CHAPTER 61 ■ SPLANCHNIC FLOW AND RESUSCITATION

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Ischemia signifies failure to satisfy the metabolic needs of the cell secondary to either impaired oxygen delivery or the impairment of cellular oxygen extraction and utilization. Incomplete splanchnic cellular resuscitation has been associated with the development of multiple organ system failure and increased mortality in the critically ill patient (1,2). For many years, the merits of augmenting systemic oxygen delivery and consumption and attainment of supranormal levels have been examined and debated as primary treatment goals (3-6). There is convincing evidence that systemic hemodynamic and oxygen transport variables fail to accurately portray the complex interaction between energy requirements and the energy supply at the tissue level (7-9), and that achieving supranormal cardiovascular oxygen transport and utilization indices does not reliably confer improved outcome (i.e., decreased mortality rates and diminished multiple organ system failure) in several clinical conditions (e.g., sepsis, acute respiratory distress syndrome [ARDS]) (10-13). These findings have led to the search for monitoring techniques that directly measure changes in regional tissue bioenergetics.

Intestinal tonometry has been proposed as a relatively non-invasive index of the adequacy of aerobic metabolism in organs whose superficial mucosal lining is extremely vulnerable to low flow and hypoxemia, and in which blood flow is sacrificed first in both shock and the cytokine milieu of the systemic inflammatory response (1,14,15). The gastrointestinal tract, therefore, acts like the “canary,” displaying early metabolic changes before other indices of adequate oxygen utilization (16). This chapter reviews the fundamental and clinical underpinnings of splanchnic ischemia and resuscitation, intestinal and subsequently sublingual tonometry, the potential applications and limitations of this technology, its use as a diagnostic and treatment end point, and, finally, a consideration of potential future directions.

THE INTESTINAL MICROCIRCULATION

The gastrointestinal tract has three major functions: motility, secretion, and absorption. Blood flow is important for each of these functions, being highest in the small intestines and lowest in the colon. The splanchnic circulation contains approximately 30% of the circulating blood volume at any given moment with the bulk of this volume held in the postcapillary venous capacitance vessels (17). Resting blood flow in the intestine is ten times higher than in skeletal muscle. Most of the blood flow is delivered to the mucosa and submucosa, reflecting the varying demands for oxygen within the intestinal wall, being highest in the mucosal layer. The arterial supply emanates from an extensive arterial plexus in the submucosa. A countercurrent blood flow exchange system exists within the superficial mucosal layer between the arterial and venous circulation, rendering this tissue particularly sensitive to neuronal and systemic vasoconstrictors (18). The arterioles, which run in parallel with the venules in the stalk of the intestinal villus, allow diffusion of oxygen from the arterioles down a concentration gradient to the venules, bypassing the capillary bed at the villus tip; thus, the mucosa at the villus tip is rendered vulnerable to changes in oxygen content. Water also diffuses from arterioles to venules because of an osmotic gradient caused by the absorption of sodium in the capillary bed at the villus tip. Therefore, the sodium concentration is higher in the venules. Plasma water content is then lowered at the villus tip compared with the base of the stalk, predisposing this area to low or absent flow in states of compensated or uncompensated shock when splanchnic circulation is compromised.

Mesenteric vasoconstriction is mediated by $\alpha$-adrenergic postganglionic sympathetic fibers, but, even more dramatically, by the effects of circulating hormones and peptides (Table 61.1). Endogenous vasoconstrictors known to be released in major injury, sepsis, and other physiologically stressful circumstances include catecholamines, angiotensin, vasopressin, myocardial depressant factor, leukotriene $D_4$, thromboxane $A_2$, and serotonin. The high concentration of receptors for these systemically released vasoconstrictors, which affect the splanchnic circulation more than any other tissue bed, has a substantial effect on peripheral (systemic) vascular resistance and, hence, on systemic blood pressure by redistributing blood from the splanchnic organs (as well as the peripheral circulation) to the central circulation (i.e., heart and brain). This effect may be compounded by tissue edema and atheroma in the splanchnic arteries. The peptides, angiotensin II and vasopressin, are the most potent splanchnic vasoconstrictors (14). The splanchnic vasoconstriction induced by these two peptides alone accounts for most of the increase in total vascular resistance recorded in animal models of cardiogenic and hemorrhagic shock. The adequacy of gut mucosal oxygenation cannot be reliably inferred from measurements of tissue oxygenation in the skin or of subcutaneous tissue because of their different response to endogenous vasoconstrictors.
PATHOPHYSIOLOGY OF MESENTERIC ISCHEMIA AND REPERFUSION

Tissues with a high perfusion-to-extraction (demand) ratio, such as skeletal muscle, have high capillary densities that act as a microvascular reserve to produce an increase in local blood flow. These organs, in situations of low flow, use a disproportionate share of the cardiac output as increased capillary recruitment lowers local vascular resistance. These tissues are characterized by low oxygen extraction ratios and high mixed venous oxygen saturations. Less “fortunate” tissues, which include the intestinal tract, possess a lower capillary density and are unable to recruit capillaries to augment local blood flow to match increases in metabolic needs. This results in low perfusion-to-oxygen demand ratios and subsequent tissue hypoxia (the “trickle down economy” of systemic oxygenation) (15). The gastrointestinal tract is characterized by a high oxygen extraction ratio, lactate release, and low mixed venous oxygen saturation; it can tolerate severe hypoxemia without a decrease in oxygen consumption but is limited in its ability to respond to decreased blood flow. Intestinal tissue injury can be induced by the initial ischemia (either from inadequate oxygen content or inadequate flow) or by the generation of oxygen-derived free radicals during reperfusion (1,7). Ischemic injury may be progressive, spanning a spectrum from mild injury characterized by increased capillary permeability with no microscopic changes to transmural infarction, depending on the severity and duration of the ischemia (1,2,19,20). Inadequate oxygen supply results in anaerobic glycolysis and systemic lactic acidosis. In the anoxic cell, uncoupled adenosine triphosphate (ATP) hydrolysis is associated with the intracellular accumulation of adenosine diphosphate (ADP), inorganic phosphate, and hydrogen ions with resultant intracellular acidosis (7,21). These hydrogen ions lead to tissue acidosis as well, with unbound hydrogen ions combining with interstitial bicarbonate to form the weak acid, carbonic acid, that dissociates to produce carbon dioxide (CO₂) plus water.

Hypoxia renders the superficial gastrointestinal mucosa susceptible to the cytolytic effects of gastric acid, proteolytic enzymes, and bacteria already present in the intestine by impairing cellular mucus and bicarbonate secretion. Disruption of the mucosal barrier is associated with the generation of myocardial depressant factors that cause a low cardiac output syndrome in animals (14,22,23). Commonly, in low flow and hypoxic states, tissue oxygen consumption (VO₂) is maintained by adaptive mechanisms that are activated when oxygen delivery (DO₂) falls below a critical level and oxygen consumption becomes delivery dependent.

Intracellular acidosis impairs cellular function by one of several mechanisms: (a) the loss of adenosine nucleotides from mitochondria by the inhibition of the ATP-magnesium/inorganic phosphate carrier; (b) inhibition of sodium–calcium exchange, resulting in the intracellular sequestration of calcium ions; (c) increases in the activity of cyclic adenosine monophosphate (cAMP) deaminase and loss of adenine nucleotide precursors from the cell; (d) decreases in the nicotinamide adenine dinucleotide (NAD); and (e) the conversion of intracellular inorganic phosphate to its inhibitory deprotenated form (7).

Hypoxia also results in intracellular calcium overload by inhibiting ATP-driven membrane transport pumps and sodium–calcium exchange. Increases in intracellular calcium are a pivotal event in cellular dysfunction during hypoxia, because calcium-activated proteases can destroy the sarclemma and the cellular cytoskeleton (7). Cellular membrane degradation seems to be related to calcium influx. Calcium stimulates phospholipase A₂ (PLA₂) and phospholipase C, which are known to degrade membrane phospholipids (24,25). The resultant imbalance between the rate of membrane synthesis and the rate of membrane breakdown results in the accumulation of arachidonic acid, the precursor of thromboxane, prostaglandins, and leukotrienes, substances that produce further cellular damage and profound alterations in microvascular control.

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### Table 61.1

<table>
<thead>
<tr>
<th>Vasconestrictor</th>
<th>Gut</th>
<th>Renal</th>
<th>Brain</th>
<th>Coronary</th>
<th>Pulmonary</th>
<th>Muscle</th>
<th>Skin</th>
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<tbody>
<tr>
<td>Catecholamines</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>±</td>
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<tr>
<td>Angiotensin II</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Vasopressin</td>
<td>+</td>
<td>±</td>
<td>0</td>
<td>±</td>
<td>±</td>
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<td>±</td>
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<tr>
<td>Myocardial depressant factor</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Leukotriene D₄</td>
<td>+</td>
<td>±</td>
<td>0</td>
<td>±</td>
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<tr>
<td>Thromboxane A₂</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>±</td>
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<tr>
<td>Serotonin</td>
<td>+</td>
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<td>±</td>
<td>+</td>
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+, vasoconstrictor; –, vasodilatation; 0, no effect; ±, effect varies; ？, undefined.

Multiple system organ failure (MSOF) (defined as failure of two or more vital organs or systems, in sequence or simultaneously, irrespective of the primary disease) and sepsis are distressingly familiar to surgeons who perform major elective cases, as well as to those involved in transplantation and trauma (26). Uncompensated or compensated shock leading to progressive oxygen debt, ischemia/reperfusion injury, and cellular dysfunction is the underlying unifying pathophysiologic mechanism (1). Throughout the world, MSOF has become the most common cause of death in the intensive care unit: The reported mortality rates vary from 30% to 100% with a mean of 50%, depending on the number of organ systems involved; the patients' intensive care unit (ICU) stay lasts for 6 weeks to many months and, in prior studies, these patients have used nearly 40% of the available ICU days (26–30). Many hypotheses link the noxious event, whether surgery or trauma, to the development of MSOF and sepsis. There have also been many attempts to use single agents (e.g., antibiotics, monocolonal antibodies against cytokines and endotoxin) or combinations of these agents to affect the process; unfortunately, no significant progress has been made with these approaches. This may result from the many redundancies in the initiation and promulgation of MSOF; so that attacking a single pathway is ineffective or, perhaps, efforts have been started too late in the sequence of events. Bacterial endotoxin in the gut may translocate across the semipermeable mucosa as a result of ischemia/reperfusion. Besides endotoxin, the products of the damaged mucosa also may contribute to the systemic inflammatory response and subsequent MSOF and death of the ICU patient. The translocation of enteric bacteria across the ischemic gut seems to be an important cause of nosocomial infection in the critically ill (14,26). However, reducing the number of nosocomial infections from enteric organisms by selective decontamination does not seem to have a dramatic effect on outcome; that is, “again, the horse is already out of the barn” (31).

While representing an oversimplification, we believe the current hypotheses can be combined. Most current thinking can be categorized as the gut starter hypothesis popularized by Moore et al. (32) and the gut motor hypothesis as described by Detch (27) and Marshall et al. (28,29).

In the gut starter hypothesis, the noxious stimulus leads to a neurohumoral response. High levels of catecholamines cause splanchic vasoconstriction and a decrease in splanchic flow. This leads to gut ischemia and, depending on the length of ischemic time, allows various reactions that prime tissue to develop a reperfusion injury once flow is restored. During reperfusion, PLAA is activated, which in turn activates platelet-activating factor (PAF). PAF attracts and primes polymorphonuclear leukocytes (PMNs) in the gut; thereafter, they are released into the systemic circulation, where they undergo activation (the two-hit model) and cause end-organ injury (32). Therefore, the PMN is implicated as the major effector of cellular damage attributed to ischemia/reperfusion through its respiratory burst and activation of cytokines and arachidonic acid metabolites.

In the gut motor hypothesis, the steps leading to ischemia are the same. During reperfusion, gut mucosal injury results from the accumulation of intracellular calcium, activation of PLAA, and generation of free oxygen radicals. This leads to bacterial translocation and initial production and amplification of numerous systemic cytokines (33,34). The end result again is MSOF. It is likely that these hypotheses are correct, although they are still incomplete explanations.

### SYSTEMIC OXYGEN DELIVERY, UTILIZATION, AND MONITORING

The determinants of arterial oxygenation include hemoglobin content, inspired oxygen tension, alveolar oxygen tension, pH, temperature, mixed venous oxygen tension, ventilation/perfusion (V/Q) mismatch, physiologic shunting, and cellular-interstitial diffusion abnormalities. Indices of adequacy of systemic perfusion include the following: (a) global systemic parameters, such as blood pressure, heart rate, central venous pressure measurements, and urine output; (b) tissue markers, including arterial pH (pHa), base excess, and serum lactate level; and (c) pulmonary artery catheter measurements and derivations, such as cardiac output, oxygen delivery, oxygen consumption, and oxygen extraction. In fact, Rivers et al. demonstrated that goal-directed resuscitation using certain systemic measures (mean arterial pressure [MAP], urine output [UOP], central venous pressure [CVP]) including improving oxygen delivery to an ScVO$_2$ > 70% can improve mortality in patients in severe sepsis and septic shock (33). Nonetheless, the interpretation of oxygen delivery and oxygen consumption measurements is challenging because (a) these parameters are global markers and do not provide any direct information regarding the oxygen requirements of specific tissues, (b) the distribution of oxygen delivery is impacted by local microvascular and neurogenic responses, (c) the effect of cytokines and endogenous peptides is unpredictable, and (d) the disease process may affect cellular metabolism directly (i.e., sepsis and ARDS) (36–38). Several prospective studies suggest that failure to achieve supranormal oxygen delivery and utilization parameters in the acute phase of major injury or physiologic stress is associated with increased mortality and shock-related complications, including multiple organ system dysfunction syndrome. The failure to reverse pathologic flow dependency, tissue hypoxia, and oxygen debt has been inferred as the cause of these adverse outcomes (34–36). In these prospective studies, both responders and nonresponders achieved normal or hyperdynamic cardiovascular function; however, more cardiovascular interventions were often used in patients who died, so, ultimately, failure of patient response to achieve therapeutic objectives could be considered as the cause of the observed increased mortality and morbidity. Several reports failed to identify either an optimal or a critical value of oxygen delivery or consumption to distinguish survivors from nonsurvivors in clinically ill patients (10–13,23). Adequate or supranormal oxygen delivery may not be tantamount to effective tissue oxygen utilization.

"Critical oxygen delivery" purportedly marks the transition from aerobic to anaerobic metabolism; however, the relationship between oxygen delivery and consumption obtained in critically ill patients with ARDS, sepsis, and heart failure has been linear (23). The lack of a clearly defined inflection point in a linear DO$_2$–VO$_2$ function makes it impossible to determine...
a critical level of oxygen delivery that aerobically satisfies cellular energy requirements.

**REGIONAL OXYGEN DELIVERY, UTILIZATION, AND MONITORING**

**A Historical Review of Gastric Tonometry**

A tonometer is composed of a semipermeable silicone balloon, which is filled with either air or fluid and allowed to equilibrate with the surrounding tissue. The fluid/air is then accessed and the pressure of CO₂ can be directly measured. Tonometry was first used by Bergofsky (41) and Dawson et al. (42) in 1964 to demonstrate that the gas tension within a hollow viscus approximates that within the mucosa of the viscus. Grum et al. (21) extended this concept to the intestinal tract of adults. Antonsson et al. (43) and Hartmann et al. (44) performed validation studies demonstrating that both the stomach and small intestine could be used as suitable sites to measure intraluminal PCO₂. They confirmed that intraluminal PCO₂ equaled that measured within the intestinal mucosa as well as approximated hepatic vein PCO₂. Moreover, it has been validated that the intramuscular PCO₂ rises and falls in parallel with changes in PCO₂ in arterial blood (45). This indirect method of measuring the pH within the intestinal mucosa (pHi) is based on the fact that CO₂ is a highly permeable gas and on the assumption that this generated CO₂ is the end result of ATP hydrolysis, with neutralization of generated hydrogen ions by intestinal interstitial bicarbonate (46).

The measurement of pH depends also on the assumption that the bicarbonate concentration in the wall of the organ is the same as that which is delivered to it by arterial blood, and that the dissociation constant (pK) is the same as that in the plasma. Using the Henderson-Hasselbalch equation, pHi is calculated as follows:

\[
\text{pHi} = 6.1 + \log[10\text{HCO}_3^-/0.03 \times \text{PCO}_2] 
\]

pK is 6.1, and 0.03 is the solubility coefficient for CO₂. The pH in plasma is not the same as that in the cytosol, but the value 6.1 is the best approximation of the pK within the intestinal fluid of the superficial layers of the mucosa (14,47,48).

Doglio et al. (49) demonstrated that gastric pH was a predictor of ICU mortality at the time of admission to the ICU and at 12 hours later. Patients admitted with a pH < 7.36 had a greater ICU mortality rate, 65% versus 44% (p < 0.04). Furthermore, patients with persistently low pH at 12 hours after ICU admission had the highest mortality rate (87%). Maynard et al. (50) repeated the study in patients with acute circulatory failure and found remarkably similar outcomes. In addition, there were significant differences in mean gastric pH values between survivors and nonsurvivors on admission (7.40 vs. 7.28) and at 24 hours (7.40 vs. 7.24), respectively (p < 0.001). There was no difference in cardiac index, oxygen delivery, and oxygen uptake, suggesting that pH is a more specific marker of resuscitation than our common global parameters.

We also confirmed that failure of splanchnic resuscitation correlated with surviving patients and increased length of ICU stay in the hemodynamically unstable trauma patient (51). The relative risk of death in patients whose pH was less than 7.32 was 4.5-fold higher and the relative risk of developing multiple organ system failure was 5.4 times higher compared with those having a pH of 7.32 or more. Global parameters of oxygen transport utilization did not distinguish survivors from nonsurvivors nor those patients who developed MOF from those who did not.

Chang et al. (52) then conducted a prospective study of 20 critically ill patients and were able to demonstrate that correction of an abnormal admission pH correlated with better outcomes. Patients with pH less than 7.32 on admission, who did not correct within the initial 24 hours, had a higher mortality (50% vs. 0%; p = 0.03) and more frequent MOF (2.6 vs. 0.62 organs/patient; p = 0.02) than those whose pH was corrected.

Ivatury et al. (53) compared correction of pH versus supranormal oxygen delivery (as defined by Shoemaker et al. [3]) in 27 critically ill trauma patients. Seventy-five percent of the patients who developed MOF had pH less than 7.3. Interestingly, four of the five patients who died in the supranormal oxygen group achieved supranormal oxygen delivery and consumption goals, but had a pH less than 7.3 at 24 hours. Moreover, they observed that a late fall in pH was often associated with a physiologic catastrophe (e.g., intestinal leak, gangrene, bacteremia).

There have been only two prospective controlled interventional studies in which therapy was instituted because the pH was low. Neither of these studies, however, attempted to normalize the pH, but rather focused on increasing oxygen delivery and utilization. Gutierrez et al. (54) observed that the hospital mortality rate was significantly greater in control patients whose pH was normal on admission (pHi ≥ 7.35) and then became abnormal during their ICU stay compared with those whose abnormal pH prompted interventions to increase oxygen delivery. Unfortunately, if admission pH was low, the mortality rates were the same in both treatment and control groups. The authors chose to increase oxygen delivery rather than restore pH to normal values.

We also specifically studied ICU patients with persistent uncorrected gastric pH who had pulmonary artery catheters to guide resuscitation (55). We observed a significant reduction in the incidence of MOF per patient (1.9 ± 0.4 to 0.9 ± 0.2; p = 0.02), length of ICU stay (35 ± 9 to 18 ± 4 days; p = 0.03), and total hospital stay (51 ± 12 to 29 ± 5 days; p = 0.03) in patients with persistent gastric intramuscular acidosis who were administered agents that increased splanchnic perfusion and that were intended to prevent free radical damage during reperfusion. We conclude that efforts to correct gastrointestinal intramuscular acidosis related to splanchnic hypoperfusion are warranted because MOF and mortality were increased in those patients whose pH never corrected (i.e., pH < 7.25).

Despite the potential benefits of regional monitoring, gastric tonometry has fallen out of favor for multiple reasons. The monitoring itself is labor intensive and time consuming, often requiring multiple attempts to ensure proper positioning and frequent catheter adjustments, lengthy equilibration times, and need for frequent troubleshooting of abnormal results. Gastric acid must be neutralized (pH > 4.5), requiring pH litmus paper analysis and adjustments to the peptic ulcer prophylaxis regimen in the ICU patient. Tube feedings also must be held. In addition, one must use a dedicated blood gas analyzer for all pH determinations. Periodic calibration of the analyzer with 10 to 20 ampules at three different PCO₂ levels must be done. The saline sample must be transported immediately on ice because of rapid loss of CO₂ from the sample and overestimation of the pH. 

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SUBLINGUAL TONOMETRY

Researchers moved more proximally in the gastrointestinal tract in search of a more reliable and efficient place to measure tissue PCO$_2$, evaluating first the esophagus and finally the sublingual space (56). Weil et al. suggested that the sublingual space would respond similarly to the splanchnic circulation (57). Mark also demonstrated good correlation of sublingual tonometry with gastric tonometry and more importantly that it was the difference between the sublingual PCO$_2$ (sIPCO$_2$) and arterial PCO$_2$ (PCO$_2$ gap) that was more predictive of survival (58). Since then, sublingual capnometry (SLC) has generated much interest as a potential splanchnic tissue monitor, overcoming the shortcomings and obstacles of the more invasive and burdensome intestinal tonometers. The device uses a disposable sensor that detects CO$_2$ and sends the information back to the handheld instrument. The sensor is placed directly under the sublingual space and is kept in place for approximately 60 to 90 seconds. Recent investigations have suggested use of SLC in the triage of patients with penetrating traumatic injuries showing statistical differences in severe to moderate (>1,500 mL) or minimal to moderate (<1,300 mL) amount of blood loss on admission (59). Our research supports Mark’s findings that the PCO$_2$ gap and to a lesser degree the absolute SLC value correlates with outcome (60). Our observations show a significant difference in development of MODS and mortality in 83 critically ill surgical patients subjected to a standard resuscitation protocol. Patients whose PCO$_2$ gap was not corrected to 9 mm Hg or less at 24 hours after admission were three times more likely to experience MODS and more than ten times as likely to die during their hospital stay. Sublingual capnometry is a quick and simple method to directly measure tissue perfusion and is a potential tool for the clinician to help guide goal-directed therapy. The product has been recalled due to infectious complications but may be reinstated in the future.

MONITORING PLAN

Intramucosal PCO$_2$ provides an intermittent direct measure of the ability of tissues to resynthesize high-energy phosphate compounds utilizing aerobic metabolism. In dysoxic states, protons accumulate and pH falls, indicative of inadequate oxidase metabolism. If this is recognized early and can be reversed, the clinician may be able to prevent or limit the duration of compensated shock. Global measurements of oxygen delivery, oxygen consumption, oxygen extraction ratio, and mixed venous blood hemoglobin oxygen saturation (S$_{O_2}$) are unsatisfactory for this purpose (74–76). The calculation of pH$_i$ can provide clinicians with a metabolic end point that may be used to determine whether the milieu is likely to create a reperfusion injury if resuscitation is successful or whether subclinical mal-distribution of blood flow persists—a reflection of a still-active neurohumoral response to stress.

Monitoring all patients likely to have had activation of the neurohumoral response and decreased splanchnic blood flow is probably beneficial because they are at risk for a reperfusion injury, MODS, and a higher mortality rate (47). Outcome can be improved by recognizing compensated shock, preventing ischemia/reperfusion injury, and ensuring that intramucosal acidosis is promptly reversed. Recognize that the window of opportunity for effective therapy is early (61). Both a preemptive intervention to block and modify the ischemia/reperfusion injury and restoration of splanchnic perfusion must be incorporated into a resuscitation algorithm to reduce the incidence of bacterial translocation and systemic white cell priming before the ensuing systemic inflammatory response (3). Because early abnormalities in the gastrointestinal intramucosa act as a marker of mortality and morbidity, efforts to correct them may improve outcome and should diminish resource utilization (62,63). If pH$_i$ falls, or if sIPCO$_2$ or the PCO$_2$ gap rise unexpectedly (the canary), look for intraperitoneal catastrophes, intra-abdominal hypertension, sepsis, tissue necrosis, line sepsis, nosocomial infection, unappreciated excess patient ventilatory work, hypovolemia, and hypoxemia (53,62,64–66).

Chapter 61: Splanchnic Flow and Resuscitation

The limited success thus far that has attended attempts to elevate an already depressed pH and an understanding of the importance of the ischemia/reperfusion injury as a fundamental part of both the gut starter and gut motor hypotheses suggest that a new perspective is needed. Two separate elements must be combined: a preemptive intervention to prevent the ischemia/reperfusion injury in high-risk patients, and restoration of oxidative high-energy phosphate synthesis as judged by a normalizing pH$_i$. As an approach to preventing intramucosal acidosis and ischemic gut mucosal injury, we suggest the following goals: (a) increase global oxygen delivery, (b) increase splanchnic flow, (c) affect ischemia/reperfusion injury and stop the cytotoxic cascade before it starts, and (d) judge reversal of ischemia and anaerobic metabolism by restoration of normal pH$_i$ or PCO$_2$ gap (9,19,32–34,67–69).

To increase global oxygen delivery, ensure adequate volume resuscitation with isotonic fluids, albumin solutions, and red blood cells. Avoid $u$ agents, which cause splanchnic vasoconstriction. This also means “tolerating” a lower mean arterial pressure, perhaps 60 mm Hg if there is satisfactory end-organ perfusion. Use splanchnic sparing isotopes like dobutamine and isoproterenol and vasodilators such as nicardipine, nitroglycerin, nitroprusside, propranolol, or proctacyclin to increase splanchnic flow (38,70–73). Reperfusion injury can be attenuated by blocking free radical generation with folic acid, and allopurinol and administering free radical scavengers such as albumin, mannitol, vitamin C, vitamin A, and vitamin E (74–76). Injury related to PLA$_2$ activity may be ameliorated by quinacrine, lidocaine, allopurinol, and steroids (34,77–79). Moreover, vitamin C and vitamin E stabilize cell membranes and prevent increased capillary permeability.

Glutamine has been implicated as sustaining mucosal architecture and function by scavenging free radicals and preventing lipid peroxidation. In addition, glutamine combines with acetyl cysteine to form glutathione (80). In the reaction catalyzed by the selenium-containing enzyme glutathione peroxidase, glutathione is transformed to oxidized glutathione. This then combines with hydrogen peroxide and degrades it to water, preventing hydrogen peroxide from reacting with superoxide to produce a hydroxyl radical. N-acetyl cysteine has been reported to favorably affect indirect indicators of tissue oxygenation (81), perhaps because it is a precursor of glutathione.
Hydrocortisone has been implicated in decreasing cytokine release from primed macrophages. Occasionally patients have an inadequate steroid response to stress and an appropriate daily stress dose of glucocorticoid (e.g., 300 mg of hydrocortisone) should be administered. Annane et al. showed a significant reduction in mortality from 73% to 63% in patients with septic shock and adrenal insufficiency who were given low-dose hydrocortisone and fluocortisone (82). Polyoxymyxin B avidly binds endotoxin; in fact, it is used in industry to clear endotoxin during production of various medical devices. Finally, albumin is another free radical scavenger and may have a place in trauma resuscitation if prior therapy can prevent increased capillary permeability. A solution of 5% albumin would then be an effective plasma volume expander while binding free radicalicals. Albumin has recently been shown to be as safe as saline in a large heterogeneous ICU population (6,997 patients), and other investigators have demonstrated improvement in organ function in specific patient populations such as hypocalumemic patients and patients with acute lung injury or ARDS (83–85). The iron-dependent reactions can be blocked by deferoxamine, a chelating agent; however, unless it forms a complex with hydroxethyl starch, its duration of action is too short and its incidence of hypotension has been too great to jus- tify use in patients (34,86,87). Activated protein C (APC) has also been proposed to reduce absolute mortality by 6.1% in severely ill patients in septic shock in an attempt to stop parts of the inflammatory cascade before it starts. APC exerts its effect by modulating the systemic inflammatory response, inhibiting production of TNF-α, interleukin-1, and interleukin-6 (88).

**FUTURE INVESTIGATIONS**

Investigators have considered serum lactate levels to be a cellular marker of oxygen debt in patients with sepsis. Serum lactate, however, may not be a reliable marker of hypoxia because it represents the net effect of production and elimination. Its level may be elevated in conditions associated with either increased lactate production or decreased clearance (i.e., sepsis associated with liver failure). Furthermore, the serum lactate level rep- resents a global index and may not be an optimal measure of the adequacy of regional or microvascular perfusion and may transiently rise during therapeutic maneuvers because of a regional washout phenomenon (89,90). Other metabolic markers include the ATP:ADP ratio and direct plasma measurements of the metabolites resulting from the degradation of adenine nucleotides (e.g., inosine, hypoxanthine, xanthine, and uric acid) (21,91). Direct measurements of tissue pH can be made with pH microprobes placed in the intestinal mucosa. This technique is invasive and is limited by local tissue artifact, electrode artifact, and an inability to recalibrate the electrode in vivo, and, therefore, is not applicable clinically (46,91).

Although results of gastric tonometry have been promising and suggestive of improved outcomes in critically ill patients, its practicability in today’s ICU remains poor. Sublingual capnometry (when made available after the recall in 2004) has good potential as an efficient and effective monitor of “splanchnic” tissue. Although pH and PCO₂ monitoring has been tested in several clinical applications, several fundamental questions remain: Is the PCO₂ gap a better predictor than sIPCO₂ for development of MOF and mortality? What are the normal and abnormal values? Should sIPCO₂ be used to initiate therapy, represent an end point, or possibly both? The available data suggest that intervention to prevent the ischemia/reperfusion injury should not wait for an abnormal pH. Restoration of a normal pH could be valuable as a marker for the restoration of oxidative metabolism. It is likely that sublingual tonometry will be used to assess organ preservation and function, as an early prognostic sign for shock states, or for the timely detection of catastrophic complications like pancreatic necrosis, anastomotic leaks, or ischemic bowel and will offer accurate information when the normal markers of resuscitation become unreliable. Sublingual tonometry may be helpful in decisions to both initiate therapy and halt resuscitation at a more appropriate end point. In addition, as the existing technology improves, continued sublingual monitoring may also become feasible, offering real-time monitoring of “splanchnic” tissue perfusion. In addition, much work is also needed to further determine the expansion of replacement steroids in septic shock to other critically ill patients. Duration of therapy, optimal dosage, and its role in the setting of hypoalbuminemia have yet to be determined.

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