Anemia and Oxygen Delivery

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KEYWORDS

• Anemia • Hematocrit • Hemoglobin • Perfusion • Viscosity

KEY POINTS

- Tissue oxygenation requires both adequate oxygen delivery and effective microvascular perfusion.
- The effects of perioperative anemia cannot be accurately assessed until normovolemia is established.
- The oxygen debt that occurs in severe anemia is caused in part by compromised microvascular blood flow associated with reductions in blood viscosity.
- Blood transfusion can improve tissue oxygenation by normalizing blood viscosity and restoring capillary perfusion as well as by augmenting oxygen carrying capacity.

INTRODUCTION

Oxygen delivery involves the unidirectional transport of oxygen from the atmosphere to the interior of the mitochondria within all of the body's cells. Red blood cells (RBCs) play a dominant role in the convective transport of oxygen from the lungs to the microvasculature. Anemia is a common comorbidity in surgical patients that can complicate perioperative care by compromising oxygen delivery and leading to tissue hypoxia. This article focuses on the effects of anemia on oxygen delivery. Quantitative aspects of global oxygen delivery and the role of hemoglobin (Hb) in gas transport are reviewed. Key concepts regarding microvascular blood flow and its impact on regional oxygen delivery are discussed. Physiologic effects of anemia are summarized. In addition, clinical assessment and management of anemia in the perioperative period are touched on from the perspective of microvascular function.

DETERMINANTS OF TISSUE OXYGENATION

Global oxygen delivery can be described quantitatively by the following familiar equations:

$$Do_2 = CO \times Cao_2 \quad (1)$$

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where Do_2 is whole-body oxygen delivery, CO is cardiac output, and Cao_2 is the oxygen content within arterial blood. Under physiologic condition, 1 g of saturated Hb binds approximately 1.34 mL of oxygen. Cao_2 can therefore be calculated as:

$$Cao_2 \text{ (in mL/dL)} = [Hb](g/dL) \times 1.34 \text{ (mL/g)} \times Sao_2 + (0.003 \times Pao_2) \quad (2)$$

where [Hb](g/dL) is the blood Hb concentration in grams per deciliter, Sao_2 is the percent saturation of Hb, 0.003 is the solubility coefficient of oxygen in plasma, and Pao_2 is the partial pressure of oxygen in the arterial blood. For animals breathing room air, dissolved oxygen accounts for approximately 2% of Cao_2, and its contribution is often disregarded. Thus, Cao_2 can be approximated as:

$$Cao_2 \text{ (mL/dL)} = [Hb](g/dL) \times 1.39 \text{ (mL/g)} \times Sao_2 \quad (3)$$

However, for animals receiving oxygen supplementation, dissolved oxygen can make up a significant proportion of overall delivered oxygen. This point is discussed in more detail later.

The amount of oxygen consumed by the body is expressed as:

$$Vo_2 = CO \times (Cao_2 - Cvo_2) \quad (4)$$

where Vo_2 is total oxygen consumption, and Cvo_2 is the oxygen content within the mixed venous blood of the main pulmonary artery. The fraction of delivered oxygen that is used by the body is the oxygen extraction ratio (o_2ER), expressed as:

$$o_2ER = Vo_2/Do_2 \quad (5)$$

Rearranging Equation 5 and substituting yields the following:

$$Vo_2 = CO \times [Hb](g/dL) \times 1.34 \times Sao_2 \times o_2ER \quad (6)$$

Equation 6 expresses the relationship between oxygen consumption and the parameters that determine oxygen delivery. For a given rate of Vo_2, a decrease in any of the parameters on the right of Equation 6 must be matched by a reciprocal change in 1 or more of the other parameters. Likewise, an increase in oxygen demand (Vo_2) can only be met by a proportional increase in 1 or more of the terms on the opposite side of the equation. Although Equation 6 refers to whole-body Vo_2, it is easy to appreciate how this basic relationship can be used to describe the balance between Vo_2 and Do_2 on regional, organ-specific, or even microvascular scales, by substituting tissue-specific blood flow for CO.

Normal o_2ER is approximately 25%; that is, the amount of oxygen delivered to the body exceeds overall tissue requirements by a factor of approximately 4.[1] A prominent exception is the myocardium, which consumes approximately 50% of delivered oxygen. The excess of Do_2 in relation to Vo_2 represents the physiologic reserve in Do_2 capacity, and is an evolutionary adaptation that ensures adequate oxygen supply to tissues despite moment-to-moment fluctuations in Do_2. As such, the relationship between Do_2 and Vo_2 is biphasic (**Fig. 1**). The upper portion of the curve represents the supply-independent region, where physiologic reserves and compensatory responses maintain Vo_2 despite a decrease in Do_2. However, below a threshold value of Do_2, termed the anaerobic threshold, compensatory mechanisms become exhausted, and Vo_2 becomes limited by Do_2 (supply dependency). The value of Do_2 corresponding with the anaerobic threshold is the Do_2crit, representing the critical level of oxygen delivery below which tissue hypoxia develops.

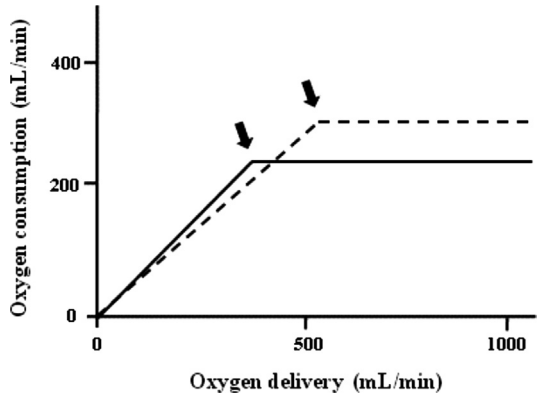

Fig. 1. Biphasic relationship between oxygen delivery and consumption. The horizontal portions of the curves represent the supply-independent phase, in which compensatory mechanisms maintain constant oxygen consumption despite decreased delivery. Below the anaerobic threshold (*arrows*), consumption becomes limited by delivery and tissue hypoxia develops. The dashed line represents a hypothetical Vo_2-Do_2 relationship for a postsurgical patient with increased oxygen demand and increased Do_2 crit (the critical level of oxygen delivery below which tissue hypoxia develops). (*Data from* Hebert J, Hu LQ, Biro G. Review of physiologic mechanisms in response to anemia. Can Med Assoc J 1997;156:S27–39.)

HEMOGLOBIN

Hb is the molecular vehicle responsible for transport of oxygen from the lungs to the tissues. Hb is a tetrameric protein complex consisting of symmetrically paired polypeptide heterodimers, each made up of alpha and beta globin subunits. Each globin molecule contains a non–covalently bound heme unit with a single iron atom. Under normal conditions, a small proportion of Hb exists as either methemoglobin or carboxyhemoglobin, neither of which is capable of binding oxygen. The association of oxygen with Hb is finely regulated through interactions with other molecules, such as protons, organic anions, and 2,3-bisphosphoglycerate (2,3-BPG).[2]

Desaturated Hb has a low affinity for oxygen; however, the initial binding of a single oxygen molecule increases the oxygen affinity of the Hb complex and facilitates additional oxygen binding. These properties are caused by allosteric changes in the Hb tetramer. Likewise, although fully saturated Hb maintains a high affinity for oxygen, dissociation of 1 oxygen molecule decreases overall oxygen affinity and promotes additional oxygen off-loading. This cooperativity in oxygen binding underlies the efficiency of Hb as an oxygen carrier, because it facilitates both oxygen uptake in the lungs and off-loading in the microvasculature. Cooperative oxygen binding is reflected in the sigmoidal shape of the familiar oxyhemoglobin dissociation curve (**Fig. 2**).

Hb also functions as a carrier of 3 other gases: carbon monoxide, carbon dioxide (CO_2), and nitric oxide (NO). Carbon monoxide binds with high affinity to the heme iron of Hb in competition with oxygen. Small amounts of carbon monoxide are produced endogenously as a product of heme degradation, and there is growing interest in the physiologic roles of carbon monoxide as a signaling molecule with cytoprotective and antiinflammatory properties.[3] CO_2 is transported primarily in solution in the plasma; however, some CO_2 may be transported by Hb through low-affinity interactions with amino-terminal residues of globin subunits.[4] NO is a gaseous free radical with potent vasodilatory properties that is produced by endothelial cells and RBCs.[5] NO can react with oxyhemoglobin to produce methemoglobin and nitrate ions, a

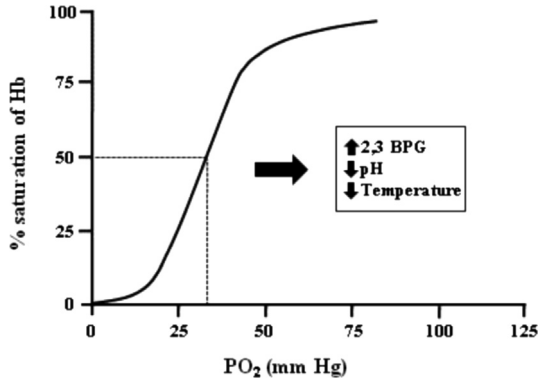

Fig. 2. The oxyhemoglobin dissociation curve representing the nonlinear relationship between P_{O_2} and oxygen saturation (S_{PO_2}). The curve shifts to the right in response to increased 2,3-BPG concentration within the RBC, severe acidemia, and hypothermia. The dashed line indicates the partial pressure of oxygen at which Hb is 50% saturated under physiologic conditions (P_{50}).

process that is reversed by erythrocytic methemoglobin reductase with the subsequent liberation of NO.[6] NO may also bind reversibly with the heme iron of deoxyhemoglobin.[7] In addition, recent evidence suggests that deoxyhemoglobin may have intrinsic nitrite reductase activity, and may generate NO through reduction of nitrite in proportion to its degree of desaturation.[8] These observations point to a role for Hb as an active regulator of microvascular tone through elaboration of NO under conditions of low P_{O_2}. At present, there is much interest in the role of Hb in the transport of NO as an endocrine mediator.[9]

MICROVASCULAR DETERMINANTS OF OXYGEN DELIVERY

Adequate levels of both CO and Ca_{O_2} are necessary to satisfy the body's oxygen demand, but they are not sufficient. Effective distribution of oxygenated blood throughout the microvascular network (perfusion) is equally important for overall oxygen delivery. A summary of several key concepts linking microvascular structure and function to tissue oxygenation is presented here.

Rheologic Control of Arteriolar Tone

Blood ejected from the left ventricle during systole passes many generations of arterial branching before reaching the arteriolar network. The precapillary arterioles are highly contractile feeder vessels that regulate capillary pressure and the passage of blood into the capillary bed. Arteriolar tone is controlled by a combination of direct autonomic innervation; humoral factors such as catecholamines and vasopressin; and paracrine vasoactive mediators such as NO, endothelin-1, prostacyclin, adenosine-triphosphate (ATP), and endothelium-derived hyperpolarizing factors.[10] Arteriolar vasoconstriction decreases hydrostatic pressure and blood flow within downstream capillaries, and is the major determinant of cardiac afterload.

Local regulation of arteriolar tone involves complex interactions between blood and the vessel wall.[11] Endothelial cells are sensitive transducers of mechanical forces associated with the flow of blood. Fluid shear stresses along the endothelial surface stimulate the release of vasoactive mediators from endothelial cells, most notably the potent vasodilator NO. Arteriolar tone is therefore regulated by changes in blood

viscosity and rate of flow, with higher levels of fluid shear leading to enhanced NO production and vasodilation.[6] ATP is also a potent vasodilator that is released from RBCs in response to hypoxia. The efflux of ATP from RBCs has been shown to be proportional to the degree of Hb desaturation, providing a mechanism by which RBCs can respond to low levels of local tissue oxygen tension by triggering vasodilation and increased blood flow to areas of relative hypoxia.[12]

Precapillary Oxygen Delivery

The capillary bed is the site of most nutrient, fluid, and metabolite exchange between the intravascular and interstitial compartments. Historically, the capillary bed has also been considered the primary site of microcirculatory oxygen delivery. This notion originated with the work of the physiologist August Krogh[13,14] in the early twentieth century. Based on observations of the highly regular spatial distribution of capillaries within skeletal muscle, Krogh[13,14] hypothesized that each capillary delivers oxygen to a defined cylindrical volume of surrounding tissue. Together with collaborator Agner Erlang, he developed the first mathematical model of microvascular oxygen delivery (the Krogh-Erlang model), in which the capillary is described as a cylindrical tube with a defined luminal diameter and length. Radial diffusion of oxygen from the central axis of the capillary to the surrounding interstitium was proposed to result in a secondary longitudinal gradient of oxygen, with the highest P_{O_2} present at the arteriolar end of the capillary, and the lowest P_{O_2} located at the venous end. The model allowed prediction of the capillary density required to satisfy regional tissue oxygen demand, based on blood oxygen concentration and flow, rate of oxygen consumption by tissue, and capillary diameter.[13,14]

Krogh's[13,14] depiction of the capillary as the primary site of microvascular oxygen delivery remains widely accepted. However, more recent experimental results have highlighted complex and important features of microvascular function that are not accounted for by the Krogh-Erlang model. Based on simultaneous in vivo measurements of P_{O_2} and oxygen saturation (Sp_{O_2}) in small cutaneous arterioles, Duling and Berne[15] described a longitudinal gradient of oxygen within arteriolar segments, indicating that a substantial fraction of oxygen may be delivered to tissues at the precapillary level. Precapillary oxygen delivery has been confirmed in a variety of settings, and in some tissues up to two-thirds of delivered oxygen may exit the microvasculature by diffusion through the walls of small arterioles.[16–18]

The diffusion of oxygen from blood to tissues at the level of the microcirculation is dictated by prevailing gradients of P_{O_2}.[19] As observed by Krogh,[13,14] arterioles and capillaries within skeletal muscle run parallel with myofibers in a highly regular distribution, and this anatomic arrangement leads to predictable longitudinal oxygen gradients within the capillary system. However, in many other tissues, capillary networks have a much less regular organization, and feeder arterioles often exist in close proximity to downstream capillaries or venules. Under these circumstances, complex patterns of oxygen exchange may develop within the microvasculature, in which oxygen diffuses freely among local arterioles, capillaries, and venules in accordance with prevailing gradients.[16,20] This patterns have been confirmed experimentally by the seemingly paradoxic finding of higher oxygen content within blood at the venous end of some capillaries compared with the arterial end.[16] Microvascular arteriovenous oxygen shunting may limit the fraction of overall D_{O_2} that reaches the capillary bed (**Fig. 3**).

Microvascular Variations in Hematocrit and Blood Viscosity

Blood flow throughout the vascular system is predominantly laminar, in which the cross-sectional area of the moving column of blood shows a parabolic velocity profile,

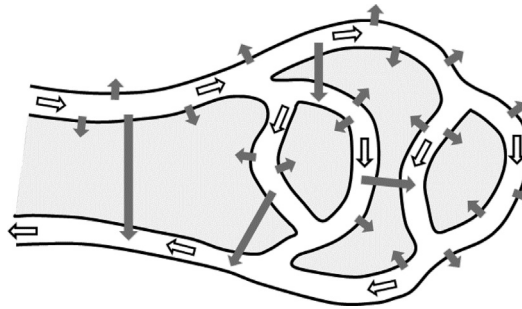

Fig. 3. Patterns of oxygen diffusion in the microcirculation. Open arrows indicate direction of blood flow. Solid arrows indicate hypothetical paths of oxygen diffusion. Oxygen does not solely undergo unidirectional diffusion from the blood to the interstitium, but is exchanged between microvessels in accordance with prevailing gradients of P_{O_2}. (*Adapted from* Ellsworth ML, Ellis CG, Popel AS, et al. Role of microvessels in oxygen supply to tissue. News Physiol Sci 1994;9:122; with permission.)

with the highest flow rates at the center of the moving column, and the lowest flow rates at the luminal surface of the vessel wall. During laminar flow, RBCs undergo axial migration toward the center of the column of flowing blood, resulting in the formation of an approximately 3-μm thick peripheral zone of cell-free plasma (the cell-free layer) adjacent to the endothelial surface.[21] This phase separation has negligible effects on the bulk properties of blood within large vessels, but has profound effects on the properties of blood within arterioles. Within large vessels, blood behaves as a uniform fluid with constant hematocrit (Hct). However, within small arterioles with a luminal diameter of less than 500 μm, blood behaves as a biphasic suspension, the physical properties of which are a function of vessel diameter.

As blood enters progressively smaller vessels, the clustering of RBCs within the central region of the vessel leads to a decrease in the Hct within that vessel, compared with the Hct within the upstream feeder vessel. This reduction in Hct with decreasing vessel diameter was first described by the Swedish physiologist Robin Fahraeus and is referred to as the Fahraeus effect.[22] Essentially, the migration of RBCs into the more rapidly flowing axial portion of the plasma column leads to an increase in the average velocity of RBCs relative to the velocity of overall blood flow. As RBCs pass through a given microvascular segment more quickly, their concentration within that segment decreases proportionally as a necessary condition for conservation of overall RBC flux. The Fahraeus effect is a major determinant of microvascular Hct, especially as vessel diameters approach the size of the transiting RBCs. Although not often taken into account clinically, microvascular Hct is typically less than half of systemic Hct, and under normal conditions can be as low as 10%.[23]

Blood is a complex suspension of deformable cells (mostly RBCs) in a proteinaceous solution (plasma). At the macroscopic level, blood is a non-newtonian fluid with viscoelastic properties. The viscosity of blood is not a fixed property, but varies with Hct, plasma protein concentration, shear rate, and temperature, and is therefore referred to as apparent viscosity.[23] Apparent viscosity is a measure of the resistance of blood to flow, and is an important hemodynamic parameter because increased viscosity requires higher intravascular perfusion pressure, and therefore greater myocardial work for effective circulation. In humans, increased blood viscosity is associated with many forms of cardiovascular disease.[24–26] In animals, pathologic increases in blood viscosity are seen with severe dehydration and hemoconcentration, as well

as with polycythemia and some hyperglobulinemias. These conditions lead to obvious perfusion deficits, and are occasionally encountered in surgical patients.

Hct is the primary determinant of the apparent viscosity of blood, and, at given temperature and shear rate, blood viscosity varies exponentially with changes in RBC concentration. Aggregation of RBCs into clusters or rouleaux formations makes a large contribution to blood viscosity; this also underlies its shear dependence, in which increasing flow rate leads to a decrease in viscosity caused by the breakup of RBC aggregates.[27] Given the effect of RBCs on blood viscosity, the Hct reductions that occur within the microvasculature associated with the Fahraeus effect are accompanied by parallel decreases in blood viscosity. This reduction in blood viscosity with decreasing vessel diameter is referred to as the Fahraeus-Lindqvist effect and plays an important role in matching perfusion pressure with microvascular flow.[28]

Plasma Skimming

At microvascular bifurcations, RBCs partition unevenly into daughter branches, with most RBCs entering the branch with the greater volumetric flow. Pouseuille was the first to describe this effect, which is termed plasma skimming.[29] This phenomenon is a direct consequence of the phase separation of flowing blood and formation of the cell-free layer. Its magnitude depends on several factors, including the relative size and geometry of the vascular branches, as well as the velocity of flow and Hct within the parent vessel (**Fig. 4**). Plasma skimming is an important rheologic phenomenon that can lead to significant hemoconcentration within larger daughter branches of successive arterial bifurcations. At the same time, extremely low concentrations of RBCs may develop within smaller daughter vessels. Across successive generations of arteriolar branching, plasma skimming leads to wide regional variations in Hct, viscosity, and flow rate.[30]

ANEMIA

Anemia refers to a decrease in whole-body RBC mass. Quantitative assessment of total RBC mass requires measurement of blood volume; therefore, anemia is most commonly expressed as a subnormal Hb concentration ([Hb]), Hct, or packed cell volume (PCV). PCV is the most commonly used measure of red cell mass in small animal practice. PCV can be used to estimate [Hb] according to the equation [Hb] $\approx$ PCV/3. In addition, many automated hematology analyzers report Hct as a calculated value based on the product of the RBC count and the mean corpuscular volume.

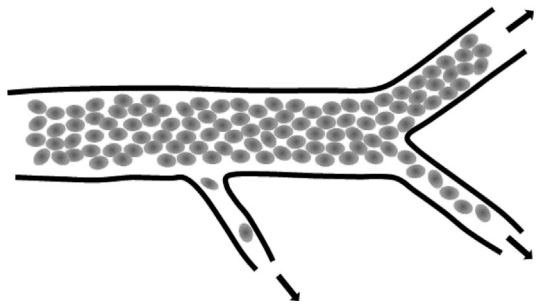

Fig. 4. Plasma skimming at arteriolar bifurcations. Arrows indicate direction of blood flow. Formation of the cell-free layer during laminar flow leads to uneven partitioning of RBCs into daughter branches of microvascular bifurcations and significant regional variations in microvascular Hct.

PCV usually provides a reasonable approximation of total RBC mass; however, animals with acute blood loss can maintain a normal PCV for several hours until plasma volume is restored through fluid shifts or fluid administration. In contrast, aggressive fluid or colloid resuscitation may decrease PCV because of dilutional effects with no change in overall RBC mass. Sequestration or mobilization of RBCs from the spleen may cause acute fluctuations of PCV, with accompanying changes in the oxygen carrying capacity of the blood, despite a constant total RBC mass. These situations are encountered frequently in the perioperative setting; therefore, caution is necessary when interpreting a single PCV in surgical patients. Serial monitoring of PCV is often necessary for accurate assessment of patients' oxygen carrying capacities in the perioperative period.

Anemia is a common condition in surgical patients, and may vary greatly in both severity and chronicity. In animals with intact compensatory responses, anemia is usually well tolerated, and tissue oxygenation can be maintained under resting conditions despite extremely low [Hb].[31] However, the pain, stress, inflammation, and hypermetabolism experienced by animals in the perioperative period may increase global oxygen demand, whereas the effects of anesthetic, analgesic, and sedative agents may simultaneously blunt normal compensatory responses.[32] As a consequence, anemic surgical patients may have an increased D_{O_2}crit and may be uniquely susceptible to tissue hypoxia in the perioperative period (see **Fig. 1**).

PHYSIOLOGIC ADAPTATIONS TO ANEMIA

The overall compensatory physiologic response to anemia consists of an increase in CO and increased $_{O_2}$ER, along with redistribution of blood flow toward vital organs, particularly the brain and myocardium. These adaptive responses involve variable changes in autonomic tone, alterations in blood viscosity and microvascular flow, and shifts in the oxyhemoglobin dissociation curve.

Cardiac Output

Increased CO is the most consistently documented hemodynamic alteration associated with anemia.[33] Two basic mechanisms underlie the increase in CO during normovolemic anemia: increase in sympathetic stimulation and reduced blood viscosity. In controlled experimental settings, the decreased Ca_{O_2} associated with normovolemic anemia has been shown to increase sympathetic tone through triggering of carotid chemoreceptors,[34] which in turn leads to an increase in CO by direct enhancement of myocardial contractility and heart rate, as well as by augmentation of preload through venoconstriction and mobilization of venous blood.[1] At the same time, anemia causes an intrinsic decrease in blood viscosity that is further compounded by the Fahraeus-Lindqvist effect. The relationship between blood viscosity and CO is complex.[33] The reduction in blood viscosity associated with anemia leads to direct and proportional decreases in cardiac afterload and increases in flow through the microcirculation. Blood viscosity is normally highest in postcapillary venules where increasing Hct and low flow rate facilitate RBC aggregation. Enhanced flow within postcapillary venules inhibits RBC aggregation through increases in local shear and leads to disproportionate reductions in viscosity within venular segments. As a consequence, venous return and cardiac preload are enhanced for a given venous pressure, which further augments CO. In contrast with hypovolemia, in which hemodynamic responses are mediated primarily by the autonomic nervous system, the compensatory increase in CO associated with anemia is attributable mostly to reductions in blood viscosity.[33]

Oxygen Extraction

Anemia also results in an increase in peripheral O_2ER. This increase occurs in all tissues except the myocardium, in which there is high basal O_2ER, and in which any decrease in DO_2 can only be compensated for by coronary vasodilation and increased organ blood flow. With mild to moderate anemia, the CO response is usually sufficient to maintain DO_2 and meet resting tissue oxygen demand; however, as anemia worsens, increased O_2ER becomes an important additional compensatory mechanism. Analogous to the DO_2crit, the threshold value of [Hb] below which compensatory mechanisms become exhausted and global tissue hypoxia develops is the [Hb]crit. In the dog, [Hb]crit corresponds with an Hct of approximately 8%.[35]

O_2ER is enhanced in chronic anemia by shifts in the oxyhemoglobin dissociation curve, which defines the partial pressure of oxygen at which Hb is 50% saturated under physiologic conditions (P_{50}). In the dog, anemia causes a rightward shift in the curve, indicating conditions that favor dissociation of oxygen from Hb, and enhanced peripheral oxygen off-loading. This effect is caused predominantly by increased levels of 2,3-BPG within the erythrocyte, synthesis of which is stimulated by a decrease in intraerythrocytic pH.[36] 2,3-BPG is an allosteric effector that binds to deoxygenated beta-globin subunits and stabilizes the lower oxygen affinity conformation of the Hb tetramer. Upregulation of 2,3-BPG is generally considered to be physiologically advantageous in the context of anemia; however, there is some evidence that Hb with a higher P_{50} (lower oxygen affinity) facilitates the formation of hypoxic foci by off-loading oxygen within oxygenated tissue regions at the expense of less oxygenated regions.[37] 2,3-BPG levels decrease markedly in stored canine blood, which may limit the oxygen carrying capacity of RBCs that are transfused after prolonged periods of storage.[36] Less is known regarding the effect of anemia on the oxyhemoglobin dissociation curve in cats; however, feline erythrocytes contain very little 2-3-BPG.[38] Moreover, feline Hb shows a higher P_{50} and greater cooperativity than that of many other species, indicating a stronger tendency to release oxygen in the periphery.[39,40]

Decreased temperature and acidemia also cause a rightward shift in the oxyhemoglobin dissociation curve; however, the clinical relevance of these effects is debated. In particular, physiologically relevant decreases in pH have very small effects on the P_{50}. The effects of pH on the oxyhemoglobin dissociation curve are thought to be mostly indirect, through stimulation of 2,3-BPG synthesis.[33,41]

CLINICAL APPROACH TO ANEMIC PATIENTS

In-depth discussion of the general clinical and diagnostic approach to anemic patients can be found elsewhere, and readers are referred to several excellent sources.[42–44] In general, clinical signs of anemia are nonspecific, and there is considerable overlap in the physical manifestations of anemia and hypovolemia. One of the cardinal rules of perioperative patient assessment is that hypovolemia must be addressed before the physiologic impacts of anemia can be adequately judged, especially in relation to acute blood loss. Even though blood loss leads to an immediate decrease in the oxygen carrying capacity of the blood, the hemodynamic abnormalities observed in animals with acute hemorrhage are overwhelmingly attributable to hypovolemia and associated perfusion deficits, and not anemia per se.

Assessment of Tissue Oxygenation

In surgical patients, assessment of tissue oxygenation is most commonly based on a combination of physical examination findings, blood gas analysis, oximetry, and plasma lactate measurements. Physical examination findings such as pallor,

tachypnea and/or hyperpnea, tachycardia, and aberrant pulse quality can suggest the presence of compensatory responses to anemia, but are generally nonspecific. Arterial blood gas analysis may show a respiratory alkalosis secondary to increased ventilation. However, it is important to remember that normal compensatory hemodynamic and ventilatory responses to anemia may be reduced or absent in anesthetized or sedated patients. Ca_{O_2} is rarely measured clinically, but can be calculated based on Equation 3. Ca_{O_2} is reduced in anemic states, although this does not necessarily indicate inadequate tissue oxygenation unless the reduction is severe. In rare instances in which CO and Cv_{O_2} measurements are available, $_{O_2}$ER may be determined. A global $_{O_2}$ER approaching 50% is generally considered to herald the onset of severe tissue hypoxia[1,35]; however, $_{O_2}$ER is an insensitive indicator of regional or organ-specific oxygen debt. Pulse oximetry is a commonly used tool for perioperative monitoring of Sp_{O_2}; however, anemia does not affect oximetric measurements, thus Sp_{O_2} values remain normal even with severe Hct reduction.

Plasma lactate concentration is a useful and important measure of anaerobic tissue metabolism, and an increased lactate level generally indicates supply-limited V_{O_2}.[45] Lactate concentration at any given point in time represents a balance between production and metabolism, thus serial lactate measurements are often important. In normovolemic dogs, increased plasma lactate level is a reliable indicator of tissue hypoxia; however, as a global measure, lactate lacks sensitivity for detection of early or regional tissue hypoxia.

These physical, hemodynamic, and biochemical parameters are important clinical variables, but they provide limited information on the adequacy of tissue oxygenation, especially at the regional level. Functional capillary density (FCD) is a parameter of microvascular perfusion that is widely used in microvascular research and that has been shown to correlate well with tissue oxygenation at the microscopic level.[46–48] FCD is defined as the total length of RBC-perfused capillaries within a defined area and is measured by specialized video-microscopic monitoring of capillary beds within small regions of tissue. Capillary pressure and blood viscosity seem to be the primary determinants of FCD.[46] Restoration of FCD is highly correlated with survival following resuscitation from experimental hemorrhagic shock, independently of the oxygen carrying capacity of the blood.[47,49] FCD is an emerging technique for clinical assessment of microvascular perfusion in humans,[50–52] and has also been used in dogs for evaluation of the microhemodynamic effects of fluid administration during ovariohysterectomy.[53]

Methods for Enhancing Oxygen Delivery and Tissue Oxygenation

Under normal conditions, dissolved oxygen accounts for a small fraction of overall D_{O_2}. However, increasing the inspired concentration of oxygen can enhance D_{O_2} by increasing the amount of dissolved oxygen in the plasma.[54] Per Equation 3, in an animal breathing 100% oxygen with a [Hb] of 6 g/dL and Pa_{O_2} of 450 mm Hg, dissolved oxygen can account for more than 20% of overall D_{O_2}. This effect was shown clearly in a human study of severe normovolemic anemia in which an increase in Pa_{O_2} to 400 mm Hg was associated with hemodynamic improvements equivalent to 3 g/dL of circulating Hb.[55]

Transfusion of RBCs remains a common clinical intervention to improve oxygen carrying capacity in anemic patients, especially in the perioperative setting. In humans, it has been estimated that approximately 50% of all units of transfused RBCs are administered to surgical patients.[56] Perioperative use of RBC transfusions in veterinary practice has not been specifically reported; however, in one large retrospective study, only 5% of transfused units of RBCs were given to surgical patients.[57] Canine and feline blood products along with their storage and use has been reviewed.[58]

RBC transfusion has been reported to improve most measured parameters of oxygen delivery in small animals, and it is generally accepted that the clinical benefits associated with the transfusion of RBCs derive from increased Do_2.[59] However, compelling experimental results suggest that the beneficial effects of transfusion may be attributable largely to improvements in the rheologic properties of blood and normalization of microvascular flow, independent of increases in oxygen carrying capacity of the blood.[60]

Studies using the hamster window chamber system, in which detailed in vivo measurements of microvascular function and tissue oxygenation can be performed on awake animals, have shown that extreme anemia leads to deficits in tissue oxygenation associated with reduced FCD. In this experimental setting, blood transfusion leads to normalization of both FCD and tissue oxygenation.[61] However, in an elegant series of studies, it was shown that both FCD and tissue oxygenation were also restored with transfusion of RBCs in which Hb was converted to methemoglobin, thereby rendering the cells incapable of oxygen transport.[46] Similarly, increasing plasma viscosity by transfusion of a high-molecular-weight alginate-based plasma expander resulted in significant improvements in FCD and tissue oxygenation, with no change in Hct.[62] This increase in microvascular perfusion was associated with increased endothelial production of NO triggered by increased shear stresses imposed on the vascular wall.[62] These studies and others point to reduced blood viscosity as a major contributor to the loss of FCD and defects in tissue oxygenation that occur in severe anemia.[37,49,63,64] The mechanism involves critical decreases in fluid shear with attendant declines in NO production and peripheral vasoconstriction, along with accentuated plasma skimming effects. There is a tight correlation between the level of blood viscosity that leads to loss of FCD and the plasma [Hb] below which Vo_2 becomes supply dependent. This correlation has led to the notion that the conventional transfusion trigger, defined as the Hct below which tissues become at risk for hypoxia, may simultaneously be a viscosity threshold, below which tissues become vulnerable to hypoperfusion because of critical decreases in FCD and microcirculatory collapse.[37]

SUMMARY

Maintenance of adequate oxygen delivery is a critical facet of perioperative care, but clinical assessment of tissue oxygenation remains challenging. Anemia reflects a decreased oxygen carrying capacity of the blood and its significance in the perioperative setting relates largely to the associated risk of insufficient oxygen delivery and cellular hypoxia. From the microcirculatory perspective, oxygen carrying capacity and flow characteristics of blood are closely connected, and the effect of anemia on blood rheology and perfusion should not be disregarded. Meaningful clinical measures of tissue oxygenation are needed in veterinary practice. In the meantime, clinicians must rely on evaluation of a patient's hemodynamic and ventilatory performance, along with biochemical and hemogasometric measurements. Blood transfusion is used commonly for treatment of perioperative anemia, and may improve tissue oxygenation by normalizing the rheologic properties of blood and enhancing perfusion, independent of increases in oxygen carrying capacity.

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