood flow.

Clearly, any given patient may demonstrate qualities that blur the separation of shock into these specific states. Still, the most common quality of a shock-like state is hypovolemia, as characterized by hypovolemic shock. In hypovolemic shock, the vascular volume is near or below the stressed volume, resulting in a profound decrease in venous return. Independent of any changes in vasomotor tone or cardiac pump function, a loss of 30-40% of the circulating volume will lead to marked hypotension and organ hypoperfusion. Although not clearly documented in humans, in animal models of hemorrhagic shock, a greater than a 40% loss of intravascular volume can result in irreversible shock and death if not treated effectively with fluid resuscitation in less than two hours.

The normal physiologic response to a hypovolemic stress is to increase sympathetic output that increases vascular tone and thus reduces unstressed volume. The resultant effect is to increase upstream pressure in the venous reservoirs increasing venous return. The associated increased sympathetic tone increases heart rate, contractility and cortisol secretion. Furthermore, the associated release of aldosterone from the adrenal cortex increases sodium and water reabsorption in the kidney. Although these endocrinological responses are effective in restoring intravascular volume in the long run, over the immediate resuscitative interval they only serve to prevent sodium excretion.

Cardiogenic shock reflects any process wherein inadequate ventricular pump function induces hypoperfusion. Cardiac arrhythmia, ischemia, infarction, valvular dysfunction, or myocardial failure are all capable of inducing cardiogenic shock.

Myocardial failure may also be secondary to systemic metabolic processes such as hypoxia, acidemia, hypothyroidism or hyperthyroidism. Only a small percentage of subjects with cardiogenic shock will demonstrate increased cardiac output in response to isolated inotropic during administration. Thus, patients demonstrating cardiogenic shock need to have their etiology quickly and accurately identified if appropriate etiology-specific therapy is to be given.
Distributive shock represents a state in which the body loses its ability to autoregulate blood flow. Loss of vascular integrity often occurs in response to sepsis (malignant intravascular inflammation), adrenal cortical insufficiency, hypocalcemia and with the infusion of vasodilator drugs. Presently, physician's interest in distributive shock focuses on systemic inflammatory states, such as severe sepsis, burns, pancreatitis and trauma. In these conditions, cytokine activation and release into the systemic circulation commonly occurs and induces a generalized inflammatory response characterized by up-regulation of vascular endothelial inducible nitric oxide synthase (iNOS), release of arachidonic acid metabolites and primary vascular smooth muscle dysfunction 4-5-6. Moreover, localized production of nitric oxide, O2 radicals, prostaglandins, platelet aggregating factor, and up-regulation of CD11b/CD18 receptors on leukocytes lead to loss of capillary integrity, adherence of circulating leukocytes to the vascular endothelium, and localized disruption of the microcirculation 4-6-8-9-10. Importantly, one needs not evoke infection to see this systemic response. Severe trauma also displays a similar sustained inflammatory mediator activation state.

Non-cardiogenic obstructive shock includes all causes of diminished cardiac output secondary to compression on the vascular system or obstruction to blood flow other than from valvular disease, such as tension pneumothorax, pericardial tamponade, constrictive pericarditis, pulmonary embolism, and acute pulmonary hypertension with acute cor pulmonale. Pulmonary embolism and acute pulmonary hypertension deserve special mention, since both cause shock by inducing right heart failure and diminished left ventricular end diastolic volume. An acute rise in pulmonary artery pressure from massive pulmonary emboli or hypercarbic respiratory failure leads to dilation of the right ventricle. This in turn displaces the intraventricular septum toward the left ventricle, and by the process of ventricular interdependence, decreases left ventricular diastolic compliance. The resulting decrease in preload leads to diminished cardiac output. Thus, treating such patients with fluid resuscitation will induce only more right ventricular dilation and worsen the obstructive state.

Goals of Therapy. The individual who is in shock may exhibit a wide range of clinical signs (associated with increased sympathetic tone). There is no universal set of variables that may be assessed to determine the presence or absence of shock. The determination of shock is often made clinically from the history and physical examination. Patients often present with tachypnea and dyspnea as early signs of cardiovascular deterioration. They may appear pale, diaphoretic, with cold, clammy skin, or may appear warm, erythematous, and dry. The blood pressure may be normal, elevated, or low, and the heart rate may be tachycardic, bradycardic, and rarely normal. Urine output is often diminished, and mentation impaired. On laboratory evaluation, a metabolic acidosis may be present with elevation of serum lactate, excesses chloride loading or be unexplained 11-12. Except in acute hypovolemic shock the metabolic acidosis is in excess to that explained by anaerobic metabolism (lactic acidosis) alone. However, this is neither sensitive nor specific for the presence of shock 13.

The arterial blood gas analysis may reveal a respiratory alkalosis, metabolic acidosis or a combination of the two. Since the signs of circulatory shock can be non-specific, it follows that the end-points of therapy may also be difficult to define.
Resuscitation of shock can be divided into primary and secondary periods. The primary period is the time from initial evaluation through the first round of resuscitation. The goals during this period are cardio-pulmonary-cerebral resuscitation. Basic and advanced life support principles are utilized with the initial goal being attainment of an adequate coronary and cerebral perfusion pressure and perfusion of the tissues with oxygenated blood. This encompasses establishment of an adequate airway and, if necessary, mechanical ventilation, restoration of productive cardiac rhythm and forward blood flow, and attainment of a mean arterial blood pressure > 60 mm Hg. Without reaching this immediate goal, all other resuscitative goals are of questionable value and thus should not be considered alone. Once mean arterial blood pressure is adequate to maintain cerebral and myocardial perfusion, then the secondary period of resuscitation begins. The goals of this period are:

1. establishment of an adequate organ perfusion pressure for all organs,
2. establishment of adequate organ blood flow, and
3. establishment of adequate O2 transport to the metabolically active tissues.

The first two goals are reached by utilizing volume expansion and vasoactive agents, often using data acquired by invasive hemodynamic monitoring via a pulmonary artery (PA) catheter. Although the utility of the PA catheter in treating patients in shock has been questioned, data derived from the PA catheter is often critical in establishing the correct etiological diagnosis.

Improving O2 content, cardiac output and vascular responsiveness accomplish the third goal in acute resuscitation. Delays in resuscitation of the previously healthy subject now in shock may render them not responsive to aggressive therapy later on, in an analogy to the irreversible shock model described by Wiggers in the 1920s.

In support of this hypothesis is the recent large single center clinical trial of early goal-directed therapy for the management of severe sepsis. This study documented a marked improved outcome when subjects were aggressively treated for circulatory shock in the Emergency Department during the initial 6 hours of hospitalization rather than waiting for them to be transferred to the ICU for better monitoring. That study focused on rapidly achieving not only an adequate mean arterial pressure, central venous pressure and urine output, but also an adequate degree of tissue perfusion, as assessed by superior vena caval SO2 (SsvcO2).

This study is in stark contrast to the negative results of numerous large studies that aimed to improve survival for subjects once transferred into the ICU using similar resuscitation end-points. These negative studies do not mean that resuscitation is ineffective to support life in the patient in shock. They merely demonstrate that there is no specific level of TO2 or mixed venous O2 saturation that one must attain to insure a good outcome. Clearly, what are needed are real time measures of tissue wellness and metabolic function, such as gastric tonometry, or functional measures of cardiovascular responsiveness. Unfortunately, such non-invasive metabolic monitoring devices have yet to be validated as superior to non-specific measures presently available. Potentially, the lack of documented benefit of these many non-invasive measures reflects inadequate study design.
Is there an optimal hematocrit? Assuming that one has established an adequate mean arterial pressure, then one needs to insure that O2 transport (TO2) out of the heart to the body is adequate to meet the metabolic demands. Traditionally, resuscitation guidelines have mirrored the determinants of TO2. TO2 is equal to the product of cardiac output and arterial O2 content (CaO2). CaO2 in turn is equal to the amount of O2 adsorbed onto hemoglobin and dissolved in the plasma. Since 1200 times more O2 is carried on hemoglobin than dissolved in the plasma one usually ignores the plasma component of TO2.

The ideal hemoglobin concentration is unknown, but based on experience with Jehovah’s Witnesses, it seems the lowest limit tolerable below which even otherwise healthy people suffer cardiovascular collapse is 2-5 gm/dl 26-27-28-29. Many patients have done well during and after surgery despite very low hemoglobin and hematocrit levels as long as they can maintain adequate tissue perfusion and cardiac output. This infers that the body is able to augment cardiac output to sustain TO2. All else being equal, there seems to be little evidence to resuscitate a stable patient with a hematocrit > 20% with red blood cells 30. Rather, packed red blood cells (PRBC’s) should be transfused to specifically correct evidence of tissue ischemia or hypoxia or to reverse a high output-induced myocardial ischemia or failure state. Animal data suggest the maximum systemic extraction ratio for O2 is about 70%, with each organ having its own O2 requirements 31. If O2 transport fails to meet this minimum, then O2 consumption will be dependent on organ blood flow 12-31-32. Although we do not know the optimal hemoglobin concentration, aiming for adequate organ perfusion and O2 delivery with PRBC transfusions is reasonable up to a hemoglobin concentration of about 7 gm/dl 33-34. Above this, any additional benefit in O2 delivery is offset by increases in blood viscosity. Moreover, stored blood is depleted of 2,3-diphosphoglycerate, causing it to be very oxygen-avid, further limiting O2 utilization 35.

Fluid Resuscitation. Patients presenting with most forms of shock, excluding acute left ventricular failure with cardiogenic pulmonary edema, are initially responsive to intravascular volume replacement. Initial resuscitation, therefore should include intravascular volume replacement as part of a diagnostic and treatment strategy. For example, failure to show any significant increase in mean arterial pressure after rapid bolus infusion of crystalloid despite an increase in right atrial pressure usually signifies the need for vasoactive drug support. An adequate fluid challenge is defined as one in which either end-organ blood pressure or cardiac output increases (volume responsive); or in which either heart rate decreases or left ventricular filling pressure or central venous pressure increases without changes in systemic blood flow measurements (volume resistant).

The choice of crystalloid or colloid solutions to treat a patient in shock is based more on religion than on science. Crystalloids are solutions that contain sodium as their major osmotically active particle 36. Lactated Ringer’s and normal saline (0.9% NaCl) are examples of frequently used isotonic crystalloids. However, normal saline is still slightly hypertonic and carries a profoundly elevated chloride content relative to intravascular fluid. Hyperchloremic metabolic acidosis is a common occurrence in the ICU and is usually due to saline resuscitation. It is unclear, however, if the hyperchloremic metabolic acidosis induced by normal saline adversely affects outcome. Colloids are fluids with large molecular weight substances that do not readily pass across capillary walls 36. Examples include albumin solutions, dextran, and hetastarch.
Hetastarch gelatins are carried in a normal saline vehicle, thus they share the chloride load problems with normal saline. However, since one often gives less colloid than crystalloid, this concern is less important. Newer gelatins include put hetastarch in a lactated Ringer's-like vehicle, thus minimizing the chloride loading.

Recent interest in excess mortality in subjects given albumin has arisen. However, a large double blind multicenter trial of crystalloid versus albumin is presently underway in Australia to address this and other issues. Thus, conclusions about the risks and benefits of albumin infusions will need to wait until this trial is concluded. Infused albumin has a plasma half-life of approximately sixteen hours, but its effect lasts for approximately twenty-four hours. 25% albumin expands the vascular volume by translocation of interstitial fluid, such that for each 100 ml of 25% albumin given, the vascular volume will increase by 450 ml. Other albumin containing solutions have a near-physiologic colloid osmotic pressure, and therefore expand the vascular volume by 1 ml for each ml given.

Dextran is a synthetic colloid that is rarely used because of its associated side effects 37-38. Hetastarch is also a synthetic colloid solution. It comes as a 6% solution in normal saline (Hesban®) or lactated Ringers (Hextend®) and functions similarly to 5% albumin solutions. It has a very long plasma half-life (17 days) and unlike dextran, is non-immunogenic 39. Potential problems with hetastarch infusions arise when massive resuscitation is given (>1500 ml) wherein one may see an elevation of serum amylase, osmotic diuresis, and increase bleeding tendency 39.

Colloids have several potential benefits, such as greater sustained intravascular volume presence and less edema formation, while being much more expensive. Despite all the potential benefits of using colloid as part of resuscitation, there is no proven benefit in outcome. A meta-analysis of eight studies in sepsis showed an overall 5.7% relative decrease in mortality in patients resuscitated with crystalloids alone, and a 12.3% difference in favor of crystalloid in trauma patients. A 7.8% difference was found in favor of colloid use in medical patients 40. Due to the relatively few studies included in this analysis, it is difficult to make any conclusions regarding benefit in survival by use of colloid versus crystalloid.

Vasopressors. Since the goal of the primary resuscitation period is to obtain an adequate cerebral and coronary perfusion pressure, if this cannot be done with volume therapy alone, or if the blood pressure is profoundly depressed, then use of a vasoactive agent is required. These agents may also be necessary during the secondary resuscitation period to maintain adequate organ perfusion pressure and cardiac output in the setting of inflammatory mediator-induced pathological vasodilation. Selective use of agents may augment blood pressure and cardiac output to achieve the desired goals, but which agent is used often does not matter as long as the desired goals are achieved.

Vasopressors induce their response by stimulating the α-adrenergic receptors on vascular smooth muscle cells. β-adrenergic receptor stimulation augments contractility and induces vasodilation and tachycardia. Several vasopressor agents are available with varying degrees of α-, β- and vasopressin-2 receptor activity.
Phenylephrine is a pure $\alpha$ agonist and isoproterenol is a pure $\beta$ agonist. All other vasoactive agents have varying degrees of effect on both $\alpha$ and $\beta$ types of receptors. The most potent vasoactive agent is epinephrine, since this will stimulate all adrenergic receptors. Dopamine is often used in states of shock to preserve renal function, however, no study has demonstrated a proven protective effect of dopamine on renal function and a recent large multicenter trial powered to show no effect documented no effect of low dose dopamine on the development of renal failure in post-operative surgical ICU patients. In septic shock, dopamine has not been shown superior to other agents such as dobutamine and norepinephrine in obtaining target values for O2 delivery and O2 consumption. Furthermore, dopamine increased splanchnic O2 requirements over that of norepinephrine. Finally, other agents such as dopexamine may produce similar hemodynamic profiles and renal preservation in patients with reduced cardiac index following coronary artery bypass surgery. Furthermore, in a retrospective study of similarly matched subjects given norepinephrine versus all other vasopressor, Martin et al. demonstrated that those subjects treated with norepinephrine had a markedly reduced mortality.

Sepsis is associated with a reduction in vasopressin-2 receptor activity, making vascular smooth muscle cells less responsive to a-adrenergic stimulation. Infusions of low does vasopressin may reverse this desensitization. However, higher does of vasopressin induce profound splanchnic vasoconstriction. Thus, it is not clear that vasopressin infusions will improve outcome in distributive shock states. A large multicenter clinical trial of vasopressin is on going. We shall need to await the results of this trial before making any conclusions about the use of vasopressin in shock.

What are the targets for cardiovascular resuscitation? Based on the clinical trials of early goal-directed therapy, vasopressor-induced ischemia and inflammation and unclear benefits from hemoglobin-based resuscitation the following approach seems reasonable. First, in the hypotensive patient restoration of a mean arterial pressure to > 60 mm Hg in a previously normotensive subject by the rapid infusion of volume and, if needed, vasopressor, is indicated to prevent and/or reverse cerebral and coronary ischemia. Second, rapid diagnosis of the etiology of shock should be undertaken. Except in the setting of obstructive or cardiogenic shock, volume resuscitation is the mainstay of initial therapy. The choice of fluid is optional, but lactated Ringers solution seems like a reasonable choice if blood products are not going to be infused simultaneously.

The choice of vasopressor agent is still not defined, but norepinephrine is gaining increased usage because of its therapeutic profile. In the setting of cardiogenic or obstructive shock, although inotropic agents may transiently increase cardiac output, every effort needs to be done to make the diagnosis and treat the primary problem because few of the etiologies that induce either of these two types of shock respond to inotropic drug infusion alone. The infusion of packed red blood cells to treat patients with concomitant anemia and circulatory shock is problematic. In the setting of reduced cardiac reserve, red blood cells may be life saving, whereas in the otherwise healthy patient, there is little data to defend transfusing to a hematocrit above 25%. Clearly, the attempt in a resuscitated ICU patient to sustain TO2 at some defined elevated level is not justified.
Targets for resuscitation from shock

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