The Clinical Physiologist

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Oxygen Delivery during Severe Anemia When Blood Transfusion Is Refused on Religious Grounds

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The Clinical Challenge

A previously healthy, 31-year-old woman was transferred to an urban tertiary care center with severe postpartum hemorrhage and acute blood loss anemia after the birth of her first child. Her delivery at a rural hospital was complicated by prolonged labor, chorioamnionitis, difficult extraction requiring vacuum assistance, perineal tear, and significant blood loss. At 48 hours after delivery, her hemoglobin concentration was 4.4 g/dl, down significantly from her last preterm-measured value of 11 g/dl, and she was transferred the same day to our hospital for additional interventions.

On arrival to our hospital, her vital signs were significant, with a resting tachycardia of 123 bpm and blood pressure of 111/68 mm Hg. She had normal mental status, and mild persistent vaginal bleeding, despite administration of uterotonic agents. She appeared well perfused, had a normal lactate of 1.5 mmol/L, and lacked signs of end-organ dysfunction. Red blood cell transfusion was recommended; however, she refused this intervention due to her religious beliefs as a Jehovah's Witness. She immediately underwent bilateral uterine artery embolization, followed by a dilatation and curettage with removal of a 10-cm portion of retained placenta, with additional blood loss. She received tranexamic acid, isotonic crystalloid, and empiric antibiotics for endometritis. She was transferred to the intensive care unit, awake and spontaneously breathing.

On Post-Transfer Day 2, she developed significant vital sign abnormalities, with sinus tachycardia to 146 bpm, respiratory rate of 30/min, temperature of 38.4°C, and mild hypotension of 97/64 mm Hg. She was intermittently agitated and confused, and her electrocardiogram demonstrated mild but diffuse ST segment depression. Her hemoglobin was 3.1 g/dl and white blood cell count was 24,000 cells/mm^3. Her surrogate decision-makers were again approached regarding consent for blood transfusion, yet her wish to avoid transfusion of red blood cells was affirmed and respected.

Questions

1. What physiologic mechanisms are responsible for maintaining adequate oxygen delivery (DO_2) to tissues in the setting of critical anemia?

2. How can systemic DO_2 and consumption be manipulated using nontraditional interventions during critical anemia, when blood transfusion is not an option?

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(Received in original form December 28, 2016; accepted in final form March 6, 2017)

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Ann Am Thorac Soc Vol 14, No 7, pp 1216–1220, Jul 2017
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DOI: 10.1513/AnnalsATS.201612-1039CC
Internet address: www.atsjournals.org

Clinical Reasoning

The change in the patient's vital signs and deteriorating mental status were interpreted as clear signs of a shock state. Her critically low hemoglobin concentration, down to 25% of her prelabor state, had led to a markedly reduced arterial oxygen content and inadequate systemic DO_2 given the metabolic demands associated with sepsis and respiratory failure. She was at high risk for multiple organ failures related to critical anemia. We recognized the urgent need to increase systemic DO_2 without red blood cell transfusion.

The Clinical Solution

Recognizing the patient's shock on Post-Transfer Day 2, several modalities were used to minimize oxygen demand/consumption ($\dot{V}O_2$) and maximize oxygen supply (arterial oxygen content [Ca_{O_2}]). The patient was intubated, sedated, and chemically paralyzed, and placed on ventilation settings to keep Sa_{O_2} greater than 95%, which required positive end-expiratory pressure of 5 cm H_2O and FI_{O_2} of 0.80–1.0 for the first 3 days. Broad-spectrum antibiotics were continued, and she was placed on a normothermia protocol using cooling blankets and antipyretics, as necessary, to prevent temperature elevation and hyperthermic increases in $\dot{V}O_2$. Blood draws were kept to an absolute minimum, with an average of once every other day. She was treated with high-dose intravenous erythropoietin, intravenous iron sucrose, folate, and vitamin B12 to support erythropoiesis.

Beginning on Post-Transfer Day 1, she received hyperbaric oxygen (HBO) therapy in a hyperbaric chamber located at our institution. During each session, in consultation with our hyperbaric medicine specialists, she was treated with 100% oxygen at a pressure of 2.4 atmospheres for 90 minutes with two 5-minute air breaks. During Post-Transfer Days 2–5, she received six HBO treatments, each associated with an improvement in her tachycardia (Figure 1). In total, she underwent 11 HBO treatment sessions, without any immediate complications noted.

After further deliberation, the patient's family deemed partial blood components and hemoglobin substitutes religiously acceptable. After the U.S. Food and Drug Administration and the local institutional review board approved emergency use of an investigational product, the bovine-derived hemoglobin substitute, hemoglobin-based oxygen carrier (HBOC)-201 (Hemopure; HbO2 Therapeutics LLC, Souderton, PA) was obtained from the manufacturer. During Post-Transfer Days 3–8, she received a total of 10 units of HBOC-201, each given intravenously over 4–6 hours. Treatment was continued until her hematocrit was measured at 12%, which indicated an endogenous hemoglobin level of approximately 4 g/dl, a level associated with a low level of mortality in young, healthy patients. She was observed to have profound, albeit transient, hypertension with the second and third units, requiring slower infusion rates and brief treatment with calcium channel blockers.

Her hemoglobin nadir was 2.3 g/dl on Post-Transfer Day 3, followed by a slow rise to 4.4 g/dl 4 days later. She developed hypoxemia and increased work of breathing on Post-Transfer Day 8 and a chest X-ray demonstrated bilateral infiltrates consistent with acute respiratory distress syndrome (ARDS; Figure 2). Over the ensuing week, she was treated with lung-protective ventilation, neuromuscular blockade, inhaled epoprostenol, diuretics, corticosteroids, and empiric antibiotics. Prone positioning was considered, but ultimately deferred at the discretion of the attending physician, given her steady clinical improvement. She was liberated from mechanical ventilation on Post-Transfer Day 20, and left the hospital 6 days later with a hemoglobin value of 7.4 g/dl to continue acute rehabilitation. After a total of about 45 days, she was reunited with her healthy baby boy at home. On follow-up 2 months later, her hemoglobin level was 11.8 g/dl, she felt well, and she was able to care for her child independently.

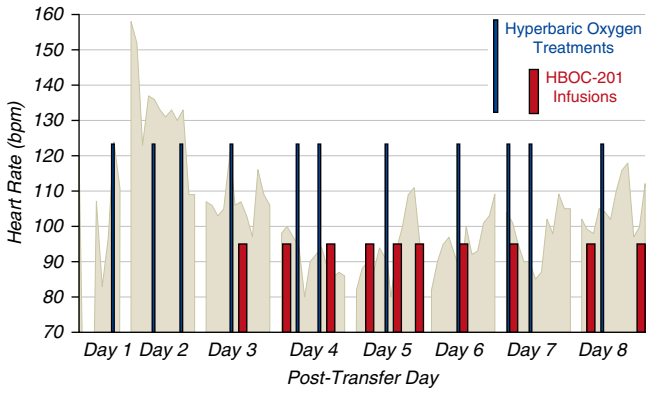

Figure 1. Trend of patient's heart rate as a surrogate for cardiac output during treatments with hyperbaric oxygen and administration of a hemoglobin substitute, hemoglobin-based oxygen carrier (HBOC)-201. bpm = beats per minute.

The Science behind the Solution

Severe Anemia

Robust human data exist demonstrating that acute anemia down to a hemoglobin concentration of approximately 5 g/dl, if accompanied by euvolemia, is well tolerated among healthy subjects at rest. In fact, only a mild increase in $\dot{V}O_2$ was observed in these subjects as compared with their preanemia baseline, and there was no elevation in serum lactate. The degree of anemia required to induce clinical shock (i.e., signs and symptoms of critically impaired tissue DO_2 leading to end-organ dysfunction) cannot easily be predicted, as it depends on age, cardiopulmonary reserve, and other factors. However, it is known that patients with a hemoglobin concentration below 3 g/dl experience at least 50% mortality based on observational data among those refusing blood transfusion, primarily in the Jehovah's Witness community.

A Chinese group reported a remarkable case involving a middle-aged man with penetrating injury to his axillary artery who was managed for approximately 12 hours in a state of extreme hemodilution

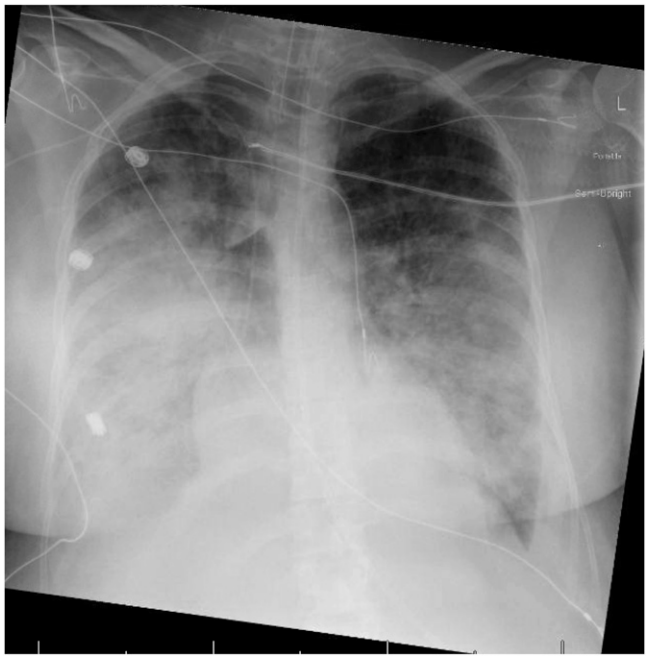

Figure 2. Anterior-posterior chest radiograph on Post-Transfer Day 9 demonstrates bilateral pulmonary infiltrates in pattern consistent with acute respiratory distress syndrome.

(hemoglobin nadir of 0.7 g/dl, or hematocrit of 2.2%) during operative repair until appropriately matched blood was available for transfusion; he survived without apparent sequelae. As was the case with our postpartum patient, this case report highlights important endogenous and exogenous compensatory mechanisms to mitigate a severely low arterial oxygen content due to critical anemia. The body will increase cardiac output primarily by raising heart rate at the same time that systemic vascular resistance decreases (due to a decrease in blood viscosity, an increase in cross-sectional area of the vascular bed, and a decrease in the scavenging of vascular endothelial nitric oxide [NO] by red blood cells). Iatrogenic compensatory support in the intensive care unit includes maintenance of normovolemia, use of high FI_{O_2}, induction of mild hypothermia, and use of deep sedation.

Institutions such as ours have adopted protocols to prevent ("bloodless" surgery, for example) or treat extreme hemodilution after refusal of blood products on religious grounds. The case presented here is somewhat unique in that traditional measures to support tissue oxygenation in the face of critical anemia were combined with HBO therapy and an HBOC, ultimately leading to a good outcome. In the next section, the physiologic foundation for these chosen therapies is discussed in greater detail.

Oxygen Content and Delivery

In a healthy individual at rest, the amount of oxygen delivered to the tissues is normally at least four times the amount actually used by the body's tissues. In other words, the ratio of DO_2 to $\dot{V}O_2$ is normally maintained at 4:1. However, in certain pathophysiologic states, such as severe anemia, heart failure, or severe ARDS, the rate of DO_2 is impaired. When the DO_2:$\dot{V}O_2$ ratio is less than 2:1, the $\dot{V}O_2$ may become dependent on the supply of O_2 and manifest as the inability to maintain oxygen-dependent metabolism in the tissues, leading to anaerobic metabolism and shock.

Importantly, DO_2 is the product of the amount of oxygen in arterial blood, represented by the Ca_{O_2} and how fast that blood is flowing, represented by the cardiac output (CO):

$$DO_2 \text{ ml } O_2/\text{min} = Ca_{O_2} \text{ ml } O_2/\text{dl blood} \times \text{CO L/min} \times 10\text{dl/L} \quad (1)$$

Due to its poor solubility and Pa_{O_2}, a negligible amount of oxygen is dissolved in plasma at sea level, generally less than 1% of the total arterial O_2 content; rather, oxygen is transported to the tissues bound to hemoglobin. Practically speaking, the determinants of Ca_{O_2}, at sea level and with normal lungs, are hemoglobin concentration (g/dl) and, less so, the oxyhemoglobin saturation (Sa_{O_2}, %) (Equation 2). In fact, if hemoglobin did not exist and the body was dependent on soluble O_2 alone, resting cardiac output would need to be around 300 L/min to maintain adequate DO_2, a physiological impossibility.

$$Ca_{O_2} = ([\text{Hgb}] \times Sa_{O_2}/100 \times 1.34 \text{ ml } O_2/\text{g Hgb}) + (Pa_{O_2} \times 0.003\text{ml/mmHg/dl}) \quad (2)$$

Our patient with critical anemia after postpartum hemorrhage (hemoglobin, 3.1 g/dl) had a Ca_{O_2} of approximately 4.5 ml/dl (normal = 20 ml/dl) despite measured Pa_{O_2} and Sa_{O_2} values within the normal range. The relationship between the three oxygen parameters (Ca_{O_2}, Pa_{O_2}, and Sa_{O_2}) is shown in Figure 3 for different hemoglobin concentrations, illustrating the fundamental importance of hemoglobin in DO_2.

Our patient initially compensated for her severe anemia and the consequent decrease in Ca_{O_2} in several notable ways. Although not directly measured, her body's tissues increased the percentage of oxygen extracted from the blood from a resting baseline of about 25% to greater than 70%. In an attempt to increase the delivery of available oxygen (DO_2), her cardiac output was increased through changes in both stroke volume and heart rate. Her resting sinus tachycardia reached 143 bpm in this setting, indicating that her cardiac output was approaching its maximum and that her physiologic compensation was nearly exhausted. Given that packed red blood cell transfusion was not an option based on her religious beliefs, other interventions were urgently required to achieve a more acceptable DO_2:$\dot{V}O_2$ ratio.

Deep sedation and neuromuscular blockade are relatively frequent critical care interventions, used most commonly in conditions such as severe respiratory failure or increased intracranial pressure. Clearly, adequate sedation to facilitate safe mechanical ventilation and patient comfort is necessary; the additional effect on oxygen demand of deep sedation and

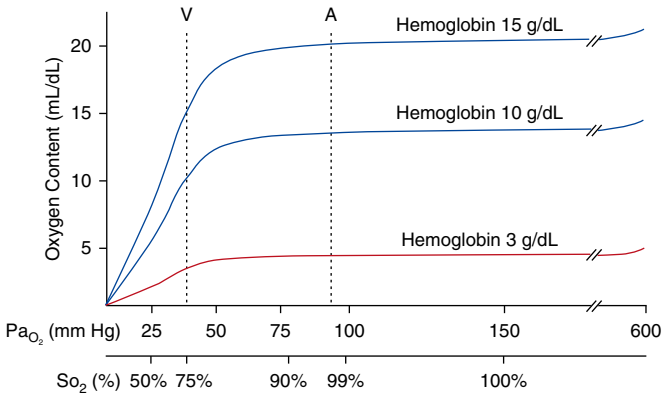

Figure 3. The effect of increasing Pa_{O_2} on the total oxygen content is shown for three different hemoglobin concentrations. The middle hemoglobin (10 g/dl) line is near the patient's prelabor baseline, whereas the lower hemoglobin (3 g/dl) line approximates her state of critical anemia. A = arterial blood; So_2 = percent oxygen saturation of hemoglobin; V = venous blood.

induced paralysis is less clear. By limiting the work of breathing, coughing, and accessory muscle use, induced paralysis has been reported to reduce metabolic demand by more than 10% in children and used successfully in the management of critical anemia in multiple case reports. The addition of therapeutic hypothermia, which may further reduce $\dot{V}O_2$ more than 5% for each 1.0°C decrease in temperature, was considered in this case. However, given the risk of worsening coagulopathy and bleeding, a noninvasive normothermia treatment protocol was chosen.

HBO was employed early in this patient's treatment course. The use of HBO to treat critical anemia dates to the origins of modern HBO therapy. In the 1950s, Boerema demonstrated, through a swine model, that animals treated with exchange transfusions of a dextrose solution to hemoglobin levels of only 0.4–0.6 g/dl could survive for an extended time in an HBO environment. The effect of this relatively low-risk, cost-effective therapy has not diminished over time, and severe anemia with evidence of end-organ damage remains a recognized indication for HBO therapy. HBO acts to dramatically increase the amount of dissolved oxygen in the plasma that can be carried to the tissues, increasing the Pa_{O_2} nearly 20-fold. Although plasma-soluble oxygen contributes little to DO_2 during normobaric conditions, in the anemic patient it can provide for the majority of DO_2. The HBO treatments given to our patient provided a Pa_{O_2} of 1,500–2,000 mm Hg, and an estimated arterial oxygen content of approximately 10 ml/dl (Figure 4, Table 1). In this manner, HBO can mitigate the risk of critical tissue hypoxia for discrete periods of time, while concurrently and temporarily allowing a stressed cardiovascular system to rest by blunting the compensatory cardiac output elevation and associated hyperadrenergic state. Furthermore, this adjuvant therapy has been successfully applied to obstetrics patients, reported as early as 1974 by Hart in the treatment of a 29-year-old woman with a hemoglobin level of 3.0 g/dl.

Hemoglobin-based Oxygen Carriers

It has become commonplace in hospitals employing "bloodless protocols" to use therapies, such as high-dose erythropoietin and intravenous iron, to stimulate red blood cell production. However, the use of alternative oxygen carriers, such as HBOCs, remains investigational. In general, HBOCs are purified, acellular hemoglobin molecules, modified through cross-linking, conjugation, and polymerization. These modifications promote intravascular stability of the hemoglobin, and minimize glomerular filtration and consequent renal tubular damage. At least 10 hemoglobin substitutes have been developed and studied in an attempt to provide an alternative mode for carrying oxygen to the tissues, yet their net efficacy and risks are unclear, and none are currently licensed for use in the United States. A meta-analysis in 2008 of 16 studies found an increased relative risk of myocardial infarction and mortality with the use of hemoglobin substitutes in trauma and surgical patients.

The hemoglobin substitute used in this case, HBOC-201 (Hemopure), is a product

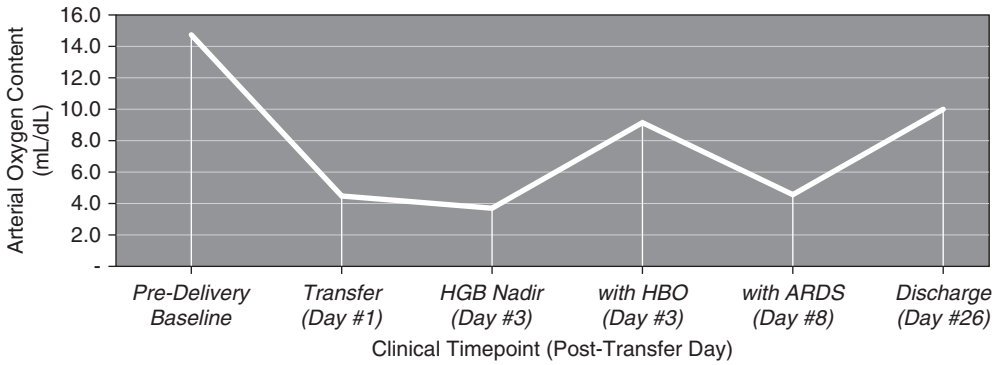

Figure 4. Graphic representation of the patient's total arterial oxygen content at different important clinical time points. Note that the effect of administration of a hemoglobin substitute on total oxygen content is difficult to quantify, and is therefore not included in this graph. ARDS = acute respiratory distress syndrome; HBO = hyperbaric oxygen therapy; HGB = hemoglobin.

Table 1. The patient's arterial oxygen content and change from baseline as calculated from oxygen saturation, hemoglobin concentration, and partial pressure of oxygen

Clinical Time Point, Post-Transfer Day	Oxygen Saturation (%)	Hemoglobin (*g/dl*)	Partial Pressure of Oxygen (*mm Hg*)	Arterial Oxygen Content* (*ml/dl*)	Relative Change (%)
Predelivery baseline	98	11.0	100	14.7	—
Transfer, Day 1	99	3.1	134	4.5	−69.3
Hemoglobin nadir, Day 3	97	2.4	193	3.7	−74.8
With HBO, Day 3	99	2.4	2000	9.2	−37.5
With ARDS, Day 8	82	4.0	48	4.5	−69.1
Discharge, Day 26	98	7.4	100	10.0	−31.9

Definition of abbreviations: ARDS = acute respiratory distress syndrome; HBO = hyperbaric oxygen.
*Arterial oxygen content(ml/dl) = (Sa_{O_2} × HGB × 1.34ml/g) + (Pa_{O_2} × 0.003ml/mmHg/dl)

of cross-linked, bovine-derived hemoglobin. It is currently licensed for human use in South Africa only, but is licensed for veterinary use in the United States as Oxyglobin (HbO2 Therapeutics LLC, Souderton, PA). Able to be stored at room temperature for up to 3 years, each 30-g unit of HBOC-201 can potentially raise plasma hemoglobin by 0.63 g/dl, with an estimated intravascular half-life of 19 hours. Primary adverse effects include methemoglobinemia and hypertension, due to avid NO scavenging occurring during intra- and extravascular leak of free hemoglobin. In human trials, this hypertensive effect was reported in approximately 5% of patients, and is likely related to the rate of infusion. Despite evidence of its efficacy in animal models and healthy volunteers, phase III clinical trials of HBOC-201 and similar products have not demonstrated a consistent clinical benefit. However, for those in whom the risk of mortality is extreme, this investigational therapy (obtained through institutional review board and U. S. Food and Drug Administration approval) can potentially be used as a bridge to hemoglobin recovery. Because it is derived from nonhuman sources and made of fractions of the primary components of blood, Jehovah's Witness patients such as ours may be amenable to such therapy.

It is not entirely clear why the patient reported here developed ARDS after the resolution of her critical anemia. The potential additional contribution to this patient's acute lung injury from HBO and multiple transfusions of a hemoblogin-based oxygen carrier cannot be excluded. Although oxygen toxicity is a recognized potential adverse effect of hyperbaric therapy, it is minimized through use of "air breaks," and the development of severe lung injury from HBO is infrequently reported. Due to NO scavenging and rapid unloading of oxygen, hemoglobin substitutes may cause precapillary vasoconstriction and contribute to pulmonary oxygen toxicity. However, myocardial infarction, not lung injury, was the major adverse event observed in clinical trials of HBOC-201 and other similar products. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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