Oxygen delivery

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Wanting to conserve whatever oxygen remained in my tank, I asked him to reach inside my backpack and turn off the valve on my regulator, which he did. For the next ten minutes I felt surprisingly good. My head cleared. I actually seemed less tired than with the gas turned on. Then, abruptly, I felt like I was suffocating. My vision dimmed and my head began to spin. I was on the brink of losing consciousness. Instead of turning my oxygen off, Harris, in his hypoxically impaired state, had mistakenly cranked the valve open to full flow, draining the tank. I'd just squandered the last of my gas going nowhere.—Jon Krakauer, mountain climber, describing the effects of improved and impaired oxygen delivery near the summit of Mount Everest (1)

From the elevations of mountaintops to the depths of the ocean, life seeks to sustain itself through its supply of oxygen. In humans, the struggle against death, from any cause, is the struggle to maintain or restore adequate oxygen delivery and consumption. Medical personnel responding to all varieties of acutely life-threatening events are governed by algorithms that begin by restoring airway patency, optimizing gas exchange, and ensuring a hemodynamic state that can support effective distribution of oxygen to the tissues. In this review, we will focus on the advances that have lead to our current knowledge of the pathophysiology of oxygen delivery.

Evolutionary Perspectives

In our absolute need for oxygen, we are no different from the unicellular organisms from which we evolved. Single-cell eukaryotes obtain their oxygen through simple diffusion, a process that is proportional to the difference in partial pressure, proportional to the area of the membrane, and inversely proportional to the distance the gas must travel. Approximately 600 million years ago, single-cell organisms evolved into multicellular forms. The earliest of these species were small, segmented, and highly adapted to meet their oxygen needs by simple diffusion. However, as body plans became more complex, there was a need to overcome the time-distance constraints of diffusion; hence, the evolution of the cardiovascular system as a means to provide bulk flow to the various tissues of the body. Indeed, the body plan of most multicellular organisms can be reduced to the scheme shown in Figure 1. There are four critical steps in the chain of oxygen transport: a) bulk flow from the environment to a highly vascularized surface, whether the skin, gills, or lung; b) diffusion into the blood; c) bulk flow to the various tissues of the body; and d) diffusion into the mitochondrial sink of each and every cell. Note that the scheme does not defy the laws of physics: oxygen transport is ultimately dependent on simple diffusion, at the level of the lung-blood interface and the blood-tissue interface.

Oxygen is poorly soluble in water and plasma. Therefore, most multicellular organisms with a cardiovascular system have evolved to a respiratory pigment that serves to bind and carry oxygen in the blood. In invertebrates, the respiratory pigment (usually hemocyanin, rarely hemoglobin) circulates freely in solution. This observation provides the rationale for developing hemoglobin substitutes in transfusion medicine. In vertebrates, the respiratory pigment (always hemoglobin) is packaged in red blood cells in which it is protected from the oxidative stresses of the environment and in which oxygen binding may be finely tuned according to allosteric and cooperative interactions. The red blood cells of fish, amphibians, reptiles, and birds are nucleated. In fact, the anucleate red blood cell is unique to mammals. There are several possible evolutionary explanations for the loss of the red blood cell nucleus. First, the exclusion of the nucleus would provide more room in the cell for hemoglobin. Second, an anucleate red cell would be predicted to have less weight and increased deformability. Perhaps the most compelling explanation is that a red blood cell without a nucleus is a cell without mitochondria and oxidative phosphorylation. Therefore, the anucleate red blood cell avoids the conflict of interest of being both a consumer and a deliverer of oxygen.

The above perspectives provide a useful framework for considering the pathophysiology of oxygen deprivation. Reduced oxygen delivery may arise from the following: a) decreased oxygen levels in the environment; b) impaired diffusion across the lung-blood interface; c) reduced cardiac output; and d) impaired diffusion across the blood-tissue interface. Oxygen consumption, as distinct from delivery, reflects the degree to which the gas is extracted from capillary blood and utilized by the underlying tissues. In short, calculation of oxygen consumption requires knowledge both of oxygen delivery and oxygen extraction. These concepts are further clarified in Figure 2. The present review is focused on shock (abnormalities of cardiac output) as a mechanism of decreased oxygen delivery.

Shock

A 21-yr-old man was involved in a high-speed, all-terrain vehicle crash in a rural area. He was found at the scene to be obtunded, with a palpable carotid pulse, but his systemic blood pressure was undetectable. He was intubated at the scene, and peripheral venous access

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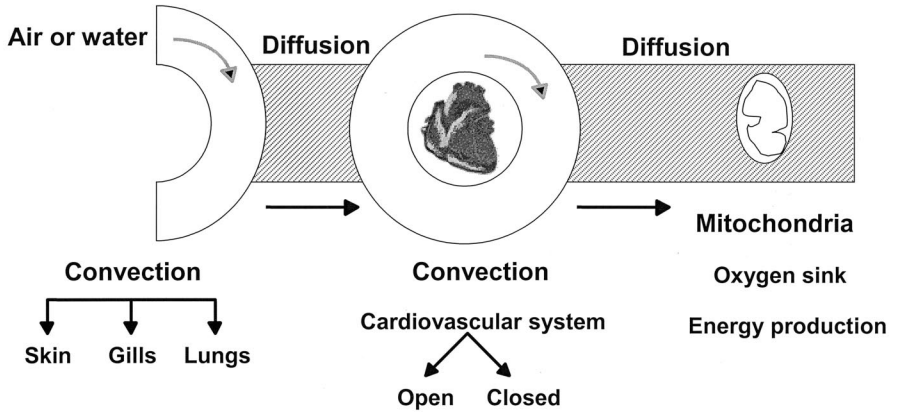

Figure 1. General scheme for oxygen delivery in multiple cellular organisms. From *left* to *right*: oxygen is delivered by convection or bulk flow from environment to vascularized surface, oxygen diffuses across into the blood, oxygen is delivered by convection or bulk flow to the various tissues of the body, and oxygen diffuses into the individual cells of the tissues. Adapted from Weibel ER: The Pathway for Oxygen: Structure and Function in the Mammalian Respiratory System. Cambridge, MA, Harvard University Press, 1984.

A. Fick's Law: O_2 Diffusion α K_x x S/t x (ΔP)

B. Poiseuille's Law: Flow = $\frac{\pi \Delta P x R^4}{8\eta L}$

C. O_2 delivery = cardiac output x O_2 content

= [SV x HR] x [(Hb g/dl)(O_2 saturation)1.39 + 0.0031pO_2]

$\alpha \frac{\pi \Delta P x R^4}{8\eta L}$ x [(Hb g/dl)(O_2 saturation)1.39 + 0.0031pO_2]

D. O_2 consumption = cardiac output x (Arterial $_{O2\ content}$ – Venous$_{O2\ content}$)

Figure 2. Equations describing oxygen delivery and consumption. *A*, according to Fick's law, oxygen diffusion is directly proportional to surface area (*S*) and pressure gradient (ΔP) and inversely proportional to distance (*t*). *B*, Poiseuille's law describes bulk flow of a uniform viscous liquid through a cylindrical tube with a constant circular cross-section. The equation emphasizes the importance of blood viscosity (η) and vasomotor tone in determining bulk flow. Red blood cells (*Hct*) are the primary cellular determinant of blood viscosity. *C*, oxygen delivery is determined by cardiac output and oxygen content. Cardiac output is the product of stroke volume (*SV*) and heart rate (*HR*). Alternatively, cardiac output may be substituted for by the variables in Poiseuille's law. *D*, oxygen consumption takes into account both the degree of oxygen delivery and the extent of oxygen extraction (arterial oxygen content minus venous oxygen content). *Hb*, hemoglobin.

was secured. At hospital arrival, 2 hrs after the traumatic event, he remained sedated, paralyzed, and persistently hypotensive, despite ongoing crystalloid infusion. In addition, he was noted to have significant abdominal distension and a pelvic fracture. In the operating room, a massive hemoperitoneum was observed to be arising from a laceration of the right external iliac vein. Early in the intraoperative course, the patient's blood pressure and end-tidal carbon dioxide became transiently undetectable.

Although this patient's clinical problem is straightforward, namely massive hemorrhage, the underlying physiologic consequences are more complex. Profound hypotension and its circulatory compensations have likely already created an environment of oxygen deprivation and cellular dysfunction or death. The pathophysiologic sequelae of oxygen deprivation could ultimately precipitate organ failure or, through a variety of mechanisms, predispose the patient to a cascade of complications. Reducing the impact of these processes would require attention to all phases of oxygen delivery, including the restoration of adequate circulation of oxygen at the cellular level.

Events at the Circulatory Level. In the setting of acute blood loss, the body compensates through a variety of feedback mechanisms. At the time of his initial rescue, the patient above was already lethargic and hypotensive, suggesting according to the American College of Surgeons classification (2) that he was in class IV shock with an estimated blood loss of >2 L. Life-sustaining circulation was likely being maintained through a combination of the actions of baroreceptor reflexes, the central nervous system ischemic response (profound sympathetic stimulation resulting from cerebral ischemia, "the last ditch stand"), reverse stress-relaxation of the circulatory system, as well as the release of angiotensin and vasopressin and redistribution of extravascular fluid to the intravascular space. Sympathetic reflexes mediated through the release of catecholamines become maximally activated within 30 secs of the hemorrhagic insult. Arterial and venous constriction mediated by reverse stress-relaxation, angiotensin, and vasopressin requires 10–60 mins before making a clinically significant impact on blood pressure. Fluid mobilization from the extravascular space is less important in acute hemorrhage because it is a relatively slow process, taking hours to days to exert an effect.

The negative feedback reflexes are collectively designed to accomplish two goals: to maintain cardiac output by increasing heart rate and preload (through venoconstriction), and more importantly, to maintain blood pressure by causing systemic arterial constriction. Blood pressure after acute hemorrhage is maintained at the expense of further impairment of blood flow to most tissues. Interestingly, the cerebral and coronary circulations do not constrict appreciably in response to sympathetic stimulation and are well preserved, despite significant systemic hypoperfusion. In effect, scarce blood after acute hemorrhage is diverted to the brain and heart until normal intravascular volume can be restored. When compensatory mechanisms are overwhelmed, blood flow to all tissues, including those protected by autoregulation, can be impaired to the point of cellular metabolic dysfunction; this phenomenon is broadly termed *shock* (Table 1).

Table 1. Classification of shock[a]

		Specific Diagnostic Characteristics
Hypovolemic	American College of Surgeons—Committee on Trauma	
	Class 1, <750 mL blood loss	Anxiety
	Class 2, 750–1500 mL	Anxiety, tachypnea (20–30/min), tachycardia (>100/min), hypotension, oliguria (20–30 mL/hr)
	Class 3, 1500–2000 mL	Anxiety, confusion, tachypnea (30–40/min), tachycardia (>120/min), hypotension, oliguria (5–15 mL/hr)
	Class 4, >2000 mL	Anxiety, tachypnea (>35/min), tachycardia (>140/min), hypotension, anuria
Cardiogenic	Forrester Classification	
	Class 1	PAOP, <18 mm Hg CI, >2.2 L/min/m^2
	Class 2	PAOP, >18 mm Hg CI, >2.2 L/min/m^2
	Class 3	PAOP, <18 mm Hg CI, <2.2 L/min/m^2
	Class 4, 51% mortality	PAOP, >18 mm Hg CI, <2.2 L/min/m^2
Vasodilatory	Most common cause is sepsis—SCCM/ACCP definitions:	
	SIRS (any two): T, >38 or <36; HR, >90; RR, >20; WBC, <4 or >12 × 10^9/L	
	Sepsis: evidence of infection + SIRS	
	Severe sepsis: hypotension, organ hypoperfusion, and dysfunction	
	Septic shock: profound hypotension (SBP, <90) despite fluid resuscitation	
Obstructive	Common causes	
	Cardiac tamponade, tension pneumothorax, pulmonary embolism	
	Clinical features	
	Elevated central venous pressures, elevated pulmonary pressures, pulsus paradoxus	

PAOP, pulmonary artery occlusion pressure; CI, cardiac index; SCCM, Society of Critical Care Medicine; ACCP, American College of Chest Physicians; SIRS, systemic inflammatory response syndrome; T, temperature; HR, heart rate; RR, respiratory rate; WBC, white blood cell count; SBP, systolic blood pressure.

[a]All forms of shock are characterized by clinical evidence of progressive organ dysfunction resulting from inadequate oxygen delivery ± compensatory hemodynamic changes: alterations in mental status, tachycardia, normal or low blood pressure, tachypnea, oliguria.

Events at the Cellular Level. Essential cellular processes, such as membrane transport, protein synthesis, and mechanical work, are driven by the energy stored in the high-energy phosphate bonds of adenosine triphosphate (ATP) (3). ATP, in turn, is generated by the interaction of carbohydrate (and protein and lipid) substrates with oxygen. Glucose entering cells is converted to pyruvate through a set of steps referred to as glycolysis. Although a small amount of ATP is generated by this process, much more is generated in subsequent metabolic steps. Pyruvate is converted to acetyl coenzyme A, which is transferred to the mitochondria for participation in the tricarboxylic acid cycle. The tricarboxylic acid cycle generates hydrogen ions, whose oxidation to water releases large amounts of energy that is harnessed by the mitochondrial chemiosmotic mechanism for the production of large amounts of ATP.

The process of oxidation in the mitochondria requires a surprisingly low intracellular oxygen tension. Oxygen usage reaches a plateau when intracellular concentrations of oxygen are >1 mm Hg; this is the critical value above which energy production is commensurate with cellular needs, governed solely by the rate of metabolic activity (i.e., adenosine diphosphate production). However, when blood flow and/or oxygen content are limited, intracellular oxygen tensions may fall below the critical value (<1 mm Hg) and consequently oxygen usage and ATP production may fall. In this circumstance, cellular function may become blood flow limited. Severe illness may compound the energy crisis by causing mitochondrial oxidative dysfunction; for example, substrate use in sepsis may be impaired, despite adequate oxygen delivery because of inhibition of electron transport, touching off a downward spiral of oxygen delivery-independent cellular and organ dysfunction (4).

Reprioritization of metabolic expenditure at the cellular level has been shown to occur and to confer survival benefit in cell lines from hypoxia-resistant organisms. Diminished oxygen tensions may promote adaptive mechanisms aimed at restricting ATP consumption to life-sustaining processes only. Such adaptive metabolic reprioritization may be mediated, in part, by the transcriptional and posttranscriptional effects of molecules, such as hypoxia-inducible factor (HIF)-1 (5).

During hypoxic conditions, protein phosphorylation and alterations in the intracellular redox state may activate and stabilize components of HIF-1, which in turn recognizes a DNA sequence (hypoxia response element) located in the promoter regions of downstream hypoxia-responsive genes. Increased expression of genes responsible for erythropoietin production or production of enzymes important in glycolysis, for example, has been shown to be related to HIF-1 activity. The hypoxia-HIF-1-transcription effects may protect cells during hypoxic conditions. Therefore, if these interactions are adversely affected by inflammatory mediators, as has been postulated, tissues suffering low-oxygen delivery during critical illness may be at profound risk of the damaging effects of hypoxemia (6).

The consequences of severe blood flow limitation on intracellular oxygen usage are varied. Myocyte dysfunction may further impair cardiac output over time, leading ultimately to cardiogenic shock. Endothelial and epithelial hypoxia can cause increased permeability and progressive tissue edema and perhaps induce bacterial or toxic translocation from the gut. Impaired blood flow and hence reduced shear stress may result in altered

transcriptional and posttranscriptional profiles in affected endothelium. Local acidosis may result from the accumulation of pyruvate and its conversion to lactate. Failure of ion transport may result in cellular functional impairment (such as in acute renal failure) or even cell swelling and death. Failure of intracellular barriers (such as lysosomes) can cause the release of toxic hydrolases. Adenosine, which is generated slowly, may diffuse out of cells and be degraded to uric acid. This chain of events may lead to intractable depletion of intracellular energy currency (ATP), a feature of irreversible shock. In sum, these processes, unless detected and addressed early, are interconnected and exert powerful positive feedback effects on each other. The natural conclusion of the cascade of pathophysiologic effects resulting from cellular hypoxia is cellular dysfunction, cell death, and multiple organ failure (7).

Compensated and Progressive Shock. The process of shock is far from linear or predictable. In compensated shock, certain vascular beds are disproportionately affected. The effects of compensation depend on metabolic and organ system reserve. If shock becomes uncompensated, that is, neurologic and hemodynamic consequences of impaired oxygen delivery become evident, the extent of cellular damage and the likelihood of progression to multiple organ failure and death (irreversible shock), even if the inciting event is controlled, are difficult to determine (8).

The effects of resuscitation may themselves be damaging; reperfusion of ischemic tissue beds could flush local inflammatory mediators into the systemic circulation, resulting in oxygen radical-mediated cellular injury, worsened interstitial edema, and/or increased metabolic demands on organs with severely depleted functional reserve. The same therapy may have markedly different effects at different times in the progression of shock-related cellular dysfunction. It is clear that the early diagnosis of shock in the presence of compensatory responses is difficult and that the pathophysiologic mechanisms at work may be highly varied. These factors have posed formidable challenges in the evaluation of oxygen delivery-based therapies.

Diagnosis of Impaired Oxygen Delivery

Clinical and Biochemical Indicators of Shock. Clinical indexes of shock, such as pulse rate, blood pressure, skin temperature, and urine output, are unreliable and slow to change in the presence of compensatory mechanisms; abnormal values may occur only in the late stages of hypoperfusion. Even hemodynamic parameters, such as pulmonary artery occlusion pressure and cardiac output, are prone to misinterpretation in different patients and can be misleading in situations of progressively worsening shock states (9).

Impaired oxygen delivery results in abnormalities in pyruvate metabolism with the subsequent accumulation of lactic acid. Base deficit, serum lactate, anion gap, and pH are used as measures of the degree of acidemia and the magnitude of shock. Although these measurements have sometimes been found to be predictive of surgical complications, multiple organ failure, and mortality, they are global measures and are not sensitive indicators of regional hypoperfusion. In some instances, these global or systemic measures of tissue oxygenation may be normal in the presence of significant regional ischemia (i.e., splanchnic dysoxia) and are, therefore, of less prognostic value than indicators of regional oxygen debt (10, 11).

Direct Measurement of Adequacy of Systemic Oxygen Delivery. In healthy subjects, resting oxygen delivery (Do_2) is approximately 1000 mL/min, and approximately 250 mL/min of this oxygen is required by tissue metabolic processes (Vo_2), so that the usual oxygen extraction ratio is 25%. If oxygen delivery decreases, oxygen extraction by the tissues increases so that oxygen consumption remains relatively constant. The efficiency of extraction varies from tissue to tissue; the myocardium, for example, extracts close to 50% to 90% of its delivered oxygen. Below a critical threshold of oxygen delivery (approximately 4.5 mL/kg/min), increased oxygen extraction can no longer compensate for the delivery deficit; hence, oxygen consumption begins to decrease. From this point, any reduction in oxygen delivery is associated with a decrease in oxygen consumption, and oxygen consumption is, therefore, said to be supply dependent (12). This threshold of oxygen delivery impairment is thought to correspond with progressive cellular functional impairment, and therapeutic efforts are typically aimed at preventing this supply dependency.

In the past, defective oxygen extraction mechanisms in critically ill patients have been thought to make the relationship between oxygen delivery and consumption more linear than biphasic; that is, oxygen consumption is dependent on oxygen delivery across a wide range rather than only below the Do_2crit. Investigators have noted incremental increases in oxygen consumption with increases in oxygen delivery across a broad range of values. This finding has suggested that critically ill patients may exist in a state of pathological supply dependence and relative cellular dysfunction and has, therefore, prompted efforts to increase oxygen delivery to supraphysiologic levels. However, it is now understood that the observed linear correlations between oxygen delivery and oxygen consumption may have been an artifact resulting from calculation of common measurements with potentially large errors. When pulmonary artery catheter-derived measures are used according to the inverse Fick method, both oxygen delivery and oxygen consumption use measurements of cardiac output and arterial oxygen content in their calculation. Errors in these measures are potentially large and by a phenomenon known as *mathematical coupling* may create the impression that cardiac output and oxygen consumption are positively correlated across a wide range of values (13, 14).

$$Do_2 = CO(Hb \times k_1 \times Sa_{O_2} + k_2 \times Pa_{O_2})$$

$$Vo_2 = CO[(Hb \times k_1 \times Sa_{O_2} + k_2 \times Pa_{O_2}) - (Hb \times k_1 \times Sv_{O_2} + k_2 \times Pv_{O_2})] \quad [1]$$

where CO is cardiac output, Hb is the hemoglobin concentration, Sa_{O_2} is the arterial hemoglobin oxygen saturation; Pa_{O_2} is the arterial partial pressure of oxygen, Sv_{O_2} is the mixed venous oxygen saturation, Pv_{O_2} is the venous partial pressure of oxygen, and k_1, k_2 are the oxygen-combining capacity with hemoglobin and solubility constants.

When Do_2 and Vo_2 are calculated using independent methods (i.e., inverse Fick method for Do_2 and indirect calorimetry for Vo_2), the effects of mathematical coupling can be eliminated. Studies using independent methods of calculation of Do_2 and Vo_2 have not demonstrated pathologic oxygen supply dependence (11).

Regional Hypoperfusion in Shock—Diagnostic Implications. The basic circulatory response to hypovolemic shock is redistribution of blood flow to vital tissue beds and away from capillaries supplying

less critical organs. Accordingly, blood flow to the splanchnic organs may be disproportionately reduced in response to hypovolemia, and measurement of this phenomenon may provide a more sensitive indication of impairment of Do_2 than the global measures outlined above. Splanchnic ischemia that leads to a reduction in gut barrier function and translocation of endotoxin, inflammatory mediators, and microorganisms through an ischemic and leaky gastrointestinal mucosa may contribute to the progression of multiple organ failure.

Although uniquely susceptible to hypoperfusion, the gut is unable to tolerate dysoxia for long periods of time. Its microvascular arrangement of a single capillary surrounded by several venules promotes nutrient absorption by creating a countercurrent flow pattern, but it is unable to significantly increase blood flow in response to hypoperfusion. Because perfusion is the most important determinant of dysoxia tolerance, organs with a capacity for recruiting numerous capillaries have great control over local blood flow and survive dysoxic conditions longer than organs with fewer capillaries, which are more predisposed to anoxic injury. Furthermore, a significant increase in splanchnic Vo_2 occurs in sepsis and may contribute to the risk of visceral hypoxia, even if blood flow is greater than normal (9).

Gastric tonometry, which provides an index of oxygen debt in the gastrointestinal tract, has been promoted both as a sentinel marker for impending global hypoperfusion and as a marker for a potentially correctable element in the pathogenesis of multiple organ failure. Therapies aimed at restoration of splanchnic flow have been postulated to be beneficial in shock management outcomes. This hypothesis rests both on the benefits of early identification of occult shock and on the theoretical benefits of maintaining gut perfusion and, thereby, avoiding phenomena such as mucosal ischemia. Unfortunately, support for this hypothesis has been highly elusive.

Gastric Tonometry. Oxygen debt is supported by anaerobic metabolism, which in turn generates organic acids. Hydrolysis of ATP stores to meet cellular energy requirements also contributes acid to the intercellular milieu. In fact, a strong correlation has been observed in experimental models between intestinal intramural pH and Vo_2 (15). Regional acidosis, however, is difficult to measure directly; carbon dioxide generated from the acid-buffering effect of bicarbonate is more readily measurable.

Experiments involving sampling of saline solution directly from polytetrafluoroethylene balloons placed in the stomachs and small intestines of dogs demonstrated a novel method of measuring gastric intramucosal acidosis (16). The unit of measurement promoted was the gastric intramucosal pH (pHi), which was calculated using the measured gastric Pco_2 levels and arterial bicarbonate concentrations in a modification of the Henderson-Hasselbalch equation:

$$pHi = 6.1 + \log_{10}[(HCO_3^-)/(.03 \times Pco_2)] \quad [2]$$

Follow-up studies demonstrated a high degree of correlation between the calculated pHi and pH microelectrode-calculated mucosal pH ($R^2 = .79$). Progressive occlusion of the superior mesenteric arteries of dogs was noted to induce a sequential fall in pHi measured in the small intestine ($R^2 = .68$), evidence that measured pHi had a strong correlation with intestinal ischemia (15). Intramucosal pH has, in fact, also been found to correlate well with the histologic degree of ischemic mucosal injury (17).

Clinical studies have also attempted to validate the tonometry tool by demonstrating associations between pHi measurements and patient outcomes. A 1993 prospective cohort study followed 83 patients with acute circulatory failure in their first 24 hrs after hospital admission (10). Of all the indexes of perfusion, gastric mucosal pH was the most reliable indicator of adequacy of tissue oxygenation and predictor of mortality. Arterial pH and standard base excess were also significantly different between survivors and nonsurvivors but were less predictive of outcome. Lactate, which is known to rely on a few pathways of metabolic clearance, was found to be neither a sensitive nor a specific marker of cellular hypoxia. The authors concluded that inadequate oxygenation of the gut is associated with poor outcome and that inadequate regional blood flow as detected by decreased gastric intramucosal pH, but not by systemic measures, is an important contributor to morbidity and mortality in intensive care units (ICUs).

Other Gastrointestinal Monitoring Sites. Carbon dioxide is measurable in other tissue beds, and the principles first described for gastric tonometry have been extrapolated to other sites in the gastrointestinal tract. Walley and colleagues (18), after studying the properties of small-bowel tonometry, concluded that gastric tonometry measurements are excessively noisy and inaccurate in the detection of gut ischemia compared with small-bowel tonometry. Unfortunately, placement of tonometers in the small bowel is more problematic than placement in the stomach. Jacques and colleagues (19) studied a more accessible tissue bed, the sigmoid colon. Aortic cross-clamping in pigs predictably resulted in steady gastric pHi and consistent depression of sigmoid pHi, but 63% remained within the baseline range. The authors suggested that wide variation in sigmoid pHi limits the value of individual pHi measurement in the detection of ischemia. The tongue and esophagus have also been used as sites of measurement of regional perfusion.

Other Techniques. Balloonless tonometry and the use of fiberoptic carbon dioxide sensors have been described as methods of measurement of the adequacy of Do_2. Interestingly, abnormalities in oxygen supply may not be strictly limited to the gastrointestinal tract. In a study of 16 septic patients and 10 nonseptic ICU control subjects, Neviere and colleagues (20) demonstrated that skeletal muscle microvascular perfusion is reduced in septic patients, despite normal or elevated whole-body Do_2. The application of near infrared spectroscopy techniques to various tissue beds may demonstrate similar findings in other regions.

New Monitoring Devices on the Horizon

Near Infrared Spectroscopy. The ideal device for monitoring the adequacy of resuscitation would have two basic characteristics. First, it would be noninvasive, not only allowing ease of placement, but also permitting it to be used in the field. Second, it would provide the clinician with an objective parameter that measures oxygenation at the tissue or ideally cellular level in end organs. Near infrared spectroscopy (NIRS) technology may provide a simple, rapid method for the assessment of the adequacy of Do_2 at the end organ molecular level.

NIRS has been utilized as a tool to determine the redox state of light-absorbing molecules. Beer's law states that light transmission through a solution with a dissolved solute decreases ex-

ponentially as the concentration of the solute increases. In mammalian tissue, only three compounds change their spectra when oxygenated: cytochrome aa3, myoglobin, and hemoglobin. Because the absorption spectra of oxyhemoglobin and deoxyhemoglobin differ, Beer's law can be utilized to detect their relative concentrations within tissue. By measuring the change in light intensity as light passes through, or is reflected by, tissue, the relative concentrations of the types of hemoglobin can be determined. Because NIRS measurements are taken without regard to systole or diastole and because only 20% of blood volume is intraarterial, spectroscopic measurements are primarily indicative of the venous oxyhemoglobin concentration.

Using a pig trauma/hemorrhage model, we found that muscle tissue oxygen saturation was as at least as reliable as invasive systemic oxygenation variables (Svo_2, arterial lactate, base excess) as an index of shock. Preliminary work from the University of Miami School of Medicine Ryder Trauma Center, using NIRS in human volunteers and in trauma patients, has shown this device to be quite promising as a noninvasive method of determining the Do_2 to peripheral muscle. Ultimately, this technology may be used as an endpoint for resuscitation.

Oxygen Delivery-Based Therapies

General Principles—Increasing Oxygen Delivery. Do_2 is dependent on cardiac output and arterial oxygen content. Arterial oxygen content is the sum of hemoglobin-bound and dissolved oxygen. (Dissolved oxygen in plasma and cells contributes only 3% to the total oxygen content of the blood under normal circumstances.) Early resuscitative efforts in shock seek to optimize each of these parameters.

Fluid resuscitation to increase preload in hypovolemic states can result in immediate improvements in cardiac output through Frank-Starling effects. However, injudicious use of fluids can promote bleeding in hemorrhagic conditions (21) and can lead to organ dysfunction secondary to worsening tissue edema. Use of inotropic agents and vasopressors to increase cardiac output and blood pressure may place increased strain on damaged myocardium. Given the limitations associated with cardiac output manipulation, increased attention is being focused on modification of oxygen-carrying capacity as a promising therapeutic strategy.

Anemia triggers a number of adaptive mechanisms that collectively serve to maintain Do_2 even at very low hemoglobin levels (22). Anemia results in increased cardiac output due to reduced blood viscosity and increased sympathetic outflow. Lowering of viscosity as hematocrit falls may also result in fewer inflammatory interactions between activated platelets and the endothelium (23). As discussed earlier, selective vasoconstriction promotes blood flow to critical organs, whereas oxygen-deprived tissue cells undergo specific hypoxia-induced adaptations. Through increased production of 2,3-diphosphoglycerate in red blood cells, anemia results in a shift in the oxyhemoglobin dissociation curve to the right, thereby facilitating oxygen unloading at the level of the tissue. The extent of new red blood cell production depends on the balance of positive and negative influences. On one hand, reduced Do_2 to the tubular epithelial cells of the kidney provides a signal for increased expression of erythropoietin expression and secondary stimulation of erythroid production in the bone marrow. On the other hand, the acute inflammatory response, commonly associated with trauma and shock, blocks hypoxia-mediated induction of erythropoietin, blunts the response of erythroid progenitor cells to erythropoietin, and leads to a functional iron deficiency state.

When the rate of blood loss outpaces these adaptive mechanisms, it is tempting to transfuse packed red blood cells (PRBCs). Besides having colloid oncotic properties, PRBCs are favored because of their ability to transport oxygen. However, oxygen transport capabilities of stored red blood cells may be limited by time-dependent depletion of ATP and 2,3-diphosphoglycerate, with resulting transient deteriorations in oxygen unloading and cellular deformability. Marik and Sibbald (24) observed that measured Vo_2 did not increase after transfusion of three units of PRBC in septic patients. Furthermore, patients transfused with blood stored for 15 days or more actually showed unexpected evidence of splanchnic ischemia, reflected by gastric intramucosal acidosis. The investigators attributed the observed deterioration in gut mucosal perfusion to capillary occlusion by poorly deformable red blood cells, adverse changes in blood viscosity, and alterations in systemic vascular resistance known to result from red blood cell transfusion. In a similar study, Fernandes and colleagues (25) noted no increase in Vo_2 (calculated or measured), no change in gastric intramucosal pH, and an increase in pulmonary vascular resistance after the transfusion of one unit of PRBC. These observations are worrisome because recent studies have noted that the mean age of transfused blood in Europe and the United States is 16.2 and 21 days, respectively (26, 27).

The Canadian Critical Care Trials Group challenged conventional transfusion (and, by extension, Do_2) practices on the grounds that red cell transfusions might have infectious, immunosuppressive, and microcirculatory risks to critically ill patients. In a multicenter, randomized trial of 838 critically ill, anemic, euvolemic, and nonhemorrhaging patients (28), protocols using hemoglobin concentrations of 7 and 9 g/dL as transfusion triggers were compared. The restrictive transfusion protocol led to transfusion avoidance in one third of patients in that group and a marked reduction in the volume of transfused blood without increasing mortality. In fact, rates of cardiac complications, organ failure, and mortality were found to be lower with the more restrictive transfusion strategy in two subsets of patients: those younger than 55 yrs and less critically ill patients (Acute Physiology and Chronic Health Evaluation score, <20) (29). A multicenter observational study from Europe (24) reached similar conclusions; transfused patients had higher mortality rates when adjustments were made for severity of organ failure and propensity for transfusion.

The results of these studies have lent support to some of the scientific reservations about the safety of PRBCs. In light of their findings, the value of augmentation of Do_2 in specific situations must come under more scrutiny than ever before.

Systemic Oxygen Delivery-Based Therapies. The risks associated with cellular hypoxia and with the standard measures to promote Do_2 may be high. However, innovative studies have been conducted to identify patient populations that may benefit from therapies aimed at increasing Do_2.

a) Goal-Directed Therapy: The Early Goal-Directed Therapy Collaborative Group designed an emergency department-based therapeutic protocol based on the rationale that augmentation of

Do_2 before the establishment of cellular hypoxic damage could improve outcomes resulting from the hemodynamic abnormalities associated with septic shock (30). This protocol was evaluated in a randomized study of 263 adult patients presenting with features of systemic inflammatory response syndrome and hypotension. The majority of subjects had medical conditions such as pneumonia and urosepsis, and patients requiring immediate surgery or urgent angiographic, cardiac, or urologic intervention were excluded from the analysis. Patients were assigned to receive either standard hemodynamic support (control group) or therapy aimed at the optimization of blood pressure and central venous oxygen saturation (intervention group). During the 6 hrs following presentation, patients in the intervention group received significantly more intravenous fluid and PRBCs (64% vs. 18.5%), but in the ensuing days, more transfusions and invasive therapy were required in the control group. In-hospital mortality in the early goal-directed therapy arm was 30.5% compared with 46.5% in the control group. The investigators attributed the relative success of their protocol to early correction of global hypoxia and prevention of resulting endothelial activation, microcirculatory failure, organ dysfunction, and ultimately cardiovascular collapse. The study has been criticized for the high rates of mortality in both arms, but it should be noted that patients were extremely ill (Acute Physiology and Chronic Health Evaluation score, >20), with hypotension at presentation. Use of blood to acutely improve Do_2 contradicts what is known about the detrimental effects of blood storage on oxygen transport and unloading, although cardiac output may have been improved through the volume-expanding effects of PRBCs. Furthermore, central venous saturation has not been thoroughly validated as a reflection of inadequacy of Do_2 but was used in this protocol as a central endpoint for resuscitation. Still, regardless of the limitations, the results support the probable significance of hypoxia in the cascade of cellular and organ deterioration that characterizes progressive shock states and may even defend the early use of blood in unstable septic patients. Although intriguing, the results of this study should be interpreted with caution until more evidence has accumulated.

b) Supranormal Do_2: A continuing debate has involved the subject of the role of universal maximization of Do_2 in critical illness. Despite the aforementioned concerns about mathematical coupling and the lack of data to support a pathologic oxygen supply dependency in critical illness, many investigators have championed the elevation of cardiac index, Do_2, and Vo_2 for all patients. Unrecognized flow-dependent Vo_2 has been postulated to contribute to the pathogenesis of multiple organ failure in patients with hemorrhagic shock. In fact, Bishop and colleagues (31) observed that patients demonstrating increases in oxygen delivery to "supranormal" levels after severe trauma had higher survival rates than patients unable to mount such a response. The hypothesis that using supranormal Do_2 (cardiac index, >4.5 mL/min/m^2; Do_2, >670 mL/min/m^2; Vo_2, >166 mL/min/m^2) as an endpoint of resuscitation would result in improved survival compared with conventional resuscitation endpoint use was evaluated in a prospective trial of 115 trauma patients. Investigators noted lower mortality and organ failure rates in the treatment group and concluded that augmentation of the supranormal Do_2 response improves survival in this group. These results have not, however, been uniformly supported by other studies, including one from the same group, which although underpowered, found that early attempts to augment Do_2 (cardiac index, >4.5; Do_2, >600 mL/min/m^2; Vo_2, >170 mL/min/m^2) did not significantly have an impact on mortality (32).

A 1996 meta-analysis of seven randomized trials of interventions designed to achieve supraphysiologic values of cardiac index, Do_2, and Vo_2 also concluded that these measures do not significantly reduce mortality, except perhaps when initiated preoperatively (33). The authors summarized the pitfalls in the interpretation of previous literature in this arena (self-generation of increased Do_2 states in some patients is associated with better survival but does not by itself imply that exogenous therapy for this purpose is similarly beneficial) and noted the difficulties associated with the design and execution of studies with high methodological quality. A more recent meta-analysis, incorporating studies published up to 2002, considered studies according to the timing of the intervention (34). When analyzed from this perspective, the authors concluded that early optimization of Do_2 in severely ill patients confers a substantial survival benefit. Hemodynamic optimization after the onset of organ failure failed to yield a beneficial effect. Interestingly, a recent, large, well-designed trial demonstrated no advantage to preoperative optimization of pulmonary artery catheter-derived hemodynamic parameters in high-risk surgical patients (35). This study was powered to detect a 5% mortality difference between patients managed with and without pulmonary artery catheters.

Gastric Tonometry-Directed Therapy: Review of the Evidence. Global therapies may ignore the divide between capillary bed-rich and bed-poor tissues and the consequences of regional hypoperfusion. Therapies aimed at restoration of splanchnic flow have been postulated to interrupt the potentially detrimental secondary effects of mucosal ischemia, which can range from increased gut permeability with bacterial translocation or endotoxin release. Three studies in the trauma literature have examined the role of pHi-directed shock resuscitation. Roumen and colleagues (36) in a prospective evaluation of pHi in 15 patients found that pHi < 7.32 within 48 hrs of admission was associated with increased morbidity and mortality. The authors concluded that "monitoring gastric pHi is useful in severely injured patients admitted to the ICU." A prospective study of 20 critically ill trauma patients by Chang and colleagues (37) noted higher mortality rates in subjects with low initial pHi that did not correct within 24 hrs (50% vs. 0%), as well as a higher incidence of organ dysfunction. Of all of the indexes of Do_2, only pHi was different between subjects who developed multiple organ failure at 24 hrs and those who did not. The authors argued that on the basis of their findings, splanchnic perfusion is an important factor in the pathogenesis of multiple organ failure and that an indicator of gastric ischemia provides useful prognostic information in underperfused patients.

The benefits of tonometry-based intervention in trauma care were evaluated in a 1996 prospective trial of 57 shock patients conducted by Ivatury and colleagues (38). Subjects were randomized to receive therapies aimed either at normalization and maintenance of pHi (blood, intravenous fluids, dobutamine) or at maintenance of Do_2 index (600 mL/min/m^2) and Vo_2 index (150 mL/min/m^2). In this trial, mortality and single-organ failure differences among the two groups did not reach statistical significance (al-

though the latter outcome trended toward significance). No differences in any endpoints apart from pHi were observed between groups. Subgroup analyses demonstrated that the mortality rate from multiple organ failure was higher in patients whose pHi did not correct to 7.3 at 24 hrs (54% vs. 6.8%) and that longer optimization times were predictive of mortality. Persistently low pHi was frequently associated with intraabdominal anastamotic leak, compartment syndrome, abscess formation, or other complications. The authors concluded that "gastric mucosal pH may be an important marker to assess adequacy of resuscitation."

Unpublished data from a prospective, randomized study of trauma patients from the University of Miami suggest that even a more comprehensive intervention to restore splanchnic perfusion and to minimize the effects of ischemia-reperfusion injury through the provision of antioxidant therapy does not significantly reduce mortality rates. In this trial, 151 critically ill trauma patients were randomized in three arms to receive standard therapy, placement of a gastric tonometer with otherwise routine management, or gastric pHi-directed therapy with inotropic agents, vasodilators, an infusion of agents designed to limit free-radical damage to the gut mucosa (including mannitol, vitamin C, selenium, and polymyxin B), and supplementation of enteral feeds with glutamine, *N*-acetylcysteine, and vitamins A and E. This trial was stopped at an interim analysis because of the remarkable outcome similarity in rates of morbidity or mortality among its arms, despite the massive deployment of effort and resources in the intervention group.

It is interesting to note that despite extensive experience with gastric tonometry, no trial has documented better outcomes with tonometry-directed therapy and that there is little evidence from randomized studies that intramucosal pH can be reproducibly and favorably influenced relative to placebo. Gomersall and colleagues (39) speculated that failure of their trial of tonometry-based therapy in critically ill patients to demonstrate a difference in outcome may have resulted from the inability of dobutamine and colloid to produce a significant change in pHi or from the fact that pHi is merely a surrogate marker of disease, as suggested by proponents of the gut-motor hypothesis.

New Directions in Oxygen Delivery Research

Limitations in and uncertainties about the modalities currently available for improving Do_2 in critically ill patients have prompted investigators to broaden the search for safe alternatives. Recombinant human erythropoietin may assist in augmenting red cell production in this population. Recently, Corwin and colleagues (40) demonstrated a 19% reduction in blood transfusion in a group of critically ill patients who received a weekly high dose of recombinant human erythropoietin compared with placebo. There were no significant differences in the frequency of adverse events or in mortality observed between the two groups. The observed transfusion reduction of 0.6 units per patient was statistically significant.

A more dramatic means of improving Do_2 may eventually be provided by blood substitutes. Hemoglobin-based oxygen carriers have been undergoing extensive evaluation as a potential alternative to the use of allogeneic blood in emergent and elective surgery. Unfortunately, intensive research and development efforts to date have led to limited success with tetramerized human hemoglobin and second-generation perfluorocarbons.

Baxter's product, HemAssist (Diaspirin cross-linked hemoglobin) underwent two phase III clinical trials. The first was a double-blind trial in perioperative patients comparing two units of HemAssist with two units of PRBCs. The trial was stopped after 181 of a planned 400 patients were enrolled due to two sentinel adverse events, namely, acute respiratory distress syndrome and multiple-organ dysfunction syndrome. These limitations notwithstanding, there was a 24% rate of transfusion avoidance in the HemAssist arm. The second trial was a single-blind trial in trauma patients. This study, which was designed to compare 1 L of HemAssist vs. 1 L of PRBCs, was terminated prematurely after identifying a statistically significant higher mortality rate of 46% for the blood substitute group compared with the controls (17%) (41). Baxter has subsequently stopped research and development efforts on this product.

Northfield Laboratories undertook a prospective, randomized trial of its product, Polyheme, in 44 trauma patients (mean Injury Severity Score, 21 $\pm$ 10). Patients received either PRBC or up to six units of Polyheme (a chemically modified hemoglobin derived from human blood). The transfusion requirements were 6.8 $\pm$ 3.9 units in the Polyheme group and 10.4 $\pm$ 4.2 units in the control group ($p < .05$) with no difference at 48 hrs (42). There were no significant adverse effects, suggesting that Polyheme might be a clinically useful blood substitute. A subsequent study compared patients who received Polyheme with an historic control group of patients who refused transfusion for religious reasons. The 30-day mortality rate was 25% in those who received Polyheme vs. 64.5% in controls (43). There is an ongoing phase III prehospital trial in collaboration with the U.S. Army.

Hemosol sought to evaluate the efficacy of Hemolink (*o*-raffinose cross-linked human hemoglobin) in a phase III trial looking at avoidance of red blood cell (RBC) transfusion or the reduction in the number of RBC units transfused in coronary artery bypass grafting patients. A higher rate of avoidance of RBC transfusion was observed in subjects who received Hemolink (17% transfused) than in subjects who received the plasma volume expander, Pentaspan (27% transfused). The first transfusion occurred at an average of 42 hrs posttreatment in the Hemolink arm compared with an average of 24 hrs posttreatment in the control arm. Overall, a lower number of RBC units were transfused in the Hemolink arm (49 units) compared with the control arm (104 units). Additional clinical trials with Hemolink focusing on transfusion avoidance are being initiated in North America (44).

Biopure has conducted 57 preclinical studies and 21 phase I–III clinical trials of its product, Hemopure (purified hemoglobin from refined cow's blood). The studies included healthy volunteers, sickle-cell patients, and surgical patients. Most of the studies showed acceptable rates and types of adverse events and a clear benefit in terms of RBC transfusion avoidance (45–47).

Perfluorochemical emulsions (for example, Fluosol-DA) initially appeared promising due to their ability to carry large amounts of dissolved oxygen. Unfortunately, clinical trials showed a lack of effectiveness in the treatment of severe anemia due to hemorrhage. The second generation of perfluorocarbons appears highly promising for use in isovolemic hemodilution, but phase III trials utilizing perflubron in the setting of cardiac surgery were recently terminated.

Conclusion

The right iliac vein was identified and ligated. With continued administration of blood products and crystalloid solutions, the patient's blood pressure was restored. Laparotomy was completed, a temporary dressing applied, lower limb fasciotomies were performed, and the patient was transferred to the ICU. Despite definitive hemostatic control and apparent restoration of stable hemodynamics, hypoxic damage had occurred. During the ensuing weeks, the patient suffered from rhabdomyolysis, acute renal failure, respiratory failure, ventilator-associated pneumonia, sepsis, and encephalopathy with delayed return to baseline cognitive function. He was ultimately discharged home with his parents after seven weeks in the trauma center.

Once hemodynamics are restored, why does it take so long for someone to get better? How much of a toll have the direct effects and the hemodynamic compensations of shock taken on the function of cells, tissues, and organs? How do metabolic processes recover from the degrees of interruption of Do_2? How can this interruption be minimized?

What is known is that shock, whether it is considered to represent inadequate perfusion to maintain the function of organs, of individual cells, or of specific cellular metabolic processes, even when compensated, results in increased mortality. When shock is overwhelming or uncompensated, prompt therapy to improve Do_2 can be life-saving. When it is compensated, diagnosis may be challenging and the risks of available therapies must be weighed against their potential benefits.

The spectra of limitations, risks, and benefits of these therapies are now becoming clearer. Continuing research into the compensatory responses to impairments in Do_2, including research at the cellular level, may provide rational avenues for intervention to optimize these responses. Guidance of therapy of shock by considerations of the nature and duration of the specific underlying pathophysiologic process may increase the chances of success of the resuscitative effort. Finally, detailed knowledge of the consequences of "cranking the valve to full flow" with novel experimental methods of Do_2 will provide us with another exciting frontier in our efforts to improve the outcomes of low Do_2 states.

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