

# Trauma: physiology, pathophysiology, and clinical implications

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## Abstract

**Objective:** To review the physiology, pathophysiology, and consequences of trauma. The therapeutic implications of hypovolemia, hypotension, hypothermia, tissue blood flow, oxygen delivery, and pain will be discussed.

**Data Sources:** Human and veterinary clinical and research studies.

**Human and veterinary data synthesis:** Trauma is defined as tissue injury that occurs more or less suddenly as a result of violence or accident and is responsible for initiating hypothalamic–pituitary–adrenal axis, immunologic and metabolic responses that are designed to restore homeostasis. Tissue injury, hemorrhage, pain, and fear are key components of any traumatic event. Trauma and blood loss result in centrally integrated autonomic-mediated cardiovascular responses that are designed to increase heart rate, systemic vascular resistance, and maintain arterial blood pressure (ABP) to vital organs at the expense of blood flow to the gut and skeletal muscle. Severe trauma elicits exuberant physiologic, immunologic, and metabolic changes predisposing the animal to organ malfunction, a systemic inflammatory response, infection, and multiple organ dysfunctions. The combination of both central and local influences produces regional redistribution of blood flow among and within tissue beds which, when combined with impaired vascular reactivity, leads to maldistribution of blood flow to tissues predisposing to tissue hypoperfusion and impaired oxygen delivery and extraction. Gut blood flow and viability may serve as a sentinel of patient survival. These consequences are magnified in animals suffering from pain or that become hypothermic. Successful treatment of traumatized animals goes beyond the restoration of blood pressure and urine output, is dependent on a fundamental understanding of the pathophysiologic processes responsible for the animals current physical status, and incorporates the reduction of pain, stress, and the systemic inflammatory response and methods that restore microcirculatory blood flow and tissue oxygenation.

**Conclusions:** Severe trauma is a multifaceted event and is exacerbated by hypothermia, pain, and stress. Therapeutic approaches must go beyond the simple restoration of vascular volume and ABP by maintaining tissue blood flow, restoring tissue oxygenation, and preventing systemic inflammation.

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**Keywords:** hemorrhage, microcirculatory blood flow, pain, stress, tissue oxygenation, trauma

## Introduction

Given the frequency and severity of traumatized patients admitted to veterinary hospitals and examined by veterinarians, veterinary technicians, and veterinary medical specialists, it is somewhat surprising that a great deal more species-specific discussion of the subject has not been published in the veterinary literature. Indeed, comparatively few reviews, case reports, or case series published in the veterinary literature discuss

or describe the physical findings, clinical course, or response to therapeutic interventions in dogs or cats suffering from naturally occurring traumatic events, other than those detailing the consequences of head trauma. With this in mind the authors of this special issue review the topic of trauma by providing a discussion of topics pertinent to the subject. The first manuscript provides a definition and overview of the cardiovascular physiology, pathophysiology, and unique aspects of trauma compared with other shock producing events (simple hemorrhage, heart failure, sepsis). Subsequent manuscripts review patient assessment, stabilization and resuscitation, fluid therapy, anesthesia and analgesia, and optimal endpoints for resuscitation of the acutely traumatized patient. It is hoped that this discussion will provide a background for understanding

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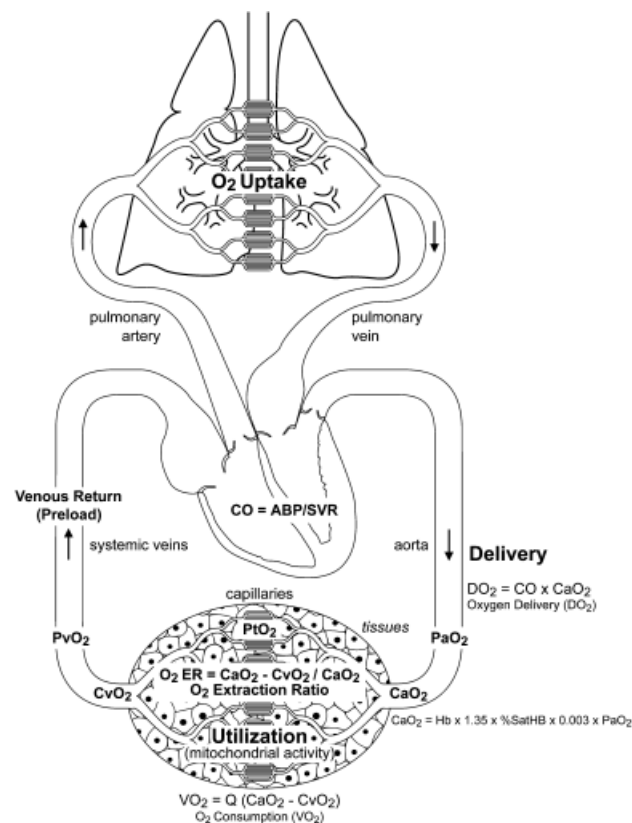
the key pathophysiologic components and consequences of trauma, highlight important diagnostic and therapeutic interventions in order to safely and rapidly achieve the desired endpoints for effective resuscitation and finally, inspire readers to relate their experiences with traumatized dogs and cats in peer-reviewed veterinary publications.

Trauma is defined as tissue injury that occurs more or less suddenly and includes any physical damage (e.g., fracture, laceration) to the body caused by violence or accident. At the very least, traumatic events generate pain, stress, and fear that individually or together initiate survival-oriented behavioral responses collectively designed to prevent further tissue injury, compensate for the injury that has already occurred and restore homeostasis.<sup>1</sup> At the worst trauma elicits exuberant physiologic, immunologic, and metabolic changes that predispose to organ malfunction, trigger inflammation and coagulopathies, promote infection, and trigger an autodestructive inflammatory process.<sup>2-6</sup> The scale and pattern of the responses to trauma are dependent upon the extent of hemorrhage, tissue injury, pain, and stress and together determine mortality. Mortality from trauma in humans has been described as following a trimodal distribution.<sup>7</sup> Severe trauma produces death immediately or within a few hours and is almost always associated with head trauma and blood loss that exceeds 30% of the total blood volume. So-called early deaths occur within hours (2–12 hours) of admission to a hospital, may or may not be associated with deteriorating CNS status and are usually caused by internal or ongoing hemorrhage, cardiovascular, or respiratory failure. Late deaths, caused by trauma, occur days to weeks after admission to the hospital and usually involve chronic acid-base imbalance, gastrointestinal malfunction, cardiorespiratory compromise, the development of hypothermia, coagulopathies, systemic inflammatory response syndrome (SIRS), and progressive sequential multiple organ failure (MOF).<sup>2,6-8</sup> Studying the response to experimentally induced and human trauma (hemorrhage, tissue damage, or both) has provided a better understanding of the pathophysiologic processes and improved early resuscitative efforts. Long-term survival is now known to be more dependent upon the metabolic responses to trauma, the early restoration and maintenance of capillary perfusion (functional capillary density), and tissue oxygenation. Oxygen (O<sub>2</sub>) is the critical catalyst required to sustain life. Without it the organism accumulates an increasing oxygen debt that can be responsible for triggering SIRS and MOF. Dysoxia is inadequate tissue oxygenation to a point that O<sub>2</sub> levels are so low that mitochondrial function, specifically ATP production, is impaired.<sup>9</sup> Dysoxia occurs as a result of an

abnormal relationship between O<sub>2</sub> delivery (DO<sub>2</sub>) and O<sub>2</sub> demand.

### Heart, Vasculature, and Blood

The lungs, heart, blood vessels, and blood are responsible for the uptake and delivery of O<sub>2</sub> to tissues (Figure 1). Although the heart is generally considered to play the principal role in maintaining DO<sub>2</sub> the importance of the lungs, the blood vessels, and hemoglobin (Hb) cannot be underestimated. Tidal breathing transfers (tidal volume; V<sub>t</sub> = 15 mL/kg) air (21% O<sub>2</sub>; approximately 150 mmHg at sea level) into the lungs and closer to the respiratory exchange units (respiratory bronchioles, alveoli), thereby establishing a favorable pressure gradient (ΔP<sub>O<sub>2</sub></sub>) for diffusion of O<sub>2</sub> into pulmonary capillary blood. The heart is the muscular pump responsible for providing the energy for the development of arterial blood pressure (ABP), and, in conjunction with systemic vascular resistance (SVR), determines cardiac output ([CO] = ABP/SVR). Cardiac function is constantly adjusted by neural (autonomic), endocrine, and humoral factors. These factors in conjunction with heart rate and rhythm, preload (venous return), afterload (ABP and



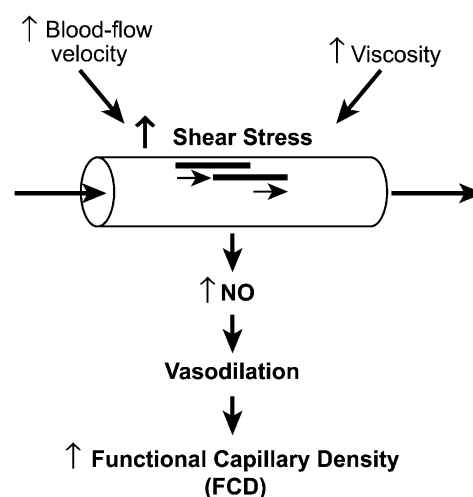
**Figure 1:** Oxygen uptake, delivery (DO<sub>2</sub>), extraction (O<sub>2</sub>ER), and utilization (VO<sub>2</sub>). See text for details.

arterial wall stiffness), and cardiac contractile (inotropy) and relaxation properties determine cardiac function, myocardial oxygen consumption ( $MVO_2$ ), and efficiency ( $MVO_2$  versus CO). Increases in heart rate, venous return, and inotropy generally increase CO and ABP whereas increases in afterload decrease CO particularly in compromised or failing hearts.

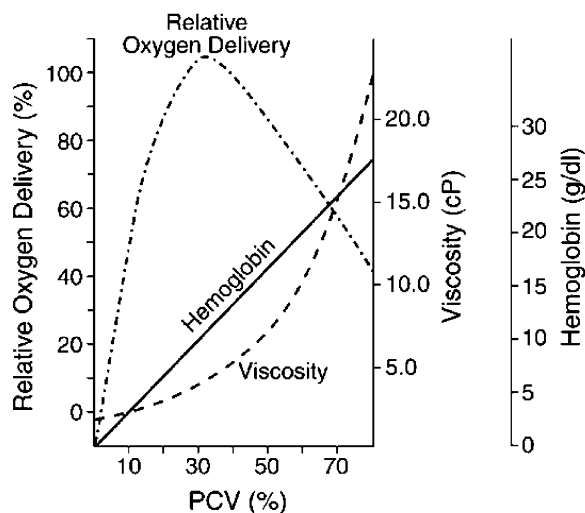
Blood vessels function as the channels or conduits whereby blood is circulated throughout the body. Small arteries ( $<400\mu$ ) regulate the distribution of blood, while capillaries serve as exchange and filtration units. Small (venules) and medium-sized veins store and collect blood before merging into larger veins that return blood to the heart for recirculation.<sup>10</sup> Blood is the circulating medium used by the body to deliver nutrients, remove wastes, and aid in the maintenance of homeostasis. More specifically, blood transports  $O_2$  and other nutrients, removes  $CO_2$ , controls bleeding following injury, defends against foreign pathogens and toxins, regulates the distribution of water to the interstitial space (osmotic and oncotic properties), buffers acid-base ( $H^+$ ), modulates vessel tone (nitric oxide), and modifies drug effects (protein binding). Hb, an iron containing  $O_2$  molecule located within red blood cells (RBCs), is essential for enhancing the oxygen carrying capacity of blood and for maintaining adequate  $DO_2$ . Without Hb it would be impossible to meet the body's  $O_2$  demands ( $VO_2$ ). For example, and assuming a normal resting  $VO_2$  of approximately  $3\text{--}4\text{ mL } O_2/\text{kg}/\text{min}$ , CO at rest would have to be more than 10 times ( $3\text{ mL } O_2/\text{kg}/\text{min} \div 0.003\text{ mL } O_2/\text{mL} = 1000\text{ mL}/\text{kg}/\text{min}$ ) normal (resting CO approximately =  $100\text{ mL}/\text{kg}/\text{min}$ ) to just meet resting  $VO_2$  requirements as plasma carries only  $0.003\text{ mL } O_2/100\text{ mL}/\text{mmHg}$  or  $0.003\text{ mL } O_2/\text{mL}$  when  $PaO_2$  is  $100\text{ mmHg}$  (normal). A  $20\text{ kg}$  dog would have to sustain a CO of  $20,000\text{ mL}/\text{kg}/\text{min}$  ( $20\text{ L}/\text{min}$ ) in order to meet basal  $O_2$  requirements. Alternatively, without Hb, the  $PaO_2$  would have to increase by a minimum of  $1000\text{ mmHg}$  for the plasma to carry an appropriate amount of  $O_2$  as  $1000\text{ mmHg} \times 0.003\text{ mL } O_2/100\text{ mL}/\text{mmHg}$  equals  $3\text{ mL } O_2$  per  $100\text{ mL}$  when the  $PaO_2 = 100\text{ mmHg}$ . The CO in resting dogs is approximately  $100\text{ mL}/\text{kg}/\text{min}$  (see above) requiring that the atmospheric pressure would have to increase to  $10 \times (760\text{ mmHg})$  normal ( $1\text{ atm} = 760\text{ mmHg}$ ; of which  $O_2$  contributes  $150\text{ mmHg}$ ) to produce a  $PaO_2$  of  $1000\text{ mmHg}$ . Imagine the increases in CO and atmospheric pressure that would be required in the absence of Hb in order to supply adequate  $O_2$  in situations that increase tissue metabolic rate (exercise, fever) or cause anemia (parasitism, autoimmune disease, hemodilution).

One of the most important physical properties of blood is its viscosity.<sup>11,12</sup> Blood viscosity ( $\eta$ ) is a key

determinant of fluid movement and is directly related to the resistance to blood flow ( $R = 81\eta/\pi r^4$ ;  $l$  is the length,  $r$  is the radius) in small vessels (Figure 2). The velocity ( $v$ ) of blood flow and the particulate content of the blood packed cell volume (PCV) are 2 important variables used to determine blood viscosity ( $\eta \approx \text{PCV}/v$ ).<sup>12</sup> Although increases in PCV increase the amount of oxygen carried to tissues per unit of blood flow, increases in resistance to blood flow created by an increased  $\eta$  decrease blood flow (Figure 2). Decreases in blood flow and increases in PCV predispose to the clumping of RBCs and the clogging of small vessels. Clinically a PCV greater than 60% produces such dramatic increases in blood viscosity that blood flow to smaller vessels can be critically reduced (Figure 3). The optimal PCV in normal dogs and cats is approximately 30% ( $Hb \sim 12\text{ g}/\text{dL}$ ). Decreases in PCV, however, are well tolerated and cause minimal readjustments in cardiovascular function (increases in heart rate and CO). In fact, a decrease in PCV to values between 20–25% ( $Hb = 7\text{--}8\text{ g}/\text{dL}$ ) following the administration of fluids (crystalloid, colloids) is known to improve blood flow because of a decrease in viscosity and resistance to blood flow.<sup>12</sup> Once the PCV begins to fall below 15–20% ( $Hb = 5\text{--}7\text{ g}/\text{dL}$ ), however, increases in CO and oxygen extraction from the blood ( $Hb$ ) are required in order to compensate for tissue oxygen demands.<sup>9,13</sup> In addition, reflex vasoconstriction may lead to the redistribution of blood flow to the heart and brain in order to improve chances for survival. Ultimately the critical Hb concentration (i.e., the Hb value below which oxygen delivery is unable to meet tissue oxygen demand) may be as low as  $3\text{--}5\text{ g}/\text{dL}$  (PCV 9–15%).<sup>12</sup> Furthermore, acidemia, hypoxemia, and circulating cytokines (TNF, PAF, IL1)



**Figure 2:** Increases in small vessel blood flow or blood viscosity increase vessel wall shear stress leading to increases in nitric oxide (NO) production, vasodilation, and functional capillary density.



**Figure 3:** A packed cell volume (PCV) of approximately 30% results in maximum relative oxygen delivery to tissues. Values greater or lower than 30% reduce relative oxygen delivery to tissues because of decreases in hemoglobin or increases in resistance to blood flow, respectively.

decrease RBC oxygen affinity for  $O_2$  and prevent RBCs from folding, thereby decreasing  $O_2$  delivery. From this discussion, it is clear that there is an ideal microcirculatory environment, PCV and  $\eta$ ; one in which blood flow and oxygen delivery to tissues are maximized with minimal cardiac energy expenditure. It is for these reasons that most critical care guidelines suggest that Hb values be maintained at values greater than 5–7 g/dL (PCV >15–20%). Values below this are associated with an increased risk of tissue hypoxia, shock, and death. Obviously, Hb values greater than 5–7 g/dL are preferred in animals that suffer from trauma, hemorrhage, or hypovolemia.

### Oxygen Delivery to Tissues

The delivery of oxygen to tissues is a complex process best appreciated by examining the macro- and micro-hemodynamic, rheologic (fluid movement), and oxygen carrying characteristics of blood.<sup>14</sup> The macro or systemic hemodynamic factors that determine tissue perfusion are the CO, ABP, and SVR ( $CO = ABP/SVR$ ). Blood pressure is generated by cardiac contraction and is transmitted throughout the arterial network. Normally changes in vessel diameter produce the greatest changes in vascular resistance and tissue blood flow as resistance to blood flow varies to the fourth power of vessel radius ( $R = 8l\eta/\pi r^4$ ). The SVR is directly related to blood pressure but inversely related to blood flow ( $SVR = ABP/CO$ ).

Maintaining adequate tissue bioenergetics is dependent upon  $O_2$  uptake by the lungs, oxygen delivery ( $DO_2$ ), oxygen extraction ( $O_2E$ ), and utilization by the metabolic machinery (mitochondria) within cells (Figure 1). Tissue dysoxia occurs when tissue  $O_2$  levels are too low to support mitochondrial respiration or when oxygen supply ( $DO_2$ ) or its extraction from blood ( $ERO_2$ ) is too low to meet tissue  $O_2$  demands ( $O_2$  demand =  $VO_2 = DO_2 \times ERO_2$ ).<sup>15</sup> The factors that determine oxygen delivery are CO, Hb concentration, the affinity of Hb for oxygen ( $P_{50}$ ), the saturation of Hb with oxygen ( $SaO_2$ ), and the  $PaO_2$ . The Fick or  $O_2$  consumption equation ( $VO_2 = CO [CaO_2 - CvO_2]$ ) contains all the essential components of this relationship. The  $VO_2$  represents the sum of all the oxidative metabolic (oxygen consuming) processes in the body and largely reflects mitochondrial electron transport, which is responsible for over 90% of  $O_2$  utilization.<sup>9</sup> It should be noted that oxygen delivery ( $DO_2 = CO \times CaO_2$ ), consumption ( $VO_2 = CO [CaO_2 - CvO_2]$ ), extraction ( $O_2E = CaO_2 - CvO_2$ ), and extraction ratio ( $ERO_2 = CaO_2 - CvO_2 / CaO_2$ ; Table 1) are all mathematically coupled because they all contain the term  $CaO_2$ . The consequences of this can be important in patients in which the oxygen capacity of Hb for oxygen is changing or has changed, which is likely the situation in sick hypothermic animals, and is not accurately reflected by a constant (e.g., 1.35 mL  $O_2$ /g Hb). The oxygen content of blood ( $CaO_2$ ) is generally calculated as  $CaO_2 = Hb \times 1.35 \times SaO_2 + PaO_2 \times 0.003$  (Table 1). Arterial blood with a Hb concentration of 15 g/dL (PCV = 45%), for example, contains approximately 20–21 mL of oxygen per dL of blood when the  $SaO_2 = 100\%$  and the  $PaO_2 = 100$  mmHg (room air). The  $CvO_2$  is generally 14–15 mL/dL yielding an  $O_2ER$  of 0.2–0.3 (20–30%). Decreased Hb concentrations following hemorrhage or hemodilution (bolus crystalloid administration) cause CO and/or oxygen extraction to increase in order to maintain the requisite oxygen delivery required by metabolizing tissues.<sup>16</sup> A 50% decrease in the Hb concentration, for example, would require a 50% increase in CO or the combination of an increase in CO and  $O_2ER$  in order to meet tissue oxygen requirements. The critical  $DO_2$  and  $O_2ER$  are known to be approximately 5.0 mL/kg/min and 0.6 (60%) in normal healthy dogs, suggesting that most dogs (mammals) have significant reserve.<sup>17,18</sup> An increase in arterial blood lactate concentrations marks the onset of dysoxia and is the cardinal sign of inadequate oxygen delivery and the point at which  $VO_2$  can no longer be maintained by metabolizing tissues, thereby suggesting that oxygen consumption has become delivery dependent (Figure 4). Importantly, this relationship holds true whether the decrease in  $DO_2$  is caused by a decrease in CO, Hb

**Table 1:** Determinants of Tissue Oxygenation and Hypoxia\*

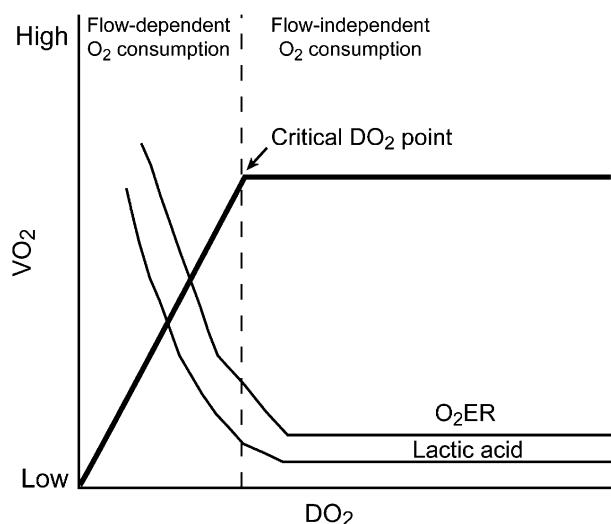
Terms	Abbreviation	Derivation
Oxygen delivery	DO <sub>2</sub>	= CO × CaO <sub>2</sub>
Arterial blood oxygen content	CaO <sub>2</sub>	= (Hb × 1.35 × SaO <sub>2</sub> ) + (0.003 × PaO <sub>2</sub> )
Oxygen extraction ratio	ERO <sub>2</sub>	= VO <sub>2</sub> /DO <sub>2</sub> = SaO <sub>2</sub> -SvO <sub>2</sub> /SaO <sub>2</sub> = CaO <sub>2</sub> -CvO <sub>2</sub> /CaO <sub>2</sub>
Oxygen uptake	VO <sub>2</sub>	= CO × (CaO <sub>2</sub> -CvO <sub>2</sub> ) = CO × Hb × 1.35 × (SaO <sub>2</sub> -SvO <sub>2</sub> ) = CO × Hb × 1.35 × SaO <sub>2</sub> × ERO <sub>2</sub>
<i>Types of Hypoxia</i>		
Ischemic hypoxia	↓ CO	
Anemic hypoxia	↓ Hb	
Hypoxic hypoxia	↓ SaO <sub>2</sub>	
Cytopathic hypoxia	↓ ERO <sub>2</sub>	

CO, Cardiac output; arterial (SaO<sub>2</sub>), mixed venous (SvO<sub>2</sub>) oxygen saturation of blood; arterial (CaO<sub>2</sub>), mixed venous (CvO<sub>2</sub>) oxygen content of blood.

Hemoglobin (Hb): 1.35 = mL O<sub>2</sub>/g Hb at 100% saturation.

\*The impact of mathematical coupling must be considered when variables are derived and not directly measured.

concentration (isovolemic hemodilution), or PaO<sub>2</sub>.<sup>9</sup> Finally, it is worth noting that the ratio of VO<sub>2</sub> to DO<sub>2</sub> (VO<sub>2</sub>/DO<sub>2</sub>) is also equal to O<sub>2</sub>ER (O<sub>2</sub>ER = VO<sub>2</sub>/DO<sub>2</sub>) as VO<sub>2</sub>/DO<sub>2</sub> = CO (CaO<sub>2</sub>-CvO<sub>2</sub>)/CO × CaO<sub>2</sub> and O<sub>2</sub>ER = CaO<sub>2</sub>-CvO<sub>2</sub>/CaO<sub>2</sub>. This means that VO<sub>2</sub> = CO × Hb × 1.35 × SaO<sub>2</sub> × O<sub>2</sub>ER can be used to classify hypoxias: decreased CO is termed ischemic hypoxia; decreased Hb is termed anemic hypoxia; decreased SaO<sub>2</sub> is termed hypoxic hypoxia; and decreased O<sub>2</sub>ER is termed



**Figure 4:** Decreases in oxygen delivery (DO<sub>2</sub>) eventually cause oxygen utilization (VO<sub>2</sub>) to become flow dependent, resulting in increases in oxygen extraction (O<sub>2</sub>ER) and lactic acid.

cytopathic or distributive hypoxia (Table 1).<sup>9,19</sup> The benefit of this approach being that by recognizing the various causes for circulatory shock appropriate therapies can be initiated to improve CO, Hb, SaO<sub>2</sub> or ERO<sub>2</sub>.

### Regulation of Blood Flow to Tissues

Tissue perfusion is regulated by the integration of multiple supraregional (central nervous system [CNS]), regional and local factors. Together these factors combine to produce immediate, intermediate and long-term adjustments that determine CO, total peripheral vascular resistance, vascular capacitance and blood volume. Higher brain centers including the hypothalamus (pain, temperature) and cerebral cortex (emotions: vigilance, fear) facilitate or modify cardiovascular responses. In addition, local tissue factors (H<sup>+</sup>, K<sup>+</sup>, adenosine) produced in response to low tissue O<sub>2</sub> or ischemia exert a direct effect on the state of contraction of smaller blood vessels (metabolic autoregulation), thereby completing a ubiquitous and comprehensive control circuit. Continuous adjustments in cardiovascular system function defend against significant changes in ABP and intravascular volume deficits and insure that an adequate amount of oxygen and nutrients are delivered to metabolizing tissues (Table 2). Decreases in ABP caused by

**Table 2:** Factors That Regulate Tissue Perfusion

#### Immediate (short term)

- Autonomic nervous system (sympathetic; parasympathetic)
  - Regulate heart rate and vessel tone and capacity
- Vascular baro- or pressoreceptor reflexes (stretch receptors)
  - Regulate heart rate and vessel tone and capacity
- Cardiac stretch receptors
  - Regulate heart rate and vessel tone and capacity
- Chemoreceptor reflexes (sense changes in O<sub>2</sub> and CO<sub>2</sub> (H<sup>+</sup>))
  - Regulate heart rate and vessel tone
- Blood-borne (humoral) responses (epinephrine, norepinephrine)
  - Regulate heart rate, vessel tone, and cardiac contractility
- Local factors
  - Arteriolar oxygen partial pressure – decreased O<sub>2</sub> produces vasodilatation and vice versa
  - Local metabolites – increased production of carbon dioxide, H<sup>+</sup>, lactate
  - Myogenic autoregulation – adjusts vessel tone to changes in blood pressure

#### Intermediate

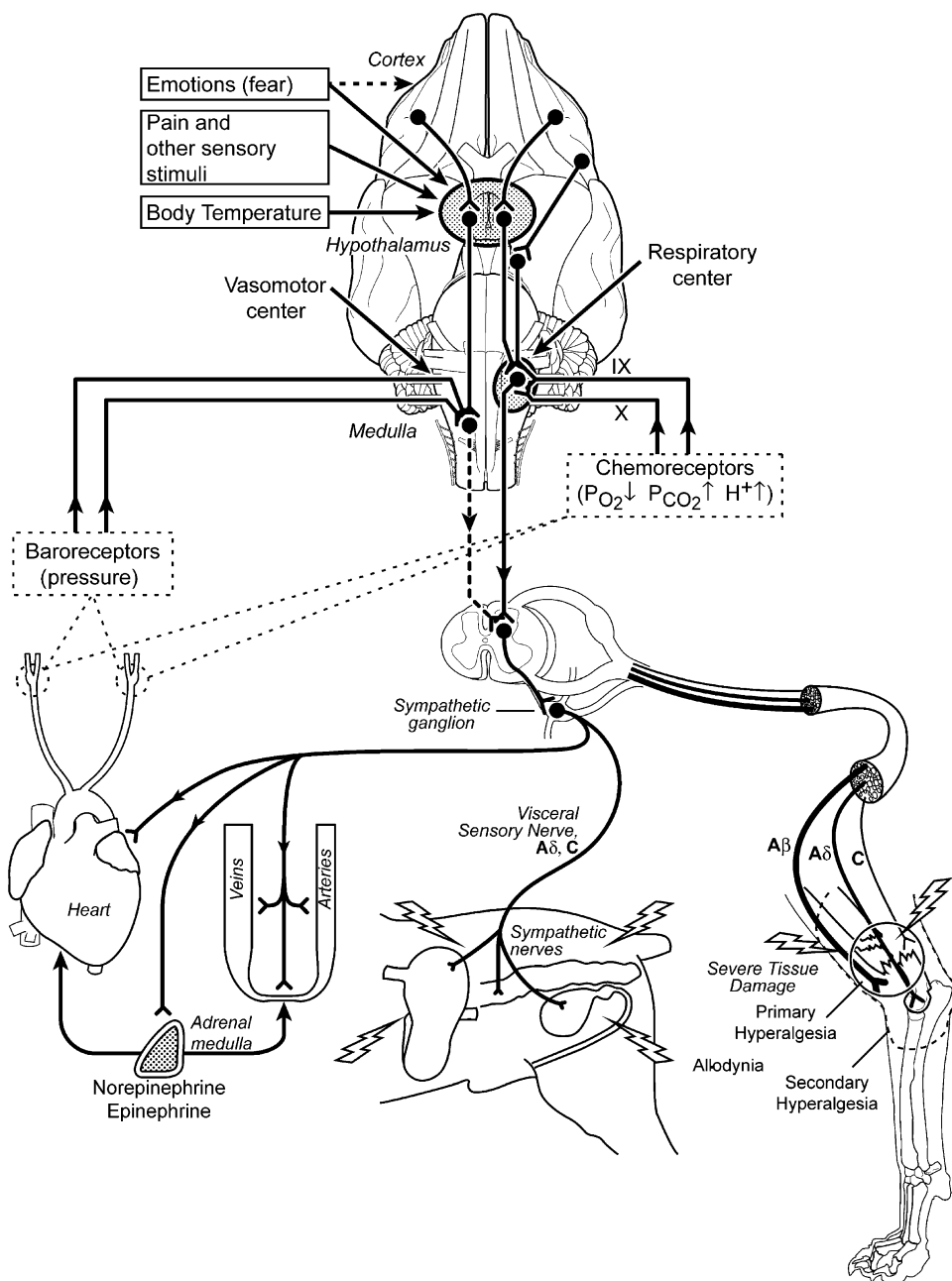
- Trans capillary fluid shifts (Starling's law of the capillary)
  - Regulate fluid filtration and reabsorption
- Hormonal responses (renin, angiotensin)
  - Regulate vessel tone and salt and water retention

#### Long term

- Oral fluid consumption
  - Regulates net fluid intake
- Renal control system (vasopressin [ADH], aldosterone, atrial natriuretic peptide [ANP])
  - Regulates renal fluid output

trauma, blood loss, bradycardia, or the acute onset of poor cardiac performance are immediately sensed by a variety of central and peripheral receptors, particularly vascular baroreceptors, which are the most important short-term determinants of ABP. Output from these receptors trigger readjustments in CNS autonomic, particularly sympathetic, output, which compensates for small changes in ABP. Local myogenic autoregulation also helps to protect the brain, heart, liver, mesentery, and skeletal muscle from small changes in blood pressure by maintaining microcirculatory blood flow via

vasoconstriction when blood pressure increases, and vasodilatation when blood pressure decreases. If ABP is reduced to a point that tissue blood flow is negatively affected, however, higher CNS centers are activated leading to sympathetic nervous system activation and substantial increases in heart rate, cardiac contractility, and vascular tone. Epinephrine and norepinephrine are released from the adrenal gland and enter the circulation amplifying sympathetic nervous system activity (Figure 5). Further increases in sympathetic tone and circulating catecholamines, activation of the renin-



**Figure 5:** Blood loss, hypoxemia, pain, and stress activate medullary cardiorespiratory centers resulting in compensatory adjustments cardiorespiratory function (hyperpnea, tachycardia, vasoconstriction, blood flow redistribution) in order to meet tissue oxygen needs or sustain life.

angiotensin system, and secretion of vasopressin (ADH) intensify vasoconstriction. Blood flow is subsequently redistributed to the lungs, heart, and brain and away from the skin, skeletal muscle, kidneys, and splanchnic viscera. Finally, peripheral chemoreceptors sense any changes in the blood oxygen tension ( $PO_2$ ) and pH. If blood pressure is not restored capillary hydrostatic pressure decreases, promoting the movement of fluid from the interstitial space into the capillaries thereby increasing intravascular volume. This intravascular shift of extravascular fluid (autotransfusion) can restore up to 50% of the intravascular volume in a relatively short period of time (hours).<sup>1</sup> The constriction of the peripheral vasculature, centralization of blood volume, redistribution of the blood flow, and increase in CO and ABP are generally capable of restoring tissue perfusion providing blood loss does not exceed the body's compensatory capabilities and is not complicated by extensive tissue trauma or severe pain. It is noteworthy that acid-base (pH <7.20) and electrolyte disturbances ( $\uparrow K^+$ ), relatively short periods (>8–10 minutes) of hypoxemia ( $PaO_2 < 40$  mmHg) or ischemia (<25% of normal blood flow), mild hypothermia (<35 °C), and prolonged or excessive exposure to depressant drugs (most anesthetics) blunt or abolish baroreceptor and chemoreceptor reflex activity and the vascular response to sympathetic stimulation, leading to a poor compensatory response and a prolonged return to normal tissue blood flow.<sup>20–23</sup>

Normally, neural, humoral, local myogenic, and metabolic autoregulatory mechanisms combine to continuously adjust vascular resistance and tissue blood flow to meet organ  $O_2$  requirements in proportion to their needs.<sup>9,15</sup> There is no guarantee, however, that microcirculatory blood flow will be proportionally distributed according to tissue needs following traumatic events or during shock. This issue is central to understanding the pathophysiology of shock, particularly traumatic shock producing events, and is key to successful resuscitative efforts as it is the restoration of microcirculatory blood flow, as assessed by functional capillary density, which is the principle determinant of survival.<sup>24–26</sup> Peripheral microvascular blood flow is in fact controlled by so-called flow controlling vessels and distribution vessels.<sup>10,27</sup> The former include small- to medium-sized arterioles (100–400  $\mu$ ) where the majority of the arterial pressure is dissipated and the latter include precapillary sphincters (20–100  $\mu$ m). The flow-controlling vessels are primarily controlled by the sympathetic nervous system, which gradually (seamlessly) give way to local control and the build-up of vasodilator metabolites (adenosine, lactate,  $H^+$ ,  $K^+$ ). Tissue maldistribution or heterogeneity of blood flow leading to hypoxia augments the production of autocooids (tissue

hormones) that modulate vascular tone and platelet function. Several endothelial derived relaxing autocooids, prostacyclin ( $PGI_2$ ), nitric oxide (NO), and endothelium-dependent hyperpolarizing factor (EDHF) act in conjunction with vasodilator metabolites to activate ATP-sensitive  $K^+$  channels in the smaller distribution vessels leading to vessel membrane hyperpolarization and vascular smooth muscle relaxation.<sup>15</sup> Importantly, the build-up of vasodilator metabolites and autocooids may be largely determined by local tissue  $O_2$  ( $PtO_2$ ) which is believed, by some, to be the principle determinant of local vessel tone (endothelial  $O_2$  sensor) and subsequent tissue perfusion; decreases in  $PtO_2$  producing vascular dilation and a restoration of  $PtO_2$  and increases in  $PtO_2$  causing vasoconstriction and a return of  $PtO_2$  to basal values.<sup>26,28</sup> Hypotension, hypovolemia, and inappropriate anemia (hemodilution) can produce rapid and profound decreases in  $PtO_2$ . If blood pressure, blood volume, and Hb concentration are restored in a short period of time (minutes) tissue blood flow generally overcompensates (reactive hyperemia) for the temporary reduction in blood flow and  $DO_2$  in order to repay the oxygen debt. The magnitude and duration of the reactive hyperemic response is dependent upon the tissues' metabolic rate and the magnitude of the oxygen debt. When decreases in blood pressure, blood volume, or Hb concentration are severe or are not restored in a timely manner or when there is evidence for septicemia (infection) or endotoxemia (gut ischemia) vascular hyporeactivity ('endothelial stunning') to both vasoconstrictor and eventually vasodilator substances ensues resulting in a reduction in functional capillary density, increases in intercapillary distances and heterogeneity in the distribution of microvascular  $DO_2$  as characterized experimentally by irregular dispersion of  $PtO_2$  values.<sup>25,29</sup> Dilation of precapillary sphincters causes capillary hydrostatic pressure to increase, resulting in fluid loss from the vascular fluid compartment into the interstitium. Experimental and clinical evidence suggests that the gut is the organ at greatest risk for the development of dysoxia during periods of reduced blood pressure, blood volume, or Hb concentration and is also the principle source for the passage of enteric bacterial endotoxin into the circulation and should be the organ targeted for therapeutic maneuvers that provide improvement in  $PtO_2$  and vascular reactivity.<sup>2,30–32</sup>

If ABP continues to fall blood may stagnate in the small arteries and capillaries. The  $PtO_2$  decreases in stagnated blood, leading to anaerobic metabolism and the accumulation of more metabolic byproducts (lactic acid), poisoning any remaining vasoconstrictor response. This sequence of events emphasizes the importance of  $PtO_2$  in regulating microcirculatory blood flow.

## Hemorrhage, Tissue Injury, and Pain

Trauma produces varying degrees of tissue injury, pain, hemorrhage, stress (fear), and severe hypothermia.<sup>1,33</sup>

Tissue trauma frequently includes orthopedic structures and nerves and should be thought of in terms of the rate and amount of hemorrhage that has occurred or is occurring, the intensity of pain, and the degree of stress that is present or is likely to occur in response to the traumatic event. With these issues in mind it is important to emphasize that trauma involves much more than simple hemorrhage (Table 3).<sup>1</sup>

Hemorrhage can be a life-threatening event, particularly when uncontrolled or when large volumes of blood are lost in a short period of time. Clinically, hemorrhage can be categorized based upon its physiologic consequences, magnitude and rate, the probability of producing death, and the response to therapy (Table 4). Most experimental studies suggest that simple blood loss exceeding 40–50% of an animal's blood volume (total blood volume = 70–90 mL/kg) produces severe sinus tachycardia, rapid development of systemic hypotension, and marked reduction in  $DO_2$  and  $VO_2$  leading to irreversible shock and death if not immediately treated.<sup>34</sup> Given the rapid rates of blood loss (grade 1: >5 mL/kg/min) associated with acute severe hemorrhage in humans, shock leading to death can occur within minutes.<sup>7</sup> Similarly, a 20 kg dog having an estimated blood volume of 1800 mL (90 mL/kg) would become seriously hypovolemic within 10 minutes ( $50\% \times 1800 \text{ mL} \div 5 \text{ mL/kg/min}$ ) and bleed to death in approximately 20 minutes. This animal would have little or no chance for being resuscitated and would likely die on the way to or shortly after arriving

**Table 3:** Key Issues in the Acutely Traumatized Patient

1. Severity and extent of trauma
Soft tissue
Orthopedic
Nervous system (including head trauma)
2. Blood loss
Total blood loss if controlled
Rate of hemorrhage and total blood loss if uncontrolled
3. Pain
Severity and extent
Primary hyperalgesia (localized to the site of trauma)
Secondary hyperalgesia (painful outside the site of trauma)
Allodynia (pain response to nonpainful stimuli)
4. Stress
Behavior
Physiologic variables (tachycardia, hyperpnea, pale mucous membranes)
5. Core body temperature
Hypothermia
6. Acid–base status
Lactic acidosis

**Table 4:** The Four Classes of Hemorrhage

Class 1	Loss of up to 15% (approximately 10–12 mL/kg)* of the circulating blood volume. Clinical symptoms are minimal as suggested by mild tachycardia, no changes in arterial blood pressure, pulse pressure, or respiratory rate
Class 2	Loss of 15–30% (approximately 12–25 mL/kg)* of the circulating blood volume. Clinical signs include tachycardia, tachypnea, and a decrease in pulse pressure
Class 3	Loss of 30–40% (approximately 25–32 mL/kg)* of the circulating blood volume. Clinical signs include pale mucous membranes, prolonged capillary refill time, tachycardia, tachypnea, depression, and a decrease in arterial blood pressure
Class 4	Loss of greater than 40% of the circulating blood volume. A potentially life threatening event. Clinical signs include very pale or white mucous membranes, prolonged capillary refill time, cold extremities, tachycardia, tachypnea, rapid thready pulse, markedly decreased arterial blood pressure, delirium, and depression

\*Assumes a total blood volume of 80 mL/kg.

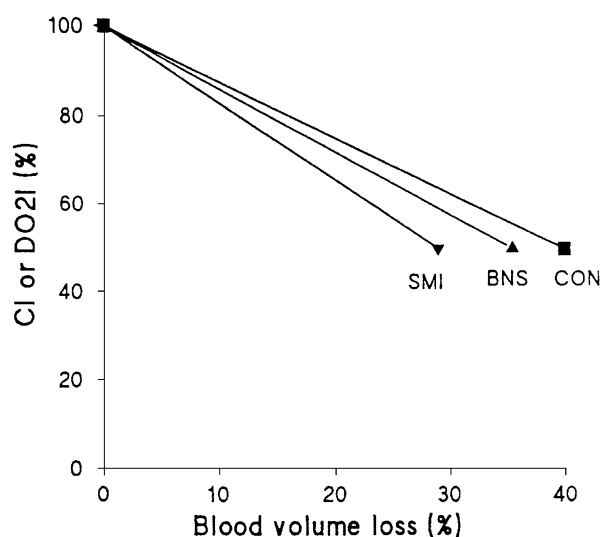
Advanced Trauma Life Support Student Manual, Chicago, American College of Surgeons, 1995.

at a veterinary hospital. Animals with moderate (grade 2) rates of hemorrhage (0.5–2 mL/kg/min) may not become critical for approximately 20–90 minutes ( $50\% \times 1800 \text{ mL} \div 0.5\text{--}2 \text{ mL/kg/min}$ ) and typically develop tachycardia and a more gradual reduction in ABP,  $DO_2$ ,  $VO_2$ , and lactic acidosis. Blood flow would be diverted to vital organs (heart, brain, lungs). Hemorrhage must be controlled or stopped and adequate volume support must be instituted if these patients are to survive and avoid the consequences of tissue ischemia. It is important to remember that patients with grade 2 hemorrhage (0.5–2 mL/kg/min) should not be treated with large volumes of fluids (>70–90 mL/kg) administered at rapid rates (>40 mL/kg/hr) until hemorrhage has been controlled (stopped) in order to avoid rapid exsanguination. These patients respond best to so-called ‘hypotensive resuscitation’ wherein fluids are administered at rates that support a systolic ABP of 50–70 mmHg until hemorrhage is controlled.<sup>35,36</sup> Finally, patients with continued slow (<0.5 mL/kg/min) rates of simple hemorrhage (grade 3) may not develop sinus tachycardia or systemic hypotension for hours ( $50\% \times 1800 \text{ mL} \div 0.5 \text{ mL/kg/min}$ ) and experimentally have been demonstrated to activate a ‘depressor reflex’ once approximately 20% of the blood volume ( $20\% \times 1800 = 320 \text{ mL}$ ) has been lost.<sup>1</sup> The physiologic role of the depressor reflex remains controversial although it is known to be mediated by the vagus and withdrawal of sympathetic vasoconstrictor tone leading to bradycardia and hypotension. One potential explanation for its initiation, although speculative, may be

the prevention of myocardial dysoxia and improved peripheral blood flow.

Although informative, experimental models of simple hemorrhage do not reproduce naturally occurring blood loss, as the rate of bleeding is usually controlled, most animals are anesthetized and hemorrhage is stopped once a predetermined blood volume or mean ABP (40–50 mmHg) has been attained. Furthermore, many studies of simple hemorrhage are carried out in splenectomized animals or under circumstances that impair the animal from initiating an appropriate compensatory (baroreceptor reflex) response. Regardless, studies of simple blood loss provide insights into the physiologic and pathophysiologic responses to rapid (tachycardia, hypotension, cardiovascular collapse, hypothermia, irreversible shock), moderate (tachycardia, hypotension,  $\downarrow$  DO<sub>2</sub>,  $\downarrow$  VO<sub>2</sub>,  $\uparrow$  ERO<sub>2</sub>, lactic acidosis), and slow (tachycardia, normotension, or hypotension; depressor reflex) rates of blood loss particularly as they relate to the distribution of blood flow to various organs (particularly gut), PtO<sub>2</sub> and the development of dysoxia (Figure 6).<sup>1,9,26,29,30</sup>

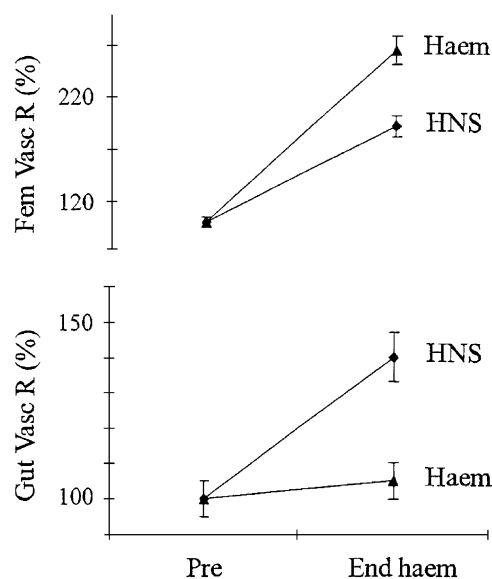
Tissue injury without hemorrhage, whether soft tissue or orthopedic, generally elicits increases in heart rate, blood pressure increases in sympathetic nervous system activity leading to relative increases in skeletal muscle blood flow, and vasoconstriction of the splanchnic viscera.<sup>1,31</sup> This defensive reaction prepares the animal for 'fight or flight' and enhances the opportunity



**Figure 6:** The effect of hemorrhage (CON), brachial nerve stimulation (pain; BNS), and skeletal muscle injury (SMI) on the amount of blood loss (as a percent of total blood volume) required to produce shock. Note that the combination of CON, BNS, and SMI reduces the total blood loss required to produce shock to values less than 30% of the total blood volume. Reprinted with permission from reference 38.

for survival providing the animal can escape from or limit the degree of trauma. Furthermore, several investigators have shown that when trauma is superimposed with hemorrhage sympathetic tone is markedly increased, the depressor reflex does not occur, there is a diversion of blood away from the gut and that mortality increased following smaller blood losses compared with hemorrhage alone.<sup>33,37–39</sup> Importantly, smaller blood loss leading to mortality was reduced by somatic afferent nerve stimulation, which negatively influenced PtO<sub>2</sub>, suggesting that pain worsened conditions and increased mortality from traumatic shock (Figure 7).<sup>33,38,40</sup>

Hemorrhage of less than 30% of total blood volume (approximately 15–20 mL/kg) when combined with tissue injury and somatic nerve stimulation produced a similar mortality rate to that produced by 50% hemorrhage alone.<sup>38</sup> This implies that our 20 kg dog having an estimated blood volume of 1800 mL (90 mL/kg) would become seriously hypovolemic within 3–4 minutes ( $30\% \times 1800 \text{ mL} \div 5 \text{ mL/kg/min}$ ) and bleed to death in approximately 12 minutes if hemorrhage were grade 1 ( $>5 \text{ mL/kg/min}$ ). This same animal would become critical in less than an hour (15–60 minutes;  $30\% \times 1800 \text{ mL} \div 0.5\text{--}2 \text{ mL/kg/min}$ ) if hemorrhage were grade 2. Importantly, these blood loss values may be even lower in traumatized patients that become



**Figure 7:** Changes in skeletal muscle (Fem Vasc R) and gut (Gut Vasc R) vascular resistance in response to a 30% of total blood volume hemorrhage alone (Haem) and somatic afferent nerve stimulation (pain; HNS). Note the marked increase in gut vascular resistance associated with hemorrhage and somatic nerve stimulation (HNS) compare with that in skeletal muscle suggesting marked reduction in gut blood flow. Reprinted with permission from reference 1.

or are allowed to become moderately hypothermic (32–34 °C; 90–93 °F). One study in humans demonstrated a 100% mortality rate in trauma victims when core body temperature was less than 32 °C compared with 21% when hypothermia occurred from environmental exposure alone.<sup>5</sup> This finding should not be surprising given the effects of hypothermia on enzyme kinetics, the coagulation cascade, the oxy-Hb dissociation curve (shift to the left), and the metabolic clearance of drugs (depressants, anesthetics) but requires further investigation in traumatized dogs and cats particularly as it is assumed that hypothermia produces antishock effects by decreasing metabolic activity and oxygen consumption.<sup>41,42</sup>

In conclusion, moderate to severe trauma produces blood loss and pain which initiate sympathoadrenal (sympathetic tone; circulating catecholamines) activation, intrinsic and extrinsic coagulation cascades, and upregulation of the immune system.<sup>43</sup> Moderate to severe trauma produces circumstances that limit DO<sub>2</sub>, VO<sub>2</sub>, and O<sub>2</sub>ER. As stated above, once enough cells in an organ or tissue become oxygen deprived, anaerobic metabolism is initiated, plasma lactic acid concentrations rise, and local inflammatory processes are triggered. The production of cytokines in conjunction with autocooids and local tissue factors leads to a loss of microcirculatory autoregulatory control, maldistribution of blood flow, vascular hyporeactivity, and the development of a pathologic heterogeneity in microvascular blood flow.<sup>9</sup> Heterogeneity in microcirculatory blood flow results in a decrease in functional capillary density causing some tissues to be overperfused (shunt flow) while others suffer from continued or worsening hypoxia. Maldistribution of blood flow is likely worsened by hypothermia, which predisposes the patient to the 'lethal triad' of hypothermia, acidosis, and coagulopathy.<sup>5,43–46</sup> The production of inflammatory mediators including tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)1, IL6, and prostaglandins sets the stage for a SIRS and progressive MOF.<sup>9,47</sup>

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