The “ins” and “outs” of shock
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The term shock is often loosely used without having a clear understanding of its meaning. Tissues, and individual cells, require oxygen (VO2). When the supply of oxygen fails to meet this demand a patient is said to be in shock. In severe cases the body is not able to compensate and cellular starvation occurs.

The bodies response to shock
Delivery of oxygen (DO2) is independent of flow. It is provided by the cardiovascular system through hemoglobin and the red blood cell. Lack of blood flow is sensed by baroreceptors and stretch receptors in the carotid and aorta as well as volume receptors in the kidney and heart. A neuro signal is sent to the brain increasing heart rate, myocardial contractility and vascular tone. Extraction of oxygen from the blood is increased but can only briefly meet tissue demands. This is termed the oxygen extraction ratio (OER, VO2/DO2). The heart and brain are unable to increase their OER. When delivery of oxygen is at a critical point (DcO2) anaerobic metabolism occurs. Anaerobic metabolism is less efficient then oxidative pathways. Glycolysis produces two ATP compared to the 34 produced in oxidative phosphorylation. Delivery of oxygen is also dependent on arterial oxygen content. This can be seen by the following formula. As seen here Hb has a larger impact on oxygen carrying capacity and delivery than PaO2.

Oxygen Extraction Ratio
OER = (SaO2 - SvO2/SaO2) x 100

Arterial Oxygen Content
CaO2 = (1.34 x Hb x SaO2) + (0.003 x PaO2)

Blood flow is also dependent on the characteristics of blood vessels. There are five major types of vessels within the cardiovascular system. The aorta contains high pressure and high velocity flow with distensible walls along with low resistance. Flow is pulsatile within the aorta. Smaller arteries distribute blood while arterioles are the site of the majority of vascular resistance. Vasodilation and constriction affects flow within these vessels. Capillaries are thin walled vessels. They have a very low velocity and are sites of diffusion. Venules, veins, and venous valves contain the majority (60-70%) of our blood volume. It is stored here and within the spleen, and is recruited in times of shock.

\[ R \propto \frac{\eta \cdot L}{r^4} \]

Poiseuille's law or equation explains the relationship between vessel length, diameter and blood viscosity.

Diameter of a vessel is the most important factor in this relationship. Small changes in diameter result in large changes in resistance. Vessel resistance (R) is proportional to the length (L) of the vessel and viscosity of the blood (n). It is inversely proportional to the radius to the 4th power. Thus a vessel having twice the length of another vessel will have twice the resistance to flow. Just as an increase in viscosity two fold will have the a similar decrease in flow. In contrast, using this formula, a change in radius by two fold will result in a 16 fold change in resistance. In vivo this will change as hematocrit changes. Blood vessels are not straight and change is dynamic but this does show an important concept.

The sympathetic system is stimulated by baroreceptors, which leads to a release of vasopressin and antidiuretic hormone (ADH) from the posterior pituitary gland. The catecholamines, epinephrine and norepinephrine, are released resulting in increased myocardial contractility and vasoconstriction. Contractility is independent of preload or afterload. In shock, blood is shunted from the periphery (skin, muscles) and gastrointestinal tract to the brain and heart.
in an effort to preserve consciousness and perfusion.

During hypovolemia decreased renal blood flow activates the renin-angiotensin-aldosterone system (RAAS). Renin found in the kidney, brain, and adrenal glands stimulates conversion of angiotensin, found in the liver, to angiotensin I. Angiotensin I is converted to angiotensin II within the lung. Angiotensin II promotes vasoconstriction within the spleen blood vessels. The contraction of the spleen releases RBC stores into the vasculature in an attempt to restore oxygen carrying capacity. Aldosterone is also released. An increase in aldosterone promotes reabsorption of sodium and chloride lending to a shift of water from the interstitial space into the intravascular space. Norepinephrine is released from the adrenals when stimulated by angiotensin II causing vasoconstriction.

The cellular response to shock when associated with dysoxia is to switch to anaerobic metabolism. Lactate and hydrogen ions are produced leading to an acidemia and metabolic acidosis. Lactate is associated with a hydrogen ion and is normally metabolized by the liver. In an anaerobic state, lactate production exceeds the liver's ability to clear it resulting in a build up of lactate. Once lactate is greater than 5mmol/L a lactic acidosis develops. ATP dependent functions are affected negatively along with the Na-K ATPase pump. Intracellular Na increases resulting in cellular edema and cell death. Transmembrane potential is changed becoming more permeable which affects the influx of calcium leading to and increase in intracellular calcium. This influx activates phospholipase C. Fatty acids, stimulation of the arachidonic acid cascade and production of free radicals follow the increase in calcium.

Reperfusion injury is the leading cause of cell death following resuscitation. The already damaged cell is further damaged by the introduction of reactive oxygen species within it. Proteins are denatured, while organelles and chromosomes cease to function correctly. The formation of free radicals in the absence of oxygen contributes to an increase in the inflammatory cytokines TNF alpha, IL-1 and IL-8. Free radicals are defined as a molecule with one or more unpaired electrons. They have a high affinity for other electrons which leads to them being “stolen” from other molecules. There are several free radicals but the hydroxyl and peroxynitrate radicals are the two most damaging. The following are the most common ROS.

- Hydroxyl
- Peroxynitrate
- Hydrogen peroxide
- Superoxide
- Hypochlorite
- Hydroperoxyl

These cause lipid peroxidation within the cell membrane. Polyunsaturated fatty acids (PUFAs) are contained in the majority of our cell membranes. These free radicals steal a proton from the the PUFAs which initiates a chain reaction (free radical stealing non-free radical) within the cell membrane leading to its degradation and destruction.

An important free radical and in a category of its own is nitric oxide. Not only is it a free radical but it is a potent vasodilator, neurotransmitter and bacteriocidal agent. Combined with superoxide, nitric oxide creates peroxynitrite, a molecule 2000 times more potent than the hydroxyl radical.

Ischemia is a lack of blood flow and thus oxygen to organs and tissues. ATP, without oxygen, is converted into hypoxanthine. Iron is tightly bound to hemoglobin and is highly reactive. Following cellular death unbound iron is released. The end result of ischemia is a build up of iron, potassium (following the failure of the Na-K ATPase pump), arachidonic acid, platelet activating factor and complement activation.

After the reintroduction of oxygen to an environment that is highly reactive cellular damage occurs as mentioned earlier. Oxygen reacts with hypoxanthine creating superoxide and uric acid. Superoxide is not in of itself highly reactive but is a precursor to hydroxyl formation. The enzyme superoxide dismutase converts superoxide to hydrogen peroxide and oxygen followed by the hydroxyl radical. It is formed following the Fenton and Haber-Weiss reaction.

1st Step of Fenton and Haber-Weiss reaction
• $\text{Fe}^{3+} + \cdot\text{O}_2^- \rightarrow \text{Fe}^{2+} + \text{O}_2$

2nd Step

• $\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH}^- + \cdot\text{OH}$

Net

• $\cdot\text{O}_2^- + \text{H}_2\text{O}_2 \rightarrow \cdot\text{OH} + \text{OH}^- + \text{O}_2$

IR injury occurs not only locally but in distant sites as well. It has been associated with acute kidney injury (AKI), acute lung injury (ALI), activation of clotting cascade through inflammation and endothelial disruption.

**Classifications of shock**

Shock is a dynamic process thus using classifications to define it are imperfect at best. Often these classifications are overlapping with one or more occurring at any given time. Using the underlying problem is one way that has been used to categorize shock: cardiogenic, hypovolemic, distributive, anaphylactic, septic and traumatic. One thing that these classifications have in common, except for cardiogenic, is the need for rapid administration of intravenous fluids. Most of the patients that present to our emergency rooms are those in hypovolemic shock.

Hypovolemia is a reduction in blood volume. It is either due to hemorrhage or fluid loss such as that in severe vomiting, diarrhea, addisons disease or third spacing. Loss of circulating volume within the kidneys is noted and the RAAS is activated. Compensatory mechanisms are activated, increasing heart rate and contractility. In the early stages of hypovolemic shock subtle signs may be easily missed. We can further classify shock into 3 stages depending on what text you read.

The early compensatory stage may show an increased heart rate, OER and cardiac output. CRT may be hyperdynamic and mucous membranes may be injected. The patients mentation may be normal. Many of our patients present in this stage of shock and if not corrected may progress to later stages resulting in an increase in morbidity and mortality.

The early decompensatory stage is indicative of continuing fluid loss. Peripheral perfusion is sacrificed by the shunting of blood to the brain and heart. The GI tract and kidney are sacrificed by this redirection of blood flow. Anaerobic metabolism occurs due also to this maldistribution. CRTs are delayed. MM are pale and cold. Blood pressure may be normal or low. Tachycardia may be pronounced while mentation is likely to be obtunded.

In the late decompensatory stage, the bodies protective mechanisms are exhausted. Hypoxemia results in global hypoperfusion and cellular starvation. The brain is experiencing hypoxia which leads to coma or stupor along with blunted neural and respiratory centers. Vasodilation with poor sympathetic tone occurs leading to pooling of blood. This is exacerbated by poor contractility of the heart, and heart rate. The heart is also experiencing myocardial hypoxia at this stage. CRTs are non-existent. Mucous membranes are pale and cold. Pulses are not palpable. Hypothermia may exist along with oliguria or anuria. This stage is generally irreversible.

Septic shock occurs following the release of inflammatory cytokines during SIRS and Sepsis. Nitric oxide contributes to this resulting in loss of vascular tone. It is unresponsive to volume resuscitation. Myocardial contractility is decreased with marked vasodilation. It has been found that not only can DO2 of oxygen be affected but cellular utilization of oxygen as well. Vasopressors are needed, after volume resuscitation has occurred, to reverse this trend.

There is a progressive nature to sepsis. Bacteremia followed by SIRS and sepsis occurs. If left unchecked, severe sepsis, septic shock and multi-organ dysfunction syndrome (MODS) results in multi-organ failure (MOF) and death. SIRS occurs following infection, trauma or neoplasia. Release of inflammatory mediators (IL-1, IL-10, TNF) activate the coagulation cascade. Activation of the coagulation cascade results in consumption of platelets and clotting
Early sepsis is characterized by an increased (early) or decreased glucose. A leukocytosis or leukopenia is present due to an overwhelming infection. Mild to moderate thrombocytopenia may also be present due to consumption and hypercoagulability. Hypercoagulability is very difficult to diagnose though FDPs, D-dimers and TEG changes may be helpful. Finally hypoalbuminemia occurs due to capillary permeability and decreased production in the liver.

Late septic shock can be identified due to hypoglycemia. Glucose stores are used up during the hyperdynamic early stages of sepsis. Leukopenia occurs due to the bodies immune system being overwhelmed. Hypocoagulability results after consumption of coagulation factors and platelets. Severe hypoalbuminemia followed by organ dysfunction and failure is the end product.

Traumatic shock is often associated with moderate to severe pain and hemorrhage. Evidence can be found within closed spaces (abdomen and thorax) or open. Vasodilation with increased cardiac output is usually identified. Open wounds are easily visible and pressure is applied making fluid resuscitation more useful. If hemorrhage exists into a closed space (FAST exam) fluid resuscitation must be restricted to low volume or hypotensive resuscitation in hopes to not disturb any clots.

Distributive shock occurs during massive vasodilation leading to pooling of blood in capillary beds. This results in poor perfusion and maldistribution of blood flow. Septic shock and anaphylactic shock are considered a category of distributive shock. Anaphylactic shock occurs following an allergic reaction that causes vasodilation and cardiovascular collapse along with constricted airways. Cortisones, antihistamines and epinephrine can be used to reverse these symptoms.

Obstructive shock is a form of distributive shock. GDV and ATE are well known forms of this type. During GDV excessive pressure on the caudal vena cava results in a lack of venous return to the heart and a lack of preload. The consequence is poor afterload and cardiac output. Perfusion is compromised leading to anaerobic metabolism. ATE due to a clot results in little if any blood flow. Tissues starve and ischemia results. Both of these syndromes can result in IR injury when blood flow and oxygen return to starved cells.

Cardiogenic shock occurs during CHF and other forms of heart disease. The heart muscle is unable to perfuse tissues due to its diseased state. Contractility is decreased. Right heart failure results in ascites, hepatomegaly and peripheral edema while left heart failure produces pulmonary edema and/or pleural effusion. The result of this is inadequate oxygen delivery due to poor gas exchange within the lung and poor perfusion due to fluid loss. Treatment is aimed at reducing preload to allow lung tissue to “dry” out thus fluid therapy must be very conservative.

Shocks prognosis depends upon the inciting factor. The underlying disease or insult must be addressed. Though in essence shock can be defined in a couple of sentences it is not as easily classified and understood. The clinician and technician must realize that it is ever changing and that more than one type shock is likely present at any given time. For example traumatic shock and hypovolemic shock are closely related but treatment may be different depending on the type of trauma. The physiology of shock can be very daunting but in emergency and critical care medicine it comes down to four words. The delivery of oxygen.

References available upon request.