ENDPOINTS OF RESUSCITATION

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Part 1: Physiology of tissue oxygenation

Shock simply defined is a failure of tissue oxygenation. The clinical features of shock that we see are actually the physiologic response to the lack of tissue oxygenation. The oxygenation of tissues is the most important function of the body. Without oxygen, cells cannot survive and tissues will die. This vitally important process of tissue oxygenation is a complex process. Oxygen must first be extracted from the air in the lungs, so that it can be transported to the tissues where it is extracted, and ultimately utilized at the cellular level for ATP production. Aberrations in any of these four steps (uptake, transport, extraction and utilization) may result in tissue hypoxia and death.

The first step is uptake of oxygen into the blood stream from inhaled air. This occurs via simple diffusion in the alveoli of the lungs. Oxygen simply travels from an area of high concentration in the alveoli to an area of lower concentration in the blood. Diffusion of oxygen is directly proportional to the difference in pressure (called the A-a gradient) and surface area of the lungs in accordance with Fick’s Law. Fick’s Law of diffusion states that gas transfer across a membrane is directly proportional to the surface area and the difference in partial pressure and inversely proportional to the tissue thickness. From this it is easy to see that alveoli are uniquely suited for gas exchange due to their large surface area and the thinness of the membrane. The average human lung has a surface area of ~ 70 m2 and an alveolar wall thickness of 0.5 micrometers. Coupled with a much higher concentration of oxygen in the alveolus compared to the blood, this allows for rapid diffusion and oxygen uptake.

Once oxygenated, blood travels from the lungs to the systemic circulation. The delivery of oxygen is dependent on both cardiac output and the arterial oxygen content. Cardiac output is the volume of blood pumped per minute by the heart. Cardiac output is dependent on the stroke volume and the heart rate. Arterial oxygen content is most dependent on the hemoglobin content with lesser contributions from oxygen saturation and dissolved oxygen. This relationship can be summarized by the following equation:

\[ DO2 = [1.34 \times Hb \times SaO_2 + (0.003 \times PaO_2)] \times CO \]

Once oxygen is delivered to the tissues it must still be extracted by these tissues. This occurs in the capillaries and oxygen is off loaded into cells and waste products (such as CO2) are loaded taken up by the RBCs and transported back to the lungs. The amount of oxygen extracted during times of health is approximately 20-30% and this is enough to meet the metabolic needs of the body (called oxygen consumption). In illness, the amount of oxygen extracted can reach 50-60%.
Once this threshold is reached however, any reduction in oxygen delivery leads to a reduction in oxygen consumption and subsequent shock.

Once extracted from the tissues the oxygen must still be utilized in the cell. Aerobic metabolism occurs in the mitochondria of cells. In some disease states such as cyanide poisoning, thiamine deficiency or sepsis, a defect in oxygen utilization is present. In these states, increasing oxygen delivery or extraction will have no effect as this increased oxygen can still not be utilized on the cellular level.

**Part 2: Endpoints of Resuscitation**

Shock can be defined as inadequate oxygen delivery or tissue perfusion. Building off this simple definition, resuscitation may be defined as restoration of oxygen delivery and/or perfusion back to normal levels. One of the most basic ways we resuscitate patients is the administration of IV fluids. Most types of shock (with the exception of cardiogenic shock) benefit from early, aggressive fluid resuscitation. In the last lecture (The Art of Triage and Initial Stabilization) different types of fluids and there uses were discussed. In the remainder of this lecture we are going to cover how to know when a patient has been adequately fluid resuscitated. We call these endpoints of resuscitation.

Traditionally, fluids were administered to a patient until there vital parameters improved. These traditional endpoints of resuscitation included mucous membrane color, capillary refill time, heart rate, respiratory rate, blood pressure, mentation, urine output, and rectal temperature. These vital parameters are still an important indicator of adequate resuscitation and we strive to obtain these when fluid resuscitating a patient. In the last few decades it became apparent that some patients were still dying despite restoration of these vital parameters to normal levels and that these patients may be experiencing “occult shock”. It is estimated that as many as 85% of human patients resuscitated to traditional endpoints of resuscitation may be experiencing occult shock and occult shock has been shown to be an independent predictor of mortality. A human study performed by Rivers, et al in 2001 showed that patients with septic shock that were resuscitated to traditional endpoints of resuscitation had a higher mortality than patients resuscitated to additional endpoints of resuscitation beyond vital signs. From this study the concept of early goal-directed therapy was born.

Various indicators of decreased tissue perfusion have been identified. Specifically I will be focusing on lactate, base deficit and mixed/central venous oxygen saturation. These are reliable and readily measurable parameters (admittedly some are easier to measure than others) that can be used clinically in veterinary patients. I will also briefly describe some more advanced diagnostics that may be available in the future but are not currently ready for primetime.
Lactate

Glycolysis is the first step in glucose metabolism and results in the production of pyruvate. It occurs in the cytoplasm of all cells with the highest rates in the brain, heart, skeletal muscle, and RBCs. Under aerobic conditions pyruvate enters the Krebs cycle and undergoes oxidative phosphorylation producing ATP necessary for cellular energy. In cells without mitochondria, such as red blood cells, pyruvate is converted to lactate via lactate dehydrogenase and glycolysis continues. This lactate is then converted back to pyruvate via the Krebs cycle or to glucose via the Cori cycle.

During times of tissue hypoxia (i.e. shock), glycolysis becomes the sole source of energy production as oxygen is not available for oxidative phosphorylation. As pyruvate accumulates, glycolysis slows and lactate dehydrogenase converts pyruvate to lactate. Lactate accumulates in the cell and eventually crosses the cell membrane, raising the blood lactate level. If anaerobic conditions are widespread, lactate is not able to be metabolized to pyruvate or glucose, leading to hyperlactatemia and lactic acidosis.

Various veterinary point of care analyzers are available that are capable of measuring lactate. A normal lactate measurement is less than 2.5 mg/dl. An elevation in lactate is called hyperlactatemia. There are two broad categories of hyperlactatemia, Type A and Type B. Type A hyperlactatemia is caused by decreased perfusion. Type B hyperlactatemia is more complex with a variety of underlying causes. Lactate physiology is a complex subject and there are numerous causes of Type B hyperlactatemia. This subject is beyond the scope of this talk however, and we are going to focus on Type A hyperlactatemia.

Numerous human studies have evaluated the use of lactate as an indicator of decreased tissue perfusion as well as a prognostic indicator. The overall consensus of the literature at this time is that hyperlactatemia is a useful marker of global tissue hypoxia; Higher venous lactate levels on admit are associated with higher mortality; failure of lactate clearance is associated with higher mortality; and rapid lactate clearance and time to resolution of hyperlactatemia are positively correlated with survival.

Numerous veterinary studies evaluated the use of lactate as a prognostic indicator have also been performed. Similar to human medicine, lactate has been shown to be a valuable indicator of occult hypoperfusion and hyperlactatemia on admission has been associated with mortality. Importantly, no single value is 100% sensitive or 100% specific for predicting mortality in any patient and the presence of hyperlactatemia should NOT be used to recommend euthanasia in an individual patient.

More recently lactate clearance and “lac-time” have evolved as additional pieces of information that may be helpful to predict patients at high risk of mortality. Lactate clearance is defined as
the initial lactate measurement minus the current lactate measurement divided by the initial lactate. This is written as:

$$\text{Lactate clearance (\%) = \left( \frac{\text{Lactate}_{\text{time 0}} - \text{Lactate}_{\text{time x}}}{\text{Lactate}_{\text{time 0}}} \right) \times 100}$$

A lactate clearance of >50% within 6-12 hrs of admission is associated with a better prognosis than patients who have a lactate clearance of <50%. Interestingly this applies even to patients that have severe hyperlactatemia on admission.

Lactate time or “Lac-time” is defined as the amount of time that a patient is hyperlactatemic. This is a relatively new concept and to the best of the author’s knowledge has not yet been evaluated as prognostic indicator in veterinary patients.

Base Deficit
The base deficit is defined as the amount of base (in mmol) required to titrate 1 liter of whole arterial blood to a pH of 7.4 (with the sample fully saturated with oxygen at 37 degrees Celsius and a PCO2 of 40 mm Hg). Therefore, base deficit is an indirect measurement of anaerobic metabolism. Changes in base deficit reflect changes in acid-base homeostasis whereby increases in base deficit reflect increased anaerobic metabolism. Human studies have established base deficit to be an important prognostic tool that is correlated with severity of injury and overall mortality.

In comparison to lactate, base deficit has been studied less frequently. In a canine model of hemorrhagic shock, base deficit was correlated with hypoperfusion and subsequent mortality. Additionally, it has been shown to be a predictor of transfusion requirement and mortality in 52 dogs that suffered blunt trauma.

Mixed Venous and Central Venous Oxygen Saturation
Mixed venous ($S_vO_2$) and central venous ($S_cO_2$) oxygen saturation are another objective measurement of tissue perfusion. Mixed venous oxygen saturation is measured via a pulmonary arterial catheter whereas central venous oxygen saturation is measured in the cranial vena cava via a central line. The venous oxygen saturation is related to the oxygen extraction ratio. As more oxygen is extracted from the tissues the venous oxygen saturation will decrease. Since mixed venous oxygen takes into account myocardial consumption of oxygen as well, the mixed venous oxygen saturation are typically 5-10% lower than central venous oxygen saturation values. During times of decreased oxygen delivery or increased oxygen consumption, the oxygen extraction ratio will increase, subsequently decreasing the measured $S_cO_2$.

The major disadvantage of measuring mixed venous oxygen saturation is the requirement of a pulmonary arterial catheter, which are not readily available in veterinary medicine. In contrast,
many critically ill veterinary patients have central lines. Therefore, the measurement of central venous oxygen saturation is readily available in many patients. Controversy exists as to whether ScvO2 can replace SvO2, however.

Recently, two veterinary studies have looked at central venous oxygen saturation in veterinary patients. These studies showed central venous oxygen saturation can be used as an indicator of occult shock and also may serve as an independent indicator of mortality in veterinary patients with septic shock.

The Future?
While the modalities listed above have been shown to be useful tools for determining global oxygen delivery there are some drawbacks. They still require multiple blood samples, are invasive and the information obtained is intermittent. The ideal tool to measure oxygen delivery would be non-invasive, continuous, measure oxygenation at the level of tissues and would allow for therapeutic interventions that would improve outcomes. Two newer technologies that satisfy some of these criteria include near-infrared spectroscopy (NIRS) and Orthogonal Polarization Spectral Imaging (OPSI). While there is very limited data at this time and these modalities are not readily available in the clinical setting, they do show promise and may one day serve as another tool in our armamentarium to help identify and address occult shock.