Editorial Comment: Recovery from Extreme Hemodilution (Hemoglobin Level of 0.6 g/dL) in Cadaveric Liver Transplantation *and* Management of a Jehovah's Witness Patient with Sepsis and Profuse Bleeding After Emergency Coronary Artery Bypass Graft Surgery: Rethinking the Critical Threshold of Oxygen Delivery

In this issue of *A&A Case Reports*, 2 reports describe patients in whom extremely low hemoglobin (Hgb) levels were reached without critical end-organ failure.[1,2] Both patients survived what would otherwise seem to be lethally decreased Hgb oxygen (O_2)-carrying capacity. In fact, the patient described by Kariya et al.[2] may be a survivor of the lowest Hgb ever recorded. When these rare, freakish cases occur, we need to pause and reconsider conventional teaching regarding hemodilution and critical O_2 delivery (DO_2) as well as the limits of human physiology. Cellular DO_2 in the end (plasma and cytosol) is via dissolved O_2, and the take-home point is that we need to appreciate the importance of dissolved O_2, especially in cases of extreme anemia.

Anesthesiologists know that compensatory mechanisms for bleeding and hemodilution include increased cardiac output (CO), improved ventricular emptying, tachycardia, decreased viscosity, and vasodilation.[3] These relatively easily measured macrovascular changes occur in large capacitance/resistance vascular beds. The capillary network/microcirculation may not be affected by the changes of anemia until perfusion pressure/CO is very low or there is intercedent vascular disease.[4]

Anesthesiologists are conversant with the concepts of supply-dependent or supply-independent DO_2. The inflection point at which cells no longer receive adequate O_2 to meet cellular demand is critical DO_2 (DO_{2crit}). DO_{2crit} defines shock.[3] The O_2 content equation ($CaO_2 = 1.36 \times Hgb \times Sao_2/100 + 0.0031 \times Pao_2$) gives an estimate of total blood O_2. Standard critical care teaching minimizes the contribution of dissolved O_2 ($0.0031 \times Pao_2$) as being negligible compared with Hgb-carried O_2.[5]

The complex physiology of DO_2/utilization, however, is not governed by any one equation and is dependent on O_2 movement in the microcirculation.[6–8] An emerging understanding of the microcirculation emphasizes O_2 movement due to a driving O_2 pressure, from erythrocytes to plasma, then across cell membranes into cytosol, and finally to the mitochondria.[6–8]

Most physicians consider cellular O_2 supply to be completely dependent on Hgb. However, a focus on Hgb must be tempered with the fact that metabolically used O_2 is exclusively dissolved O_2. Hgb serves as a bank or O_2 reserve to supercharge the plasma with dissolved O_2. The largest O_2 diffusion difference occurs between the arterioles and tissues.[6] Capillary O_2 partial pressure is at equilibrium with tissue O_2—5 to 25 mm Hg O_2.[6] Lymphatics (without Hgb) have the same O_2 tension as intracellular cytosol—15 to 25 mm Hg. The plasma, cell membranes, and cytosol all represent impediments to O_2 movement.[6–8]

Changes in calculated blood O_2 content due to anemia versus hypoxia can point out the importance of dissolved O_2. An example is useful. If one calculates O_2 content in a patient with Pao_2 of 90 mm Hg having 15 g/dL Hgb, and then recalculates it at an Hgb of 7.5 g/dL (e.g., a normal Hgb decreases during cardiopulmonary bypass), the reduction in O_2-carrying capacity is 49.5%; however, if one calculates O_2 content at 15 g/dL, but the Pao_2 decreases 50% to 45 mm Hg (the level at Everest base camp 5300 m elevation), the reduction in O_2-carrying capacity is only 18.9%. Thus, although the patient with the Hgb loss is fine, the patient with that 50% reduction in Pao_2 (dissolved O_2) is in distress, even though he does not undergo nearly as much loss of total O_2-carrying capacity as the patient with the Hgb loss. Thus, calculated O_2 content shifts alone do not explain clinical DO_2; dissolved O_2 is critical clinically.

Decreased Hgb alone does not cause tissue hypoxia until it becomes severe, that is, until the Hgb level is reduced to less than DO_{2crit}.[9–13] In small studies in humans with young volunteers undergoing progressive hemodilution, anemia <5 g/dL created a subjective feeling of energy loss, a decrease in cerebral processing (P300 latency), and tachycardia, although lactate did not increase and DO_{2crit} was not reached.[14–17] These changes were taken as evidence of an O_2 deficit. Although these studies showed that subjective and objective changes did occur, DO_2 remained adequate for cellular metabolism (no lactate shift). Resolution of the cerebral slowing occurred with an increase of inspired O_2 to 100% (which increased dissolved O_2 dramatically but increased total O_2 by only 8%).[1] Tachycardia was relieved equally well by the subject breathing an increased inspired O_2 concentration or by increasing Hgb.[16]

Hgb is, at best, a surrogate for O_2-carrying capacity and is not an estimator for tissue DO_2/utilization or metabolic demand. An underappreciated fact is that decreased circulating Hgb/hematocrit (Hct) does not affect the microcirculation until the Hct reaches a level at which DO_{2crit} occurs. The Hct of the capillaries is relatively fixed at 15% ± 5% (for all mammalian species),[4] but Hct in the microcirculation is highly regulated by capillary guard cells along with fluid

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dynamics.[3,12] Also, O_2 flux in the microcirculation is very complex and is regulated by localized cellular biochemistry (adenosine, adenosine triphosphate, nitric oxide, and O_2 partial pressure). In addition, the functional capillary density (number of capillaries per gram of tissue) can change rapidly depending on tissue O_2 demand and other complex signaling (e.g., nitric oxide and adenosine diphosphate).

Furthermore, O_2 transfer between arterioles, venules, and counter-current vessels is complex. There is a redundant 3D architecture of microcirculation that is different from the overly simplistic Krogh tissue cylinder models.[7] In brief, in response to anemia, the microcirculation cannot increase red cell concentration due to physical fluid dynamic limits known as the Fahraeus-Lindqvist effect.[4] Rather, it increases red cell transit time, rapidly increasing intracellular erythrocyte O_2 extraction ratio, and opening nonflowing capillaries, etc. to increase O_2 in the microcirculation. There is a DO_2 (crit) of 184 mL/M²/min that is reached at 3 to 3.5 g/dL Hgb or 15% Hct (animal data) if preload is maintained and CO is maximized.[4] This actually should be no surprise. Shock occurs at a DO_{2crit} of 15% Hct (in mammals studied to date) if all other physiologic compensatory mechanisms are intact.

In trauma, O_2 debt—calculated as the length of time a patient's DO_2 is less than DO_{2crit} multiplied by the severity of degree below DO_{2crit}—is a predictor of morbidity and mortality.[18–21] O_2 debt must be repaid, and the patient's survival prospects are increased if this happens quickly. The longer it takes to repay O_2 debt, the greater the risk of multisystem organ failure.[18–21]

The 2 case reports in this issue are unique in that the patients' DO_2 closely approached or exceeded DO_{2crit} for a considerable period of time, yet both survived without multisystem organ failure or indolent courses leading to death. Why did they survive? Fortunately, it appears that both teams of physicians understood the importance of maintaining, indeed increasing, circulatory volume.

One of the patients discussed actually had a >50% reduction in O_2 demand,[2] which is fascinating and suggests that there are still many mysteries to unravel to determine the best ways to electively decrease O_2 demand. What cellular signals trigger the patient's body to reduce O_2 demand? Are there ways to induce such a reduction, with either drugs or ischemic preconditioning? Cooling cells by just a few degrees promotes their survival during hypoxia or ischemia, whereas profound hypothermia to a degree approximating that achieved during complex congenital cardiac surgery or drowning in frigid water allows the "pump to be turned off" without causing cellular injury. Cold also increases dissolved O_2. In other words, perhaps we should abandon the concept that a given transfusion trigger (or O_2 demand level) is static and absolute. Although the DO_{2crit} level of 3.5 g/dL (animal data) usually appears to be a threshold of cellular shock, the Hgb level was much lower in both of the cases reported, without apparent organ damage.

Historically, the 3.5 g/dL level is exactly what the transfusion trigger was in the early 1900s.[22,23] Unlike transfusions today, early transfusions used fresh whole blood, with red cells having normal O_2 function, normal cell deformability, and few or no storage lesions.[23] Therefore, these early transfusion of cells were immediately effective.

Currently, treatment of Jehovah's Witness (JW) patients with extremely low levels of Hgb occasionally gives scientists another glimpse into the world of extreme reductions in O_2-carrying capacity. In a recent cohort matched series of JW patients undergoing cardiac surgery, the JW patients had better clinical outcomes at lower (sometimes shockingly low) Hgb levels than those patients treated with normal (transfusion based) cardiac care.[24] There must be ways, yet to be discovered, that cells can signal themselves to down-regulate their O_2 demand in response to anemia.

This brings the question full circle: "Is our understanding and teaching of physiology and clinical medicine (transfusion) and Hgb O_2 content/DO_2 correct?" Dissolved O_2 is what actually keeps us alive, albeit supported by O_2 content of the Hgb. It is dissolved O_2 that must migrate from red cells across the plasma, cell membranes, and cytosol into the mitochondria. That physiology is very complex and occurs without Hgb. The relative contribution of dissolved O_2 becomes even more important in severe anemia, perhaps necessitating the use of 100% inspired or hyperbaric O_2 to maximize dissolved O_2 content. Exactly how O_2 moves in the microcirculation and even through the cell membrane/cytosol is fascinating.

Clearly, we still have a great deal to learn about the limits of human physiology!

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Recovery from Extreme Hemodilution (Hemoglobin Level of 0.6 g/dL) in Cadaveric Liver Transplantation

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Decompensated hepatic failure occurred in a patient with a rare blood type. The patient had extreme hemodilution due to massive bleeding during liver transplantation. A shortage of matched and universal donor blood prompted us to transfuse albumin and fresh frozen plasma for intravascular volume resuscitation. The lowest hemoglobin was 0.6 g/dL, accompanied by ST depression and a serum lactate of 100 mg/dL. The accuracy of the measured value of 0.6 g/dL was confirmed. However, the patient recovered from this critical situation after transfusion, and he was eventually discharged from the hospital without significant sequelae. Maintaining normovolemia, administering pure oxygen, ensuring appropriate anesthetic depth, and maintaining minimal inotropic support were essential for this patient's survival during massive bleeding. (A&A Case Reports. 2015;4:132–6.)

Massive bleeding is a primary cause of intraoperative cardiac arrest. Affected patients often experience poor outcomes, including death.[1] The tolerable limit of anemia, that is, the threshold hemoglobin value below which patients develop ischemic organ dysfunction associated with elevated serum lactate levels, is not known with certainty.

We report the case of a patient with a rare blood type who developed extreme hemodilution during liver transplantation. The lowest measured hemoglobin concentration was 0.6 g/dL, which was associated with an episode of ventricular tachycardia (VT), sustained ST segment depression on the electrocardiogram (ECG), and a precipitous increase in serum lactate level. Despite these serious conditions, the patient recovered and was discharged without significant sequelae.

The patient reviewed the Japanese translation of this manuscript and gave written permission for the authors to publish the report.

CASE DESCRIPTION

A 45-year-old Japanese man was admitted with decompensated hepatic failure resulting from primary biliary cirrhosis. He had previously been diagnosed with hepatocellular carcinoma and had been treated successfully with percutaneous radiofrequency ablation. However, because his state of decompensated hepatic failure had persisted, cadaveric split liver transplantation was indicated. The patient had a history of splenectomy and devascularization of the esophagus (the Hassab procedure). He also had a rare blood type, A-RhD(–), having a prevalence of 0.5% in Japan,[2] and coagulopathy secondary to hepatic dysfunction. He did not have any cardiovascular disease. His height was 173 cm, and his weight was 91 kg.

Blood products (2800 mL of red cell concentrates–leukocytes reduced [RCC-LR], 6000 mL of fresh frozen plasma–leukocytes reduced [FFP-LR], and 250 mL of platelet concentrates) were available. General anesthesia was induced with thiopental and fentanyl. Vecuronium was administered to facilitate tracheal intubation. Mechanical ventilation was established, and general anesthesia was maintained with air, oxygen, sevoflurane, midazolam, and fentanyl. Central venous lines, a large-bore venous sheath, and a pulmonary arterial catheter were inserted. Dopamine and norepinephrine were administered by continuous infusion for inotropic support.

During separation of dense adhesions in the abdominal cavity, bleeding persisted at a rate of approximately 5000 mL/h. Seven hours after the initial incision was made, the patient's hemoglobin concentration was 3.6 g/dL, after preoperatively prepared 2800 mL of RCC-LR blood product had been transfused, as well as large quantities of other blood derivatives, including FFP-LR and 5% albumin. We ordered additional units of A(–) and O(–) RCC-LRs.

Ten minutes after portal reperfusion, a transient ST elevation was noted in the inferior leads. Pure oxygen and nicorandil, a drug with coronary vasodilator properties attributable to nitrate and K^+-ATP channel agonist activities, were started in an effort to improve the coronary oxygen supply. Monomorphic nonsustained VT developed after the first minute of ST segment elevation. The VT and ST segment elevation resolved immediately after lidocaine administration (Fig. 1). Arterial blood gas and laboratory values obtained just after ST segment resolution revealed acidemia (pH 7.157), normokalemia (4.2 mmol/L), a low ionized calcium level (0.64 mmol/L), and anemia (hemoglobin 8.0 g/dL). At that time, we had transfused 5600 mL of A(–) and O(–) RCC-LR in total. Acidemia and hypocalcemia were treated using boluses of sodium bicarbonate and calcium chloride. The next arterial laboratory values, measured 13 minutes after the VT, showed improved pH and ionized calcium, 7.275 and 0.91 mmol/L, respectively.

Because the ST segment elevation and VT had resolved, we proceeded to perform a microscopic hepatic arterial reconstruction to completely restore

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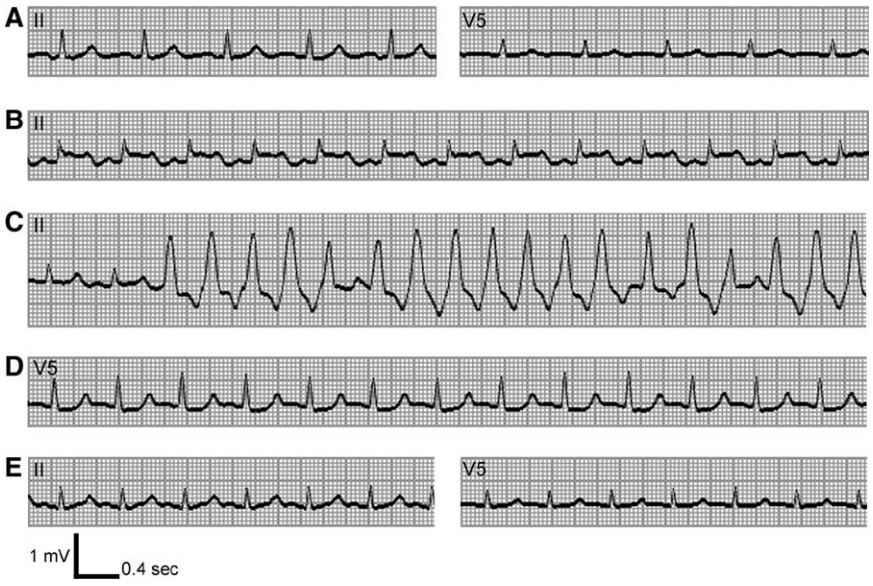

Figure 1. Traces from the monitored electrocardiogram of the patient, a 45-year-old Japanese man. Preincisional trace (A) (leads II and V5) showed sinus rhythm without ST-T change. The ST segment was elevated (B) 2 minutes after the portal reperfusion (lead II) and was followed by nonsustained ventricular tachycardia (C) (lead II). ST segment depression (D) occurred during extreme anemia (hemoglobin 0.6 g/dL) (lead V5). ST segment depression was resolved (E) concomitantly with red cell concentrates transfusion (hemoglobin 5.6 g/dL) (leads II and V5).

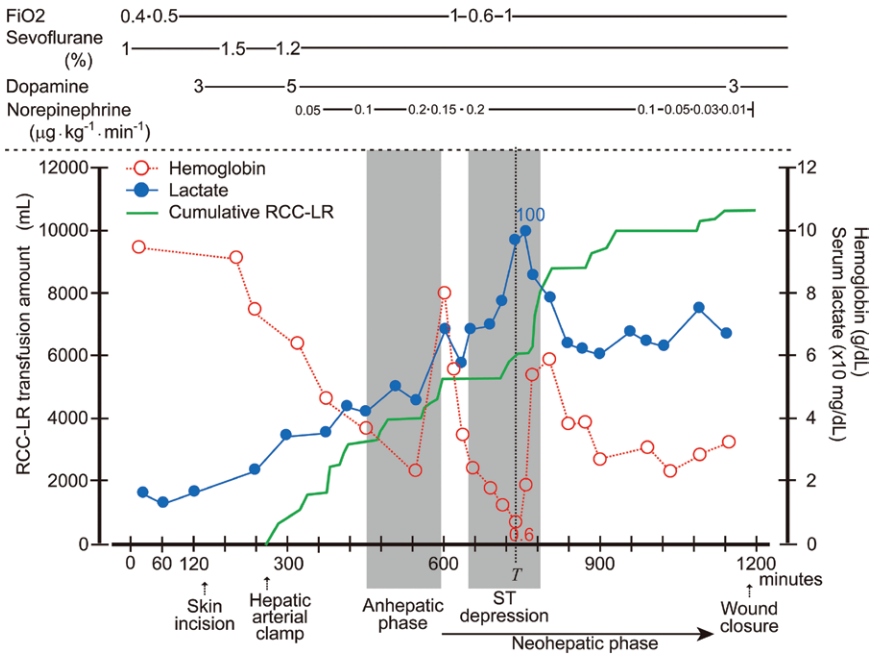

Figure 2. Overview of the patient's anesthetic care. The serial changes in the serum lactate level, hemoglobin concentration, and cumulative amount of transfused red cell concentrates–leukocytes reduced (RCC-LR) are shown, along with the dosages of oxygen, sevoflurane, and inotropic drugs. *T* is the time when the hemoglobin concentration was the lowest. F_{IO_2} = fraction of inspired oxygen.

graft perfusion. After the hepatic arterial reconstruction, because of a shortage of A(−) and O(−) RCC-LRs, the procedure was temporarily interrupted until additional RCC-LRs arrived. During that waiting period, 5% albumin solution was transfused for intravascular volume resuscitation. This resulted in progressive extreme anemia, with a nadir hemoglobin level of 0.6 g/dL (Fig. 2, Table 1). This low hemoglobin level was associated with ST segment depression on the monitored ECG (Fig. 1D) and rapid increase in serum lactate to a maximum level of 100 mg/dL (Fig. 2).

We confirmed that the patient had not previously received A(+) RCC transfusion, and A(+) RCC-LRs were ready to use in the operating room. However, we did not transfuse the A(+) RCC-LRs because the patient's hemodynamics had been maintained, hemostasis had been achieved, and we were aware that additional A (−) and O (−) RCC-LR concentrates would arrive shortly.

The procedure resumed after A(−) and O(−)RCC-LRs arrived and were administered. The patient's extreme anemia, ST depression, and excessive serum lactate concentration improved immediately after transfusion of an additional 2600 mL of RCC-LR (Figs. 1E and 2). The procedure was completed successfully, and the patient was transferred to the intensive care unit with a hemoglobin concentration of 3.1 g/dL, requiring only low-dose dopamine infusion for inotropic support.

Throughout the procedure, noninvasively measured systolic blood pressure was maintained >60 mm Hg, and central venous pressure was maintained at around 10 mm Hg. To protect the liver, we infused 0.01 μg/kg/min of prostaglandin E1 and 1 μg/kg/min of gabexate mesilate. Arterial

Table 1. Blood Count, Arterial Blood Gas, Electrolyte, and Metabolite Data Obtained During Nadir Hemoglobin Concentration (0.6 g/dL)

Item	Value
Blood count	
White blood cells	3300/μL
Red blood cells	19,000/μL
Hemoglobin	0.6 g/dL
Hematocrit	1.8%
Platelets	61,000/μL
Blood gases, electrolytes, and metabolites	
pH	7.286
Pco_2	39.7 mm Hg
Po_2	535 mm Hg
Na^+	144 mmol/L
K^+	3.8 mmol/L
Cl^-	99 mmol/L
Ca^{2+}	0.53 mmol/L
Bicarbonate	18.3 mmol/L
Glucose	110 mg/dL
Lactate	97 mg/dL
Base excess	−7.0 mmol/L

Results were obtained at time *T* in Figure 2. The blood count was measured with an MEK-6318 Celltac α (Nihon Kohden, Tokyo, Japan). Blood gases, electrolytes, and metabolites were analyzed with an ABL 800 FLEX (Radiometer, Copenhagen, Denmark). Ten minutes after *T*, the serum lactate concentration reached 100 mg/dL.

Table 2. Intraoperative Fluid Balance

	Content	Amount (mL)
In	Crystalloid	4910
	Colloid (5% albumin)	28,000
	Blood transfusion	
	A(−) RCC-LR	8260
	O(−) RCC-LR	2240
	FFP-LR	20,400
	PC	1900
	Subtotal	65,710
Out	Estimated blood loss[a]	61,600
	Urine output	570
	Subtotal	62,170
Net		+3540

FFP-LR = fresh frozen plasma–leukocytes reduced; PC = platelet concentrates; RCC-LR = red cell concentrates–leukocytes reduced.
[a]The estimated blood loss included 5000 mL of peritoneal and pleural fluids.

pH was maintained between 7.2 and 7.5, except during the episode of VT, with administration of periodic boluses of sodium bicarbonate. Calcium chloride was administered to maintain the plasma ionized calcium level at normal values. Bladder temperature was maintained between 36°C and 38°C. Sevoflurane was administered at an end-tidal concentration of 1.2%, along with periodic boluses of midazolam and fentanyl for the maintenance of general anesthesia, up to 13 mg and 1.2 mg, respectively. Bispectral Index (Aspect Medical Systems, Norwood, MA) values were maintained in the 40s to 60s. The pulmonary arterial (mixed venous) oxyhemoglobin saturation was continuously monitored but not recorded.

The total duration of general anesthesia was 20 hours and 18 minutes. The fluid balance of the case is summarized in Table 2. On postoperative day 7, the patient's trachea was extubated uneventfully. He was discharged on postoperative day 57 without significant sequelae.

DISCUSSION

To the best of our knowledge, 0.6 g/dL is the lowest hemoglobin value ever observed in an anesthetized patient who survived. This extreme result led us to question the accuracy of the blood-counting instrument we used: a Celltac α Hematology Analyzer (MEK-6318; Nihon Kohden Corporation, Tokyo, Japan). For hemoglobin, this instrument has a measuring range of 0 to 29.9 g/dL and a reproducibility within 1.5% of the coefficient of variation.[3] We tested the accuracy of the MEK-6318's hemoglobin measurements at low concentrations using diluted whole blood with a hemoglobin concentration set to 0.64 g/dL. All 10 measurements produced the same result, 0.5 g/dL, confirming that the MEK-6318 is accurate to within 0.15 g/dL in measuring extremely low hemoglobin concentrations (approximately 0.6 g/dL). Therefore, we believe that the hemoglobin values obtained in the present case were accurate.

The patient's extreme anemia is attributable to preoperative hepatic dysfunction, the large area of visceral adhesion to be separated, a long and highly invasive operation, and the scarcity of the RhD(−) phenotype in Asian countries. Because the prevalence of this phenotype is low in Japan (approximately 0.5%[2] vs 15%[4] in Western countries), blood products are not always readily available for RhD(−) patients with massive bleeding. We used 8260 mL A(−) and 2240 mL O(−) RCC-LRs and used up all the matched and universal donor RCC-LRs readily available in Japan at that time.

Because the patient's hemodynamics were stable and hemostasis was nearly achieved, we did not transfuse A(+) RCC-LRs. In retrospect, we believe that we could have transfused A(+) RCC-LRs without much hesitancy because the patient had not undergone an A(+) RCC transfusion. From an ethical standpoint, if a patient has compromised hemodynamics due to anemia, ABO-incompatible RCCs should be considered as a lifesaving measure.

The physiological limit of dilutional anemia in clinical settings has been implied in many case reports. Dai et al.[5] reported a nadir hemoglobin level of 0.7 g/dL without signs of hypoperfusion during surgery for axillary artery trauma in a 53-year-old man. Zollinger et al.[6] reported a 1.1 g/dL hemoglobin level accompanied by ST depression during a spine operation in a patient with lumbar metastasis of renal cell carcinoma. In those cases, serum lactate levels were not measured.

We were able to record serum lactate levels, which increased more rapidly during profound anemia (hemoglobin <2 g/dL) in the neohepatic phase than before portal reperfusion. It has been reported that serum lactate levels normally decrease in the neohepatic phase of liver transplantation because the lactate clearance of the liver increases.[7] Findings from animal studies suggest 2 major causes of hyperlactatemia in hemorrhagic shock: anaerobic glycolysis due to tissue hypoxia, and endogenous or exogenous catecholamine stimulation of β2 adrenoceptors with subsequent Na^+, K^+-ATPase activation, facilitating aerobic glycolysis in skeletal muscle.[8–10] In the present case, we assume that facilitated anaerobic glucose metabolism contributed, at least in part, to the markedly elevated serum lactate levels. After RCC-LR transfusion, the serum lactate level decreased (Fig. 2).

The critical hemoglobin concentration (Hb_{crit}) is typically defined as the hemoglobin concentration at which the oxygen consumption of vital organs starts to decline, depending on the oxygen delivery during isovolemic hemodilution.[11–16] Further hemodilution beyond Hb_{crit} results in tissue hypoxia; ST segment depression develops, and the serum lactate concentration increases.[6,17,18]

In humans, previous reports have emphasized the importance of maintaining normovolemia during extreme hemodilution for hemodynamic stabilization.[5,6] During normovolemic hemodilution, hyperoxic ventilation with a fraction of inspired oxygen (F_{IO_2}) of 1.0 increases the amount of dissolved oxygen in the plasma, improving oxygen availability in the microcirculation.[17] In pigs, rescue hyperoxic ventilation compared with room air ventilation during a period of Hb_{crit} resulted in maintenance of tissue oxygenation and reduced mortality.[14,17] Also, prophylactic hyperoxic ventilation reduced the Hb_{crit} level in pigs.[15] In dogs, increased anesthetic depth led to decreased tolerance to acute isovolemic anemia,[19] suggesting that appropriate anesthetic depth should also be considered in normovolemic hemodilution.

In our patient, ST segment depression was seen for 80 minutes, while the patient's hemoglobin was <2 g/dL (Fig. 1). The increasing serum lactate levels, as well as ST depression during this period, suggested that the patient's Hb_{crit} with the new liver graft was approximately 2 g/dL. We estimated the patient's oxygen supply and demand from the values in Table 1. The calculated arterial blood oxygen content (CaO_2) was 2.41 mL per 100 mL of blood ($1.34 \times 0.6 \times 1.0 + 535 \times 0.003$). Setting the hemoglobin concentration to 1.0 and 2.0 g/dL results in CaO_2 values of 2.95 and 4.29 mL/dL, respectively. Given the increase in the patient's cardiac output from 5 to 8 L/min due to the increase in the heart rate (from 70 to 110 bpm), systemic oxygen deliveries ($\dot{D}O_2$) are 192.72 (hemoglobin 0.6 g/dL), 235.60 (hemoglobin 1.0 g/dL), and 342.80 (hemoglobin 2.0 g/dL) mL/min.

Reportedly, systemic oxygen consumption ($\dot{V}O_2$) values during liver transplantation for a single patient with cirrhosis are 1.18 (preincisional), 0.62 (anhepatic phase), 3.49 (30 minutes after portal reperfusion), and 2.79 (60 minutes after portal reperfusion) mL/kg/min.[20] The $\dot{V}O_2$ declines by 45% in the anhepatic phase and increases by 130% in the neohepatic phase compared with the preincisional value. In our patient, the increase of $\dot{V}O_2$ in the neohepatic phase partly explains why ST depression and precipitous lactate increase were seen only in the neohepatic phase. If the abovementioned values were simply applied to the present case, the $\dot{V}O_2$ would be 56.42 (anhepatic phase), 317.59 (30 minutes after portal reperfusion), and 253.89 (60 minutes after portal reperfusion) mL/min. It is likely that the $\dot{D}O_2$ decreased below the $\dot{V}O_2$ during the patient's ST depression. The increased heart rate and cardiac output probably largely compensated for the decreased CaO_2, thereby facilitating survival.

We maintained normovolemia by infusing 5% albumin solution and FFP-LR (because of the shortage of matched and universal donor RCC-LRs). Also, we maintained the F_{IO_2} >0.5 and at 1.0 during the latter half of the period of anesthetic care. Furthermore, we monitored the anesthetic depth with a Bispectral Index system and avoided inappropriate fluctuations in anesthetic depth. Finally, minimal amounts of inotropes were administered to maintain perfusion pressure. We did not attempt to induce mild hypothermia due to concerns regarding causing platelet dysfunction, although its effectiveness in preventing the adverse effects of severe hemodilution has been discussed.[21,22]

In severe dilutional anemia, if matched and universal donor RCCs are unavailable, and the patient experiences hemodynamic collapse or has an uncontrollable lactate increase related to low oxygen supply, ABO-incompatible RCC transfusion should be considered. In massive bleeding with severe hemodilution, transfusing any available, even uncrossmatched, RCCs should always be considered to avoid patient death due to lack of red cells. An increase in serum lactate may be an indication for additional RCC transfusion or conversion to an abbreviated surgical procedure with plans for future definitive repair.

However, in our patient, despite extreme intraoperative hemodilution due to massive bleeding, administering 100% oxygen, maintaining normovolemia, ensuring an appropriate anesthetic depth, and minimizing inotropic support resulted in a good clinical outcome. These actions should be considered for other patients with massive bleeding if sufficient matched and universal donor RCCs are not available. Trends in serum lactate levels, as well as abnormal ECG findings, can serve as warnings of tissue hypoperfusion due to Hb_{crit}. Monitoring the mixed or central venous oxyhemoglobin saturation may also be helpful.

Previously, the lowest reported intraoperative hemoglobin level was 0.7 g/dL.[5] In that trauma case, the patient had been previously healthy. In contrast, our patient had several preoperative comorbidities. The fact that our patient tolerated severe anemia supports the effectiveness of the strategies we used. Refining the best strategies for treating massive bleeding will require additional reports of similar cases with detailed monitoring and records.

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Management of a Jehovah's Witness Patient with Sepsis and Profuse Bleeding After Emergency Coronary Artery Bypass Graft Surgery: Rethinking the Critical Threshold of Oxygen Delivery

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The duration and extent of acute hemodilution that the human body can withstand remains unclear. Many consider 184 mL/m^2/min to be the oxygen delivery (Do_2) threshold below which oxygen consumption (Vo_2) begins to decrease. We describe a critically ill Jehovah's Witness patient who tolerated a much lower level of Do_2, coupled with severe acute anemia that persisted for >10 days without any sequelae. This case challenges the currently accepted critical Do_2 threshold and highlights the need for a comprehensive approach to increase Do_2 and decrease Vo_2 for best patient outcomes. Minimizing Vo_2, which is usually underemphasized in current clinical practice, probably played an important role in the survival of this patient. (A&A Case Reports. 2015;4:127–31.)

The degree to which the human body can tolerate extreme levels of acute hemodilution without organ dysfunction remains undefined.[1] Oxygen delivery (Do_2) to the organs is dependent on cardiac output and the arterial oxygen content, so progressive hemodilution causes reduction in Do_2. However, oxygen consumption (Vo_2), which is dependent on the metabolic rate, remains constant until the Do_2 reaches a critical threshold (Do_{2crit}), after which further reductions in Do_2 cause the Vo_2 to become supply dependent, and tissue hypoxia ensues. On the basis of a report of a Jehovah's Witness patient who died after massive bleeding, this threshold has been reported to be 184 mL/m^2/min (4.9 mL/kg/min) for a Vo_2 of approximately 2.4 mL/kg/min at a hemoglobin (Hgb) level of 3.9 g/dL.[2] We describe the case of a critically ill cardiac surgical patient with sepsis who tolerated much lower Do_2 levels for 72 hours without noticeable residual end-organ injury.

Written informed consent was obtained from the patient to publish this case report.

CASE DESCRIPTION

A 59-year-old, 68-kg male patient of the Jehovah's Witness faith, with diabetes mellitus, chronic obstructive pulmonary disease, gout, and deep vein thrombosis was admitted to another institution for necrotizing fasciitis of the left upper extremity. His treatment there included surgical debridement, a cadaver skin graft, and aggressive IV antibiotics. His hospital course was complicated by a non–ST-segment elevation myocardial infarction. Cardiac catheterization revealed severe multivessel coronary artery disease involving the ostial left main, left anterior descending, left circumflex, obtuse marginal, and right coronary arteries, and a left ventricular ejection fraction of 40%. He was transferred to our institution for further care. Shortly thereafter, he developed sepsis, respiratory failure (which necessitated tracheal intubation), and hemodynamic instability.

On admission to our institution, the Hgb level of the patient was 9 g/dL. He underwent emergent coronary artery bypass grafting (CABG) surgery and drainage of pleural effusions. During the pre–cardiopulmonary bypass (CPB) phase, 400 mL of autologous blood was obtained while a continuous circuit was maintained, as requested by the patient. To avoid unnecessary hemodilution, crystalloid infusion was restricted, and the total volume was retrospectively calculated to be approximately 800 mL in the pre-CPB period. Replacement of the drained autologous blood with 250 mL of 5% albumin was guided by the mixed venous oxygen saturation and continuous cardiac output measurements, which remained >75% and 5.89 L/min, respectively, during the entire pre-CPB period. Immediately after autologous blood collection, aminocaproic acid was infused at 5 g/h for 1 hour and then at 1 g/h until the case was completed.[3] The same dose was continued in the intensive care unit (ICU) and throughout the re-exploration period until hemostasis was achieved. Total CPB time was 60 minutes, and aortic cross-clamp time was 30 minutes. Approximately 300 mL of cell saver blood was processed and reinfused into the patient. After CPB, there was mild respiratory acidosis, which was deliberately not corrected to facilitate a rightward shift of the Hgb dissociation curve.

While his trachea was still intubated, the patient was transported to the ICU while receiving epinephrine, nitroglycerin, amiodarone, and aminocaproic acid infusions. His Hgb level was 6.8 g/dL on arrival. His immediate postoperative course was complicated by bleeding that was temporized by the administration of 3 mg factor VIIa, 70 mL cryoprecipitate, and 20 μg (0.3 μg/kg) desmopressin,

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Table 1. Systemic Hemodynamic and Oxygenation Measurements

	HR (beats/min)	MAP (mm Hg)	PAD (mm Hg)	CO/CI (L/min/m²)	CVP (mm Hg)	SVR (dyne/m⁵)	Hgb (g/dL)	Sao_2/Po_2 (%/mm Hg)	Svo_2 (%)	Bicarbonate/BE (mEq/L)	Do_2 (mL/m²/min)	Vo_2 (mL/m²/min)	ER (%)
Before CABG	85	66	23	6.12/3.43	10	731	8.2	92/64.8	71	27.4/−1.6	357	81	22
After CABG	80	58	20	5.84/3.28	10	659	6.8	100/249	75	27.0/−1.3	548	137	25
Re-exploration	72	59	33	3.10/1.74	31	722	3.3	100/318	52	25.8/−0.9	79	38	48
POD 1	80	68	25	4.50/2.53	15	942	4.5	97.8/197	45	28.4/4.2	152	81	53
POD 2	94	70	22	6.60/3.71	9	739	4.4	94.9/89	50	28.2/4.3	213	98	46

BE = base excess; CABG = coronary artery bypass grafting; CO/CI = cardiac output/cardiac index; CVP = central venous pressure; Do_2 = oxygen delivery; ER = oxygen extraction ratio; Hgb = hemoglobin; HR = heart rate; MAP = mean arterial blood pressure; PAD = pulmonary artery pressure; POD = postoperative day; Sao_2/Po_2 = arterial oxygen saturation/oxygen partial pressure; Svo_2 = mixed venous oxygen concentration; SVR = systemic vascular resistance; Vo_2 = oxygen consumption.

while arrangements were made for surgical re-exploration. Closed-circuit, autologous transfusion of shed mediastinal blood was accomplished with an Atrium Oasis 3650 ATS blood-recovery system and an Atrium 2450 Self-filling ATS blood bag (Atrium Medical Corporation, Hudson, NH). No specific bleeders could be identified during the re-exploration.

At the start of re-exploration, the Hgb level of the patient had decreased to 3.3 g/dL. Hemodynamic and oxygenation measurements (Table 1) revealed that his Do_2 was 79 mL/m²/min for 24 hours and then 152 mL/m²/min for >48 hours. He also had transient right ventricular (RV) dilatation and RV hypokinesis, which responded to a 2 mg bolus of milrinone. We combined appropriate intravascular volume resuscitation with titration of epinephrine and milrinone infusions in an effort to optimize the patient's hemodynamics. In the ICU, we allowed his body temperature to drift down to 35.5°C while providing high concentrations of inspired oxygen, and we maintained adequate sedation and muscle paralysis to reduce brain and muscle Vo_2. The patient remained hemodynamically stable during the next 12 hours while receiving 0.2 µg/kg/min milrinone, 0.05 µg/kg/min epinephrine, 2 units/h vasopressin, 1 mg/min amiodarone, and insulin infusions. During the subsequent 24 hours, inotrope administration was gradually discontinued. His Hgb level remained at 4.5 g/dL, but his calculated oxygen extraction ratio increased from 0.48% to 0.53% (Fig. 1). Although his trachea was still intubated, he was awake and responsive to verbal commands.

On postoperative day (POD) 2, the chest tubes and pulmonary artery catheter were removed, and a feeding tube and peripherally inserted central catheter line were placed. On POD 3, the patient was transferred back to the outside hospital for further management of the necrotizing fasciitis. His discharge medications included broad-spectrum antibiotics and 20,000 units erythropoietin subcutaneous injection daily, which had been started preoperatively at the outside hospital; IV infusions of 2 units/h vasopressin; and 0.5 mg/h amiodarone. His trachea was extubated on POD 15. His Hgb level increased to 6.7 g/dL on POD 10 and to 10.6 g/dL on POD 35 when he was discharged. No neurological deficits or any other permanent end-organ injuries were observed during the 18-month follow-up.

DISCUSSION

Although the critical Hgb value below which organ dysfunction occurs has not been clearly defined,[4] the consensus is that transfusion is almost always indicated when the Hgb level is <6 g/dL because this is when neurocognitive function degrades in healthy humans.[5] An Hgb level <4 g/dL is associated with abnormal regional myocardial blood flow distribution in animals with normal coronary anatomy.[6] However, there are only a few reports with systemic hemodynamic and oxygenation data in humans experiencing extreme acute anemia.[7] Important questions, such as the degree and duration of profound hemodilution that can be tolerated by a critically ill patient without detectable organ injury, the effect of comorbidities, and the susceptibility and compensatory responses of different types of patients, have remained unanswered so far in the literature.

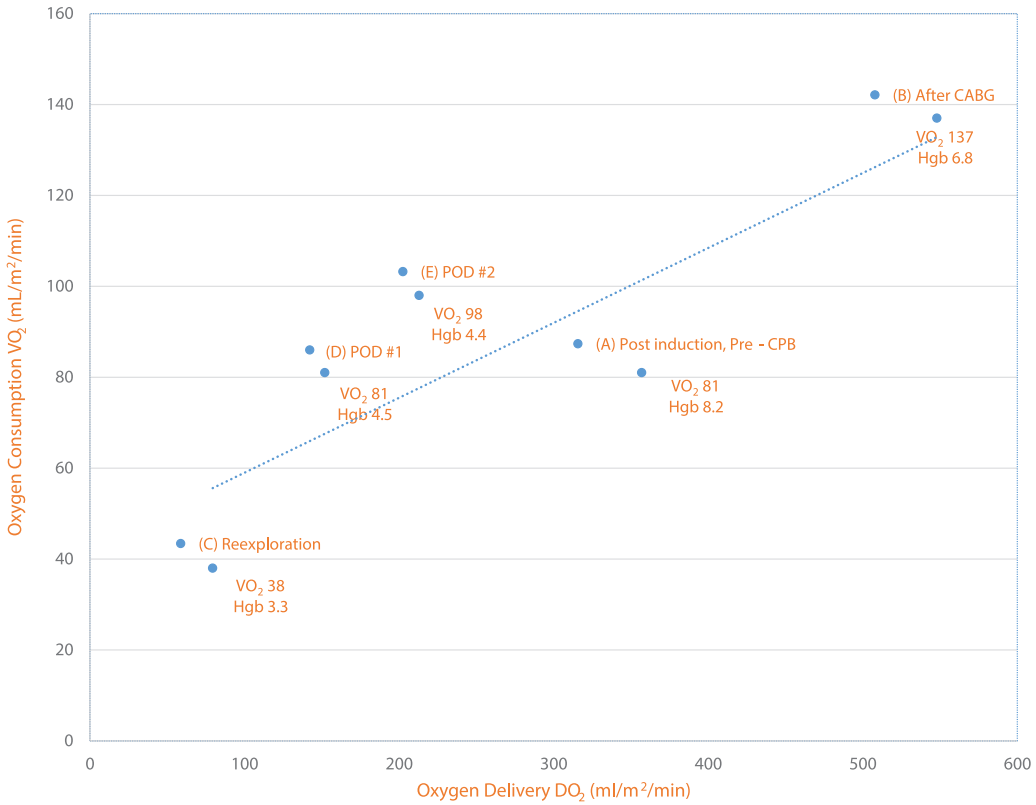

Figure 1. Relationship between oxygen delivery (Do_2) and oxygen consumption (Vo_2). CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; Hgb = hemoglobin; POD = postoperative day.

Optimizing Do_2/Vo_2 Balance

Preventing permanent tissue injury because of profound reductions in Do_2 caused by acute hemorrhage can be challenging in Jehovah's Witnesses and requires attempts to maximize the patient's Do_2 while simultaneously minimizing Vo_2. Because Hgb concentration is an important determinant of Do_2, aggressive blood conservation strategies acceptable to Jehovah's Witness patients should be maximized.[8]

Increasing the fraction of inhaled oxygen to 100% can significantly improve the Do_2 by increasing the arterial oxygen content. The physically dissolved oxygen may be particularly important for cellular metabolism in severe coronary artery stenosis because its availability is independent of Hgb dissociation characteristics, which may be deranged due to other factors, such as hypothermia and alkalosis, or favored by mild acidosis. Maintaining normovolemia by intravascular volume replacement after autologous blood harvesting is of paramount importance because it helps maintain cardiac output, which is yet another factor in the Do_2 equation.[9] In fact, hemodilution may be of benefit in many disease states by improving the rheological properties of blood.[2] Reinfusing autologous blood after CPB improves not only coagulation status but also Do_2,[10] which could be another reason for the significant increase in our patient's Do_2 immediately after CABG (Table 1).

Simultaneous with efforts to preserve Do_2, Vo_2 reductions can be achieved through the appropriate use of sedation and paralysis in combination with mild hypothermia[11] although moderate and, to a lesser degree, mild hypothermia may incite or worsen coagulopathy in the immediate postoperative period. Hypothermia should be induced only after antishivering drugs and/or muscle relaxants are administered because it may paradoxically increase Vo_2 by causing shivering. Also, the beneficial effects of hypothermia may be slightly offset by the shift of the oxyhemoglobin dissociation curve to the left, with a resultant decrease in Do_2.

Do_{2crit}

The oxygen transport system normally operates to maintain Vo_2 despite wide variations in Do_2. However, as Do_2 continues to decrease, a point of maximal oxygen extraction, called the Do_{2crit}, is reached. Any further reduction in Do_2 will result in tissue hypoxia, conversion to anaerobic metabolism, and production of lactic acid, leading to metabolic acidosis.[12] In a prospective study of resting, healthy, conscious humans, a decrease in Do_2 to 7.3±1.4 mL/kg/min (274 mL/m²/min) by acute hemodilution did not produce evidence of inadequate systemic oxygenation, suggesting that the critical Do_2 may be less than this value.[13] Furthermore, on the basis of a case report of an otherwise healthy Jehovah's Witness patient who died of massive surgical bleeding, it has been suggested that the Vo_2 starts to decline at a Do_2 of 4.9 mL/kg/min (184 mL/m²/min).[2] Our patient, however, tolerated a much lower Do_2 of 2.1 mL/kg/min (79 mL/m²/min) and an Hgb level of 3.3 g/dL for 24 hours, followed by an Hgb level of 4.5 g/dL for 72 more hours without any apparent neurological dysfunction, challenging the notion that neurologic injury is inevitable when O_2 delivery decreases below the critical threshold of 184 mL/m²/min.

Oxygen Debt

When Do_2 decreases below Do_{2crit} because of either anemia (anemic hypoxia) or shock (stagnant hypoxia), an O_2 deficit arises, which is the difference between the Vo_2 of the tissues under normal conditions and the reduced Vo_2 at the time of crisis. This deficit, when accrued over time, is called oxygen debt, and its severity can be assessed by the degree of base deficit and lactic acid production. On restoration of Do_2, the body goes through a phase of "debt repayment," when the Vo_2 may be transiently higher than the Vo_2 before the oxygen debt occurred.[14]

To better understand and illustrate the coupling relationship between Do_2 and Vo_2 in our patient and to compare our data with those of other researchers, we rearranged the data incrementally instead of chronologically (Fig. 1). On cursory examination, it appears that Do_2 and Vo_2 have a linear relationship, with both increasing after the surgery,[15] decreasing during re-exploration, and finally, increasing progressively on PODs 1 and 2. Our patient had sepsis, and a derangement in the oxygen extraction ability of the tissues could have been to some degree protective[16]; however, other factors responsible for these changes need to be considered.

Low Do_2 before CPB (Fig. 1, point A) despite adequate Hgb could reflect a combined effect of a large pleural effusion (which probably caused a decrease in arterial oxygenation) and the low cardiac output state; the low Vo_2 could be explained by the reduction in the metabolic rate due to the effect of anesthesia. After the CABG and drainage of pleural effusion (Fig. 1, point B), a higher Do_2 was recorded despite lower Hgb, probably because of improved cardiac function and improved pulmonary oxygenation. Also, Vo_2 was found to be higher at 137 mL/m^2/min, probably because the patient had started recovering from anesthesia and his core temperature was 37.2°C, similar to baseline values of 110 to 150 mL/min/m^2 reported in a healthy awake subject.[17] Both the Do_2 and the Vo_2 nadir were seen during re-exploration (Fig. 1, point C); however, surprisingly, neither significant metabolic acidosis nor base deficits were detected by arterial blood gas analysis. It appears that a clinically significant oxygen debt did not occur in this patient even though Do_2 decreased to as low as 79 mL/min/m^2, suggesting that sedation, paralysis, hypothermia, and maybe sepsis may beneficially reduce Vo_2. To conserve blood, we did not measure blood lactate levels; rather, we used pH, bicarbonate levels, and base deficits as surrogate markers of organ perfusion. Because these values remained stable throughout, we believe that cellular metabolism was not significantly deranged during this period. Some researchers have even suggested that blood lactate levels may not be reliable indicators of tissue hypoxia. Depending on which metabolic pathway is affected, lactate levels may be normal or elevated during tissue hypoxia or may be elevated without any tissue hypoxia.[17]

On POD 1 (Fig. 1, point D) and POD 2 (Fig. 1, point E), with the recovery of Do_2, the Vo_2 appears to be higher than expected although we continued to keep the patient sedated, paralyzed, and hypothermic. It is possible that during the recovery phase, to "repay" the oxygen debt, the extraction ratio was higher than expected. This putative mechanism would restore tissue metabolism, which had been deranged as a result of hypoxia (the so-called, "hysteresis of the anemia recovery curve").[18] This may also partly reflect a metabolic cellular adaptive response resembling hibernation that may protect the cells during periods of diminished Vo_2.[19]

Although our patient did not have any neurological dysfunction during his hospital stay, the transient RV dysfunction observed during re-exploration could have been due to the much higher oxygen extraction ratio of myocardium compared with other tissues, making myocardium particularly susceptible to cellular injury during the periods of low Do_2. Although compensatory tachycardia helps augment Do_2 in peripheral tissue, it also increases myocardial Vo_2 and, therefore, the risk of ischemic injury to the myocardium. Therefore, to prevent tachycardia, we used a relatively deep level of anesthesia, and we administered occasional boluses of esmolol. Of note, our patient continued to have low systemic vascular resistance throughout the operation and in the immediate postoperative period (Table 1), probably because of a combination of hemodilution and ongoing sepsis.

Many other mechanisms may have contributed to our patient's favorable outcome, including ischemic preconditioning of the vital organs due to preoperative anemia, sepsis, and myocardial infarction; "hibernation" strategies that reduce Vo_2 and increase oxygen extraction from surrounding tissues[17]; enzyme adaptations that allow continuing metabolism at low Do_2; and genetic polymorphisms related to susceptibility and compensatory responses to hemodilution. These possibilities warrant further studies.

To our knowledge, this is the first reported case of a critically ill Jehovah's Witness patient surviving such low Do_2 levels for >72 hours and tolerating an Hgb level of <6 g/dL for >10 days without any permanent neurologic or end-organ injury. Our case calls into question the current definition of the critical threshold of Do_2 and, at the same time, highlights the need for a multimodal approach to improving the Do_2/Vo_2 balance.

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