State of the Art Review

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Optimal endpoints of resuscitation and early goal-directed therapy

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Abstract

Objective: To review the available endpoints of shock resuscitation, including traditional perfusion parameters, oxygen-transport variables, lactate, base deficit (BD), venous oxygen saturation, and gastric mucosal pH, and to discuss the currently accepted methods of assessing successful reversal of oxygen (O_2) debt in shock patients.

Human-based studies: Early goal-directed therapy has unequivocally been shown to positively affect outcome in human patients experiencing cardiovascular shock. However, specific endpoints of resuscitation to target in critically ill patients remain controversial. Reliance on traditional endpoints of resuscitation (heart rate [HR], blood pressure [BP]) appears insufficient in detection of ongoing tissue hypoxia in shock states. A multitude of publications exist suggesting that indirect indices of global (lactate, base deficit, mixed/central venous oxygen saturation), regional (gastric intramucosal pH [pH_i]) and cellular (transcutaneous oxygen) oxygenation are more successful in outcome prediction and in assessing adequacy of resuscitative efforts in this patient population.

Veterinary-based studies: While there are several large studies evaluating endpoints of resuscitation in experimental canine shock models, this author was unable to find similar research pertaining to small animal veterinary patients. The few articles in which blood lactate is evaluated for prognostic purposes in canine patients are included in this review.

Data sources: Veterinary and human literature review.

Conclusions: Optimization of early resuscitative efforts has proven to have a survival benefit in human shock patients, and major strides have been made in determining which endpoints of resuscitation to target in this patient population. Similar clinical trials designed to evaluate indices of ongoing global and regional tissue hypoxia in small animal veterinary shock patients are warranted.

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Keywords: base deficit, central/mixed venous oxygen saturation, endpoints of resuscitation, gastric intramucosal pH, lactate, shock, trauma

Introduction

During the evaluation of patients with acute injury, indicators of illness severity, success of resuscitative efforts and outcome are invaluable to clinicians. Ongoing tissue hypoxia in critically ill patients is a comorbid variable in the development of multiple organ failure (MOF), and contributes to morbidity and mortality.[1] According to Shoemaker, 'The most common life-threatening hypodynamic state is that of the inadequately volume-resuscitated postoperative and trauma patient.'[1] Optimization of early resuscitative efforts is, therefore, paramount to successful treatment of hypoperfused patients.

Traditional endpoints of resuscitation, including restoration of normal clinical perfusion parameters (i.e., mentation, capillary refill time [CRT], heart rate [HR], peripheral pulse quality, and rectal temperature), blood pressure, and urine output remain the standard of care.[2] However, it has been documented that up to 85% of severely injured human patients have evidence of ongoing tissue hypoxia despite normalization of vital signs, suggestive of occult oxygen (O_2) debt (defined as the cumulative deficit in cellular oxygen consumption)[3] and the presence of compensated shock.[4] The need for rapid recognition and correction of this state has prompted the search for more sensitive markers of adequate resuscitation. Evaluation of O_2 transport varia-

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bles (cardiac index [CI], oxygen delivery [DO_2], and oxygen consumption [VO_2]) has been advocated for documentation of ongoing O_2 debt in patients suffering from acute injury,[5] and several investigators have demonstrated a survival advantage associated with the achievement of supranormal DO_2 in certain patient populations.[6–9] Additionally, measurements of blood lactate, base deficit (BD), and mixed venous oxygen saturation (S_VO_2)/central venous oxygen saturation ($S_{CV}O_2$) have been investigated for evaluation of resuscitative efforts, detection of occult global tissue hypoxia, and outcome prediction in critically ill patients.[10–28]

More recently, investigators have turned their focus on methods of evaluating perfusion status at regional tissue beds.[29–40] Gastric tonometry provides a clinical method of estimating intestinal perfusion, and gut-related parameters have been shown to be useful markers of shock severity.[32–35] Additional means of assessing the adequacy of cellular oxygenation are via tissue O_2 electrodes or infrared spectroscopy.[36,37] Sublingual capnometry and measurement of transcutaneous CO_2 provide alternative methods of evaluating a shock patient for ongoing hypoperfusion at the tissue level.[36,38–40]

The purposes of this article are to review the advantages and shortcomings of the various endpoints of resuscitation mentioned above, and to discuss the currently accepted methods of assessing successful reversal of O_2 debt in shock patients. The author will comment on the history of early goal-directed therapy (EGDT) and its recent reemergence in the human medical arena. Additionally, a brief discussion of the assessment of regional cellular oxygenation will be incorporated in this paper. This review was compiled from available review articles and original and retrospective studies evaluating human patients and experimental animal models of hemorrhagic shock. Articles evaluating endpoints of resuscitation in small animal veterinary patients are few in number; those available are incorporated in this review.

Pathophysiology of Shock States

The underlying pathology common to all causes of shock is poor tissue perfusion resulting from low or unevenly distributed blood flow. In a healthy subject, cardiac output (CO) is continuously adjusted to meet systemic O_2 demands and consumption. Irrespective of underlying cause, acute injury results in a decrease in CO (and DO_2), disrupting the normal O_2 balance. This may result in global tissue hypoxia and O_2 debt. The imbalance in DO_2 and VO_2 associated with low-flow states is initially tolerated by increased oxygen extraction ratio (O_2ER) of blood, a mechanism by which initial VO_2 deficit (O_2 debt) is minimized. If O_2 debt is repaid via reestablishment of adequate tissue perfusion (either through physiologic compensations or therapeutic interventions) homeostasis is restored. If hypoperfusion persists, a critical decrease in tissue VO_2 and resultant cellular dysoxia and anaerobic metabolism, cell death, and MOF ensue.[1,3,41–44]

Shock syndrome can occur subsequent to any severe injury or trauma. Hemorrhage or hypovolemia, with resultant decreased circulating blood volume, trigger a series of compensatory mechanisms designed to reestablish normal blood flow. Activation of the sympathetic nervous system and release of epinephrine and norepinephrine from the adrenal medulla result in peripheral vasoconstriction, increased HR, and increased myocardial contractility. This primary response is augmented by activation of the renin–angiotensin–aldosterone system (RAAS), and release of antidiuretic hormone from the posterior pituitary and adrenocorticotropic hormone from the hypothalamus, which function to increase fluid conservation to stabilize circulating blood volume. Fluid shifts from the interstitial space into the vasculature to support intravascular volume as well. Regional autoregulatory mechanisms and changes in capillary blood flow maintain perfusion to vital organs (heart, brain, kidney) at the expense of others (liver, muscle, gastrointestinal tract).[45]

Compensatory shock is difficult to recognize as vital signs are normal despite ongoing tissue hypoperfusion. This stage of shock progresses to decompensatory shock, when endogenous responses are exhausted and therapeutic intervention is inadequate or delayed. Early decompensatory shock is characterized by abnormalities in perfusion parameters, including altered mentation, increased CRT, tachycardia, hypotension, and oliguria. While this stage of shock is amenable to early intervention, late decompensatory shock secondary to prolonged tissue hypoxia, autoregulatory failure, and hemodynamic collapse is not responsive to resuscitative efforts.[44,45]

Traditional Endpoints of Resuscitation

Conventional vital signs, including HR, BP, and urine output are commonly utilized to assess hemodynamic stability and recognize shock in acutely ill patients. However, many patients who have life-threatening illnesses present to the emergency room with apparently normal or stable vital signs.[46,47] Tachycardia, hypotension, and oliguria occur during the early decompensatory stage of shock, whereas many victims of acute injury are in a state of compensated shock.[4] In the early stages of injury, neurohumoral mechanisms increase CO by increasing HR and stroke volume (SV) and maintain the BP at near normal values by increasing

systemic vascular resistance. This stress response limits the usefulness of these cardiovascular variables in the assessment of the acutely ill patient.[3]

BP is often used to gauge the adequacy of resuscitation and to define criteria for the severity of shock. Wo et al.[46] demonstrated poor correlation between mean arterial blood pressure (MAP) measured via radial artery cannulation and CO measured with the thermodilution technique in high-risk human trauma and postoperative ICU patients. In nonsurvivors, the drop in cardiac index (CI) (i.e., the ratio of CO/body surface area) that was observed several hours after ICU admission was not accompanied by a decline in MAP. The development of hypotension was delayed for 3–12 hours after the observed decrease in blood flow, suggesting that the physiologic stress response to injury transiently maintained BP in the face of decreasing flow.

Another group of investigators compared conventional vital signs (HR, systolic BP [SBP], and diastolic BP [DSP]) and the stroke index (SI) to identify acute critical illness in the human ER.[47] Stroke index is the ratio of HR/SBP and has been shown to be inversely related to left ventricular stroke work in acute circulatory failure.[48] In a healthy adult, the SI ranges from 0.5 to 0.7.[48] These investigators demonstrated that conventional vital signs (HR and SBP) measured individually failed to identify patients requiring immediate treatment and hospitalization, and that, in the absence of overt hypotension, the SI (>0.9) appears to be superior in recognition of ongoing shock.[47] Other investigators have similarly documented the inadequacy of commonly monitored variables (HR, MAP) in assessing severity of acute illness in human patients, showing marked variability in the predictive value of each variable when measured individually depending on the stage of circulatory failure.[49]

Additionally, several investigators have shown that relying on the normalization of HR, BP, and urine output as endpoints of resuscitative efforts can mask significant deficiencies in systemic oxygenation, leading to the accumulation of O_2 debt and increased morbidity and mortality.[4,50–52] Siegel et al.[50] utilized a canine model of hypovolemic shock to quantify the critical level of partial blood volume replacement necessary to guarantee short-term survival and avoid end-organ damage secondary to prolonged tissue hypoxia. These investigators demonstrated that while both arterial lactate concentration and BD trended significantly with the O_2 debt response following hemorrhage and partial resuscitation in experimental subjects, neither BP nor CI were good indicators of protection against cellular hypoxia in this setting.[50] Scalea et al.[51] evaluated the success of resuscitative efforts in human patients with multisystem trauma and concluded that 80% had evidence of inadequate tissue perfusion despite the attainment of normal HR, BP, and urine output. Ongoing tissue hypoxia in these subjects with normal vital signs was evidenced by elevated lactate and decreased S_VO_2.[51] Another group of investigators reported on the necessity of additional resuscitation efforts to combat ongoing tissue hypoxia (as evidenced by elevated lactate and central venous O_2 desaturation) in human critically ill patients who had achieved normal HR and BP.[52]

Because of the unreliability of traditional vital signs in documentation of early shock states and assessment of the success of initial resuscitation efforts, much research has focused on the identification of more sensitive markers of ongoing O_2 debt.

Hemodynamic and O_2 Transport Monitoring

Oxygen delivery represents the amount of O_2 delivered to the peripheral tissue per minute, and is affected by CI, hemoglobin (Hb), arterial oxygenation saturation (SaO_2) and, to a much lesser extent, the partial pressure of arterial oxygen (PaO_2). Oxygen consumption is the rate of O_2 uptake from the microcirculation, and represents the sum of all oxidative metabolic reactions in the body.[3,53] Oxygen consumption can be determined indirectly utilizing the thermodilution technique to measure CI and the Fick equation to calculate VO_2, or can be measured with metabolic carts and analysis of the volumes and fractions of expired gases.[3,53] The ratio of VO_2 to DO_2 represents the O_2ER. DO_2 normally exceeds VO_2 by a wide margin; normal O_2ER is about 25–30%. As DO_2 falls, O_2ER increases to maintain normal VO_2 ('supply independence'). A critical DO_2 is eventually reached below which an increase in O_2ER is no longer able to compensate for the fall in DO_2. Below this critical DO_2, VO_2 decreases with decreasing DO_2 ('supply dependence'), anaerobic glycolysis predominates and tissue hypoxia and resultant O_2 debt ensue.[3,41–43,53]

According to Shoemaker, in shock states, DO_2 and VO_2 represent the best available means of assessing functional adequacy of circulation and metabolism and the accumulation of unpaid O_2 debt.[5] Shoemaker et al.[6] have previously demonstrated that the ability of a human patient to attain supranormal DO_2 during acute operative trauma confers a survival advantage. Furthermore, this investigator has derived criteria for prediction of death from the pattern of circulatory changes evident in nonsurvivors.[6] Subsequent attempts to utilize survivor values of CI, DO_2, and VO_2 as endpoints of resuscitation have met with conflicting results.[7–9,54–60]

Declines in DO_2 and VO_2 were early changes seen in nonsurvivors in the aforementioned Shoemaker study.[6] A decrease in VO_2 to subnormal values ($<120\,mL/min/m^2$) has been shown by other investigators to be an ominous prognostic sign in human patients, predictive of impending cardiovascular collapse.[54,55] Rady et al.[54] demonstrated that a reduction of VO_2 following acute myocardial infarction predicted the development of cardiogenic shock and death. A different group of investigators evaluated the response of severely ill patients with known risk factors for development of MOF, to a resuscitation protocol designed to obtain a VO_2 of $>150\,mL/min/m^2$.[55] In this study, patients with baseline VO_2 $<150\,mL/min/m^2$ and patients who failed to achieve a 12-hour VO_2 greater than this value ('nonresponders') were more likely to develop MOF.[55]

While O_2 transport variables appear to be useful predictors of outcome, their role as endpoints of resuscitation is controversial, and has been the subject of much debate.[56–61] Shoemaker et al.[7] demonstrated that achieving 'supranormal' values for O_2 transport variables in human surgical patients with high-risk criteria early in the postoperative period reduced mortality when compared with the use of standard resuscitation goals. Mortality rates in this study were 4% in patients who achieved supranormal values for CO ($>4.5\,L/min/m^2$), DO_2 ($>600\,mL/min/m^2$), and VO_2 ($>170\,mL/min/m^2$) perioperatively versus 33% in patients whose target goals for CO and O_2 transport variables were in the normal range.[7] Tuchschmidt et al.[8] demonstrated that human patients with septic shock who were randomized during initial resuscitation to obtain a supranormal DO_2 via manipulation of CI to $6\,mL/min/m^2$ had a reduction in mortality when compared with patients whose target CI during resuscitation was $3\,mL/min/m^2$. Bishop et al.[9] similarly found that attaining supranormal values for O_2 transport variables within 24 hours of hospital admission in human trauma patients decreased mortality, ICU-days, shock-related organ failures, and days on mechanical ventilation compared with conventional resuscitation protocols. This group of investigators concluded that increased CI, DO_2, and VO_2 are compensatory mechanisms with survival value, and that augmentation of these variables during resuscitation can positively affect outcome.[9]

Conversely, Hayes et al.[57] found that targeting supranormal values for CI, DO_2, and VO_2 with dobutamine therapy in critically ill human patients who failed to achieve these values following initial resuscitation offered no survival benefit over conventional therapy. In hospital mortality was higher in the treatment group than in the control group.[57] Similar results were demonstrated by Gattinoni et al.[58] In this study, critically ill human patients randomized into 1 of 3 groups (i.e., achievement of a normal CI, a supranormal CI, or a S_VO_2 $>70\%$, respectively) showed no difference in hospital mortality.[58]

The contrast between the results of these 2 studies and those reported previously may be in part because of differences in patient populations. Patients in the studies performed by Hayes et al.[57] and Gattinoni et al.[58] were randomized postoperatively and often after complications had occurred, whereas therapy for patients in earlier studies was initiated preoperatively or before the onset of clinical deterioration. Furthermore, the patients in Hayes' study failed to reach hemodynamic goals with fluid resuscitation before randomization, suggesting smaller physiologic reserve and more severe illness when compared to many of the patients in the study by Shoemaker et al.[7] An additional criticism of the paper by Gattinoni was that failure to improve outcome could have resulted, in part, from a difficulty in attaining treatment goals, as 33% of patients in the O_2-saturation group and 55% of patients in the CI group either did not achieve or sustain target values during the study period.[56,58]

The conflicting results in the aforementioned studies call into question the utility of invasive placement of pulmonary artery catheters (PACs) in critically ill patients for the purposes of measuring and augmenting O_2 transport variables. A recent meta-analysis of hemodynamic optimization concluded that the timing of goal-directed therapy is paramount to successful outcome.[59] Hemodynamic bedside monitoring by PACs and attainment of supranormal values for O_2 transport variables does not appear to be an effective adjunctive treatment in the late stage of illness, after the development of MOF. However, PACs goal-directed therapy, administered early or prophylactically in patients with high-risk factors for mortality, does appear to positively affect outcome in postoperative and trauma victims.[59–61]

However, the placement of PACs to measure O_2 transport variables is expensive, technically demanding and can be associated with catastrophic complications. Additionally, measurement of DO_2 and VO_2 involves the use of cumbersome equipment (metabolic carts) and complex calculations.[3,53,62] Therefore, over the last several decades, much research has focused on the recognition of early stages of shock and the evaluation of resuscitative efforts through the use of less invasively obtained surrogate markers of ongoing tissue hypoxia.[13,14,17,19–23,26,27,29–40,63–66]

Lactate

Lactate is produced from pyruvate by the enzyme lactate dehydrogenase. This reaction occurs in the cytosol

of all cells, predominately during periods of O_2 deficiency (anaerobic glycolysis). The major lactate producers are skeletal muscle and the intestinal tract, with lesser contributions by the brain, red blood cells, leukocytes, platelets, and skin.[67] When cellular O_2 balance is restored, this reaction is reversible, allowing the regeneration of pyruvate from lactate and resumption of the more energy-efficient process of aerobic metabolism (Figure 1). Blood lactate increases when its production by hypoxic tissue overwhelms its elimination by the liver and kidneys (the liver is the predominant organ responsible for lactate clearance, handling approximately 50% of the daily lactate load).[67] Therefore, tissue hypoperfusion and resultant hypoxia is an important cause of hyperlactatemia.

The utility of blood lactate concentration in the indirect assessment of tissue O_2 balance in critically ill shock patients has received much attention. Arterial blood lactate level has been shown by several investigators to be an approximation of the severity of shock, correlating with the success of resuscitative efforts and mortality in both human and experimental animal patients.[10–13] In a canine hemorrhagic shock model, investigators found that lactic acidosis was more predictive of severity of hemorrhage (i.e., had a stronger correlation with O_2 debt) than were conventional hemodynamic parameters (BP, CO).[10] Furthermore, these investigators demonstrated that arterial lactate correlated with probability of death in these experimental subjects.[10] Similarly, Davis et al.[11] in a porcine model of hemorrhagic shock, showed that serum lactate correlated with severity of hemorrhage and lactate levels decreased significantly with adequate resuscitation.

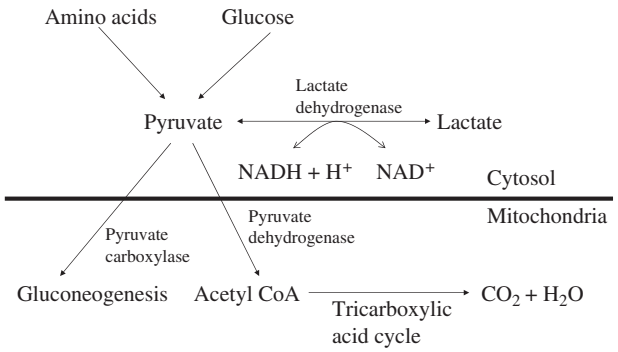

Figure 1: Lactate is the end product of glucose metabolism, and is formed in the cytosol when pyruvate is converted to lactic acid by the enzyme, lactate dehydrogenase. Most lactic acid is produced during anaerobic glycolysis. When normal oxidative metabolism is restored, cells of the liver (and kidney) metabolize lactate back to pyruvate, which then enters the mitochondria for conversion into either CO_2 and H_2O or glucose.

An early clinical study by Rashkin et al.[12] demonstrated that, in a group of critically ill human patients, there was a nonlinear negative correlation of CO and DO_2 with lactate, suggesting that arterial lactate concentration is a good marker of tissue oxygenation. Other investigators demonstrated that in human patients suffering from septic shock, blood lactate was superior to O_2-derived variables in outcome prediction.[13]

Not only are admission lactate levels prognostically important, but the response of the lactate to intervention (fluid resuscitation) has been shown to add predictive value.[63–65] Vincent et al.[63] evaluated serial arterial lactate concentrations during the resuscitation of human patients with noncardiogenic shock. Patients who demonstrated a decrease in blood lactate concentration with fluid therapy survived, while those whose lactate concentrations remained elevated despite resuscitative therapy died. In this small group of patients ($n = 17$), a reduction in lactate greater than 5% in the first hour with volume resuscitation was associated with a survival rate of 100%.[63] Other studies have similarly shown that the time interval to normalize serum lactate has prognostic value.[64] In a study evaluating lactate clearance in human trauma patients, all patients whose arterial lactate level normalized in 24 hours survived, whereas the survival rate if lactate levels were normal by 48 hours decreased to 75%. Only 14% of patients who did not have a normal serum lactate concentration at 48 hours survived.[64] This group of investigators also demonstrated no significant difference in CI, DO_2, and VO_2 between survivors and nonsurvivors, and that attainment of supranormal O_2 transport variables conferred no survival benefit.[64] Nguyen et al.[65] evaluated the prognostic importance of early lactate clearance in human patients suffering from severe sepsis or septic shock, and found that a higher arterial lactate clearance within 6 hours of initial resuscitation was associated with improved survival compared to a more prolonged lactate clearance time. In this patient population, APACHE II score and initial vital signs were not associated with outcome.[65]

There are limitations to the exclusive reliance on blood lactate concentration as a surrogate marker of tissue oxygenation. Even though the most clinically significant cause of hyperlactatemia is systemic tissue hypoxia (type A lactic acidosis), the presence of hyperlactatemia is not specific for a global oxygenation defect. Type B lactic acidosis has been characterized as an acidosis that exists without documented tissue hypoperfusion and hypoxia.[67] Increased lactate production occurs with processes that speed glycolysis (which occurs more rapidly than the oxidation of pyruvate) such as alkalemia or glucose infusion. Additionally, lactate levels will increase when energy requirements exceed

the capacity of aerobic metabolism (e.g., strenuous exercise, trembling, and seizures). Sepsis is associated with alterations of cellular metabolism that result in hyperlactatemia independent of the effect of tissue hypoxia. This effect is secondary to endotoxin-mediated inhibition of pyruvate dehydrogenase. In addition, administration of catecholamines for the treatment of septic shock results in altered lactate metabolism and an overestimation of the actual O_2 debt.

Other causes of Type B lactic acidosis in critically ill human and animal patients include inborn errors of metabolism, systemic neoplasia, renal failure, and hepatic dysfunction.[53,66,67] As the blood lactate level is a reflection of the balance between lactate production and its elimination, and lactate is primarily cleared via the liver, patients with severe hepatic dysfunction may demonstrate delayed lactate clearance following resolution of shock states. Additionally, restoration of blood flow may result in release of sequestered lactate from regional tissues, where it accumulated during the period of tissue hypoperfusion ('wash-out' phenomenon) and result in delayed lactate clearance.[53,67,68]

Base Deficit

As mentioned previously, as shock states progress, they become associated with anaerobic metabolism at the cellular level. Another method available for determination of the degree of anaerobic glycolysis is through determination of the BD.[56] BD is the amount of base, in millimoles, required to titrate 1 L of whole arterial blood to a pH of 7.40, with the sample fully saturated with O_2 at 37 °C and a PCO_2 of 40 mmHg.[69] As PCO_2 is held constant, any change in BD will be because of a metabolic derangement in acid–base homeostasis. In the past 2 decades, several investigators have found that BD is a sensitive indicator of compensated shock, and that the magnitude of BD early in the course of illness correlates with eventual development of MOF and mortality in experimental animals and human patients.[14–21] In a swine hemorrhagic shock model, Davis et al.[14] demonstrated that BD correlated with hemodynamic (MAP) and tissue perfusion (S_VO_2, DO_2/VO_2 ratio) variables both during hemorrhage and resuscitation. Furthermore, during the period between hemorrhage and the onset of resuscitation, when physiologic compensatory mechanisms resulted in the improvement of several of the experimental variables, BD remained depressed, reflecting ongoing O_2 debt.[14] In a dog model of acute hemorrhage, Waisman et al.[15] reported that of 30 parameters studied (acid–base status, BP and flow, oxygenation and ventilation parameters), arterial BD had the strongest association with blood volume loss. Venous BD was also strongly predictive of blood volume reduction in this model. Other investigators have verified the strong correlation between arterial and venous BD and the ability of both to reflect ongoing tissue hypoxia in laboratory animals with hemorrhagic shock.[11,16] Therefore, while arterial BD has been shown by several groups to be the best predictor of change in blood volume in shock models, venous BD is considered a reliable indicator of physiologic status in shock and resuscitation when arterial samples cannot be obtained.[11,16]

In a group of human trauma patients instrumented with PACs, investigators demonstrated that patients with persistently high BD had lower VO_2 and VO_2 utilization coefficients compared with patients with low BDs. DO_2, however, was not significantly different between high- and low-BD groups.[17] The investigators suggested that this uncoupling of DO_2 and VO_2 during periods of decreased O_2 tension occurs secondary to a reduction in the cellular redox state. In this situation, the regeneration of ATP from its substrates is hampered, leading to an accumulation of hydrogen ions, intracellular acidosis and elevation of BD.[17] Mitochondrial oxidative dysfunction has been previously documented in human trauma patients.[18]

Patients in the Kincaid study with persistently high BD had higher rates of MOF and death compared with patients who achieved low BD with resuscitation.[17] The ability of BD to predict clinical course and outcome has been shown by other investigators.[10,19–21] Davis et al. stratified a group of human trauma patients according to initial BD (mild [2 to -5], moderate [-6 to -14] and severe [< -15]). This stratification indicated the magnitude of volume deficit and correctly predicted the aggressiveness of early volume resuscitation.[19] A later study by Davis et al.[20] reported that transfusion requirements, hospital length of stay, the development of MOF, and mortality all increased with worsening admission BD in human trauma patients. In a canine model of hemorrhagic shock, Dunham et al.[10] demonstrated that of the single-variable predictors included in their study (lactate, MAP, and CO), BD correlated most closely with accumulating O_2 debt and subsequent mortality. The best prediction of O_2 debt in this study was obtained using both plasma lactate and BD together.[10] Rutherford et al.[21] in a large retrospective study found that an admission BD of -15 mmol/L in human trauma patients <55 years age without head injury was predictive of mortality.

Mixed/Central Venous O_2 Saturation

An additional global marker of the adequacy of tissue oxygenation is $S_VO_2/S_{CV}O_2$. Venous HbO_2 saturation is measured from the pulmonary artery (S_VO_2) via PACs

or from the superior vena cava or right atrium ($S_{CV}O_2$) through the use of a central venous catheter. Blood samples are analyzed for venous oxyhemoglobin saturation with a co-oximeter or by utilizing a special fiberoptic fiber attached to a centrally placed catheter. Central venous O_2 saturation may alternatively be extrapolated from the P_VO_2 through the use of the HbO_2 saturation curve (Figure 2). Venous HbO_2 saturation is influenced by SaO_2, VO_2, CI, and Hb where $S_VO_2 = SaO_2 – VO_2/(CI\ Hb)$. Therefore, in the absence of anemia and hypoxemia, the measurement of S_VO_2 reflects the relationship between VO_2 and CI (or DO_2). [53]

Under a normal systemic O_2 balance, the $S_{CV}O_2$ and S_VO_2 are in excess of 65% and 75%, respectively.[44] As an early response to tissue hypoxia, systemic O_2 extraction from venous blood increases, resulting in a concurrent decline in $S_{CV}O_2$ and S_VO_2. Therefore, venous desaturation is one of the major compensatory mechanisms to maintain peripheral VO_2 in low-flow states, and its measurement in critically ill patients reflects systemic O_2 balance and cumulative O_2 debt.[44]

Measurement of S_VO_2 requires placement of a PAC, which may be technically challenging, not readily available, expensive, and associated with serious complications. Central venous O_2 saturation is monitored through a central venous catheter, the placement of which is less costly, more routinely performed, and associated with fewer complications.[44] Controversy exists as to whether or not $S_{CV}O_2$ can replace S_VO_2 when evaluating the hemodynamic state of a patient by giving an estimate of tissue O_2 extraction. However, several investigators have documented a strong correlation between these 2 measurements, and both have proven valuable in the assessment and treatment of shock patients.[22–28]

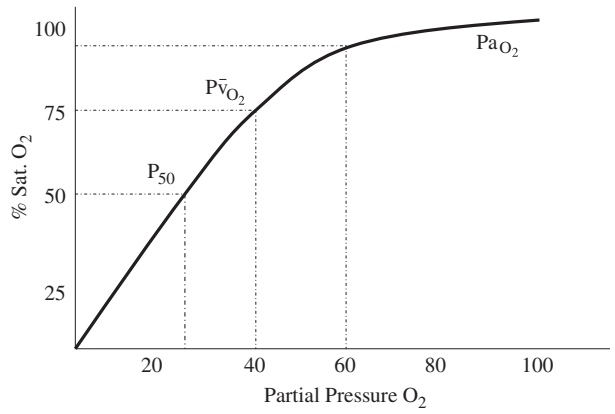

Figure 2: This curve illustrates the relationship between plasma oxygen partial pressure and the extent to which hemoglobin (Hb) is saturated with oxygen. Normally, hemoglobin is 50% saturated at plasma PO_2 of about 27 mmHg in humans and dogs and 36 in cats (P_{50}). Normal arterial blood has an oxygen partial pressure (PaO_2) of 97 mmHg and an oxyhemoglobin (HbO_2) saturation of 97%. Normal mixed venous blood has an oxygen partial pressure (PvO_2) of 40 mmHg and an HbO_2 saturation of 75%.

In a dog model of hemorrhage, Reinhart et al.[22] evaluated subjects for correlations between S_VO_2 and $S_{CV}O_2$ during hemorrhagic shock and resuscitation. The mean difference between S_VO_2 and $S_{CV}O_2$ was $3.7 \pm 2.9\%$ (SD), and these experimenters observed a strong correlation between these measurements throughout the study ($r = 0.96$).[22] Scheiman et al.[23] simultaneously monitored S_VO_2 $S_{CV}O_2$, and right atrial oxygenation saturation (RAO_2) in human patients suffering from acute myocardial infarction. These investigators documented a strong correlation between mean $S_{CV}O_2$ and S_VO_2 in mildly affected patients ($r = +0.98$). This strong correlation was lost, however, when evaluating patients in severe cardiogenic shock.[23] The authors postulated that the loss of correlation between these 2 measurements during severe shock was consequential to alterations in renal, splanchnic, and cerebral perfusion that occur in low-flow states.[23] Other investigators have similarly found that $S_{CV}O_2$ underestimates the imbalance between VO_2 and DO_2 during periods of low CO.[24,25] In the study by Scheiman's group, RAO_2 did not differ from S_VO_2 and these measurements showed excellent correlation regardless of shock severity.[23]

Scalea et al.[26] evaluated the ability of both S_VO_2 and $S_{CV}O_2$ to gauge severity of blood loss in a canine model of hemorrhagic shock. In the first group of anesthetized dogs, the r value for mean S_VO_2 versus percent blood loss was 0.94. In a second group of unanesthetized animals, the r value for mean $S_{CV}O_2$ versus percent blood loss was 0.92.[26] In both instances, these measurements were more sensitive for predicting severity of blood loss than were CI or pulse pressure.[26] These investigators went on to evaluate the sensitivity and reliability when $S_{CV}O_2$ was applied in a clinical setting.[27] In this follow-up study, 39% of human trauma patients with suspected blood loss were found to have $S_{CV}O_2 < 65\%$ despite the presence of normal vital signs (e.g., BP, pulse pressure, HR). Compared with patients with $S_{CV}O_2 > 65\%$, patients with more pronounced venous desaturation had more serious injuries, larger blood losses, and required more transfusions.[27]

Rivers et al.[15] recently reexamined the benefit of EGDT in affecting outcome in septic human patients. While Shoemaker and others in earlier studies targeted normal to supranormal values in DO_2 and VO_2 during initial resuscitative efforts, Rivers' group targeted attainment of a normal $S_{CV}O_2$ as the resuscitative endpoint in their septic study patients. Patients were randomly assigned to standard therapy versus EGDT (correction of $S_{CV}O2$ to $>70\%$, with the addition of

vasoactive agents, packed red blood cell transfusion, and inotropes to standard therapy to achieve this endpoint in less than 6 hours) immediately upon hospital admission. In hospital mortality was 30.5% in patients who received EGDT, versus 46.5% in the group assigned to standard therapy ($P = 0.009$). Additionally, patients assigned to EGDT had lower lactate concentrations and BD and reduced ISS/organ dysfunction.[28]

Limitations to the use of $S_{CV}O_2$ and S_VO_2 for evaluation of critically patients include the influence of Hb concentration and SaO_2 in determination of these variables and the loss of correlation between mixed and central venous O_2 saturation in low-flow states (if measuring $S_{CV}O_2$). Additionally, an underlying defect in systemic O_2 extraction seen in certain clinical situations (e.g., sepsis) can lead to normal or high $S_{CV}O_2$ and S_VO_2 in the presence of significant O_2 debt.[44,66]

Organ-specific Oxygenation

As blood flow is not uniformly distributed to all tissue beds in low-flow states, global markers of tissue perfusion may not adequately detect regional ischemia. Measurement of gastric intramucosal pH (pHi) has been investigated as a means of obtaining a more local, or regional, indicator of hypoxia in shock patients. This technique (gastric tonometry) involves insertion of a gas-permeable, saline-filled balloon into the gastric lumen. After approximately 30 minutes of equilibration time between the saline solution and the PCO_2 of the gut lumen, a sample is drawn for analysis of PCO_2 with a blood gas analyzer. The Henderson–Hasselbach equation is then utilized to calculate the pHi, where $pHi = 6.1 + \log [HCO_3^-]/0.03PCO_2$. Arterial bicarbonate is used in this calculation.[53,69] Cited values for normal pHi vary slightly, ranging from 7.3 to 7.35.[32–35]

The use of gas tonometry rather than saline tonometry has been advocated to avoid procedural problems associated with manipulation of the saline solution and to allow for more rapid equilibration times. *In vitro* and *in vivo* results correlate well with those obtained using the saline method.[29,30] Additionally, there are now monitors available that can continuously sample the CO_2 in the balloon for pHi measurements.[31]

Gastric intramucosal pH has been utilized by several investigators in the evaluation and/or management of shock victims, and has been shown to correlate with outcome.[32–35] Gutierrez et al.[32] compared tonometric measurements of pHi with traditional vital signs and concurrently obtained O_2 transport variables in predicting outcome in critically ill human patients. Only mixed venous pH and pHi were able to separate survivors from nonsurvivors in this study population.[32] All patients who died in this study, except for one, had final pHi values of <7.32.[32] Doglio et al.[33] similarly found pHi to have prognostic value. Critically ill human patients in this study group with low admission pHi (<7.35) had increased frequency of sepsis and MOF and higher mortality rates than patients who presented with pHi >7.35.[33] Furthermore, patients who failed to obtain normal pHi after 12 hours of hospitalization and treatment had higher mortality rates than those patients who normalized pHi after resuscitative efforts.[33] Chang et al.[34] evaluated the ability of pHi to stratify human trauma patients into survivors and nonsurvivors. Patients with low pHi (<7.32) on admission who did not correct within 24 hours of hospitalization in this study had a 50% mortality, compared with a 0% mortality for those who obtained adequate intestinal perfusion within the same time period.[34] These investigators found that pHi was more predictive of outcome than were O_2 transport variables and lactate.[34]

Ivatury et al.[35] evaluated pHi as an endpoint of resuscitation in human trauma patients. In Group 1, normalization of pHi (>7.3) was the primary endpoint of resuscitation. Group 2 comprised patients for whom obtainment and maintenance of a DO_2 index of 600 and a VO_2 index of >150 were the endpoints of resuscitation. Ninety-three percent of patients who normalized pHi at 24 hours survived. Conversely, the survival rate for patients who had a 24-hour pHi <7.3 (regardless of DO_2 and VO_2 achieved) was 46%.[35] In subgroup analysis, both optimization times for lactate and pHi were significantly different between survivors and nonsurvivors.[35]

A significant assumption when calculating pHi and a major drawback of gastric tonometry is that arterial and mucosal bicarbonate levels are considered equivalent and are used interchangeably. Patients with renal failure, for example, may have a low-calculated pHi without necessarily having splanchnic hypoperfusion. Bicarbonate administration will lead to a discrepancy between arterial and mucosal bicarbonate levels. An additional limitation of tonometry is that extraneous CO_2 (e.g., back-diffusion of CO_2 generated by the buffering of gastric acid by pancreatic bicarbonate) may falsely lower the pHi. For this reason, nasogastric feedings are typically withheld and H_2 receptor antagonists (which prevent intraluminal CO_2 production) are commonly administered before obtainment of tonometric measurements.[53,69]

Cellular O_2 Utilization

In addition to evaluation of splanchnic oxygenation, there are now several experimental and clinical techniques available for assessment of oxygenation in other

regional tissue beds. Cellular perfusion can be directly measured at the skin, subcutaneous tissue, and muscle beds. Oxygen electrodes can be placed on the surface of tissues or organs or fit within the tip of a micropipette and inserted into tissue to measure microcirculatory oxygenation. Limitations of this technology include limited depth penetration of the electrode, the ability to measure PO_2 at only specific points within a given tissue, disturbed performance in the presence of certain gases (i.e., halogenated anesthetic gases), and secondary to tissue disruption/distortion caused during electrode insertion and the dependence of transcutaneous oxygen ($P_{tc}O_2$) on fraction of inspired oxygen (FiO_2).[36,37]

Despite the limitations, direct measurement of cellular oxygenation in shock victims appears to have clinical utility. Tatevossian et al.[36] evaluated $P_{tc}O_2$ and transcutaneous carbon dioxide ($P_{tc}CO_2$) in severely injured human patients. These investigators found that nonsurvivors had significantly lower $P_{tc}O_2$ and higher $P_{tc}CO_2$ values compared with survivors.[37] Furthermore, the length of time with high $P_{tc}CO_2$ (>60 torr) was strongly related to mortality. Conversely, admission HR and BP shared no relationship with outcome in this study population.[37]

Sublingual capnometry has been investigated as a method of diagnosis and quantification of ongoing circulatory compromise. This technology is based on the premise that global tissue hypoperfusion is reflected by systemic hypercarbia. Sublingual PCO_2 ($P_{SL}CO_2$) in normal healthy human volunteers averaged 45.2 mmHg in 1 study.[38] These same investigators evaluated the predictive value of $P_{SL}CO_2$ measurements in human patients with acute critical illness.[38] Shock patients had an initial mean $P_{SL}CO_2$ of 81 mmHg, compared with an initial mean $P_{SL}CO_2$ of 53 mmHg in patients without shock. Initial $P_{SL}CO_2$ was higher in nonsurvivors (92.6 mmHg) than in survivors (58.4 mmHg).[38] $P_{SL}CO_2$ was highly correlated with blood lactate at hospital admission. Following resuscitative efforts, the investigators witnessed an increase in MAP and a concurrent decrease in $P_{SL}CO_2$, whereas there was a delay in the decline of blood lactate.[38] Other investigators have demonstrated $P_{SL}CO_2$ to be a useful indicator of illness severity and to have prognostic value in both experimental animal and human critically ill patients.[39,40]

Another noninvasive, optical technique that shows promise is near-infrared spectropy (NIR). HbO_2, deoxyhemoglobin, and cytochromes of the mitochondrial respiratory chain demonstrate varying absorption peaks when exposed to near-infrared light. Assessment of pathologic impairment of tissue VO_2 is possible by comparing tissue HbO_2 levels (reflecting local O_2 supply) with cytochrome aa3 (the terminal cytochrome) redox (reflecting mitochondrial O_2 consumption).[36] This technique is currently under clinical investigation and may contribute to moving the endpoints of resuscitation to the cellular level.

Endpoints of Resuscitation in Small Animal Veterinary Patients

The above discussion has focused on a review of the human literature evaluating and redefining the optimal endpoints of resuscitation. While there are several large studies utilizing experimental animal models to evaluate markers of tissue oxygenation and adequate resuscitation following hemorrhage, there is a paucity of information pertaining to clinical small animal veterinary patients.

Among the endpoints of resuscitation discussed above, lactate has received the most attention in recent veterinary literature. The usefulness of lactate for prognostic and therapeutic purposes has been previously documented in equine patients suffering from colic.[70,71] Lagutchik et al.[72] evaluated venous blood lactate in healthy and acutely injured dogs. The median venous lactate concentration in clinically normal dogs in this study was 1.38 mmol/L, compared with median lactate levels of 2.48 and 3.85 mmol/L in sick dogs that survived and died, respectively.[72] Lactate level correlated with survival in this population of dogs.[72] Papp et al.[73] evaluated preoperative lactate levels in dogs presenting with GDV and found that elevated lactate (>6 mmol/L) during the resuscitation period was predictive of gastric necrosis. Additionally, survival rate of dogs with plasma lactate <6 mmol/L (99%) was higher than survival rate of dogs with lactate >6 mmol/L (58%).[73] Boysen et al.[74] found that dogs with free abdominal

Table 1: Targeted endpoints of resuscitation in shock patients

Endpoint	Value	Units
CI	3.5–5.5	L/min/m^2
DO_2	>600	mL/min/m^2
VO_2	>150	mL/min/m^2
SBP	80–100	mmHg
MAP	60–80	mmHg
Base deficit	-2–2	mEq/L
Lactate	1 ± 0.5	mmol/L
SvO_2	>70	%
$ScvO_2$	>65	%
pH_i	>7.32	

Haskins SC. The balloon-tipped, multilumen, thermodilution catheter. *5th International Veterinary Emergency and Critical Care Symposium*, San Antonio, TX, 1996, 85p.

CI, cardiac index; DO_2, oxygen delivery; VO_2, oxygen consumption; SvO_2, mixed venous oxygen saturation; $ScvO_2$, central venous oxygen saturation; SBP, systolic BP; MAP, mean arterial pressure.

fluid detected by focused assessment with sonography (FAST) following motor vehicle accidents had higher lactate levels than dogs without free abdominal fluid, suggestive of previous or ongoing blood loss. Because lactate levels were retrospectively evaluated rather than used as an endpoint of resuscitation in the aforementioned investigations, it is difficult to interpret the role of lactate normalization in early resuscitative efforts in small animal veterinary patients.

Conclusion

Early goal-directed therapy has unequivocally been shown to positively affect outcome in human shock patients. However, which endpoints of resuscitation to target in critically ill patients remain controversial. A recent review article evaluating optimal endpoints of resuscitation in human trauma patients recommends the use of lactate, BD, and pHi as appropriate endpoints.[41] No such recommendation can be made for veterinary practitioners as limited data are available. There is evidence that normal vital signs, blood lactate, BD, and $S_VO_2/S_{CV}O_2$ in concert are more sensitive markers for adequacy of tissue perfusion than any of these variables alone. Therefore, until stronger support exists for preferential selection of one endpoint over the others, utilization of a combination of available markers of global and/or cellular oxygenation to assess illness severity and guide resuscitative efforts in emergent small animal patients seems advisable (Table 1).

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