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 $20\,\mu g$ ($0.3\,\mu g/kg$) desmopressin,

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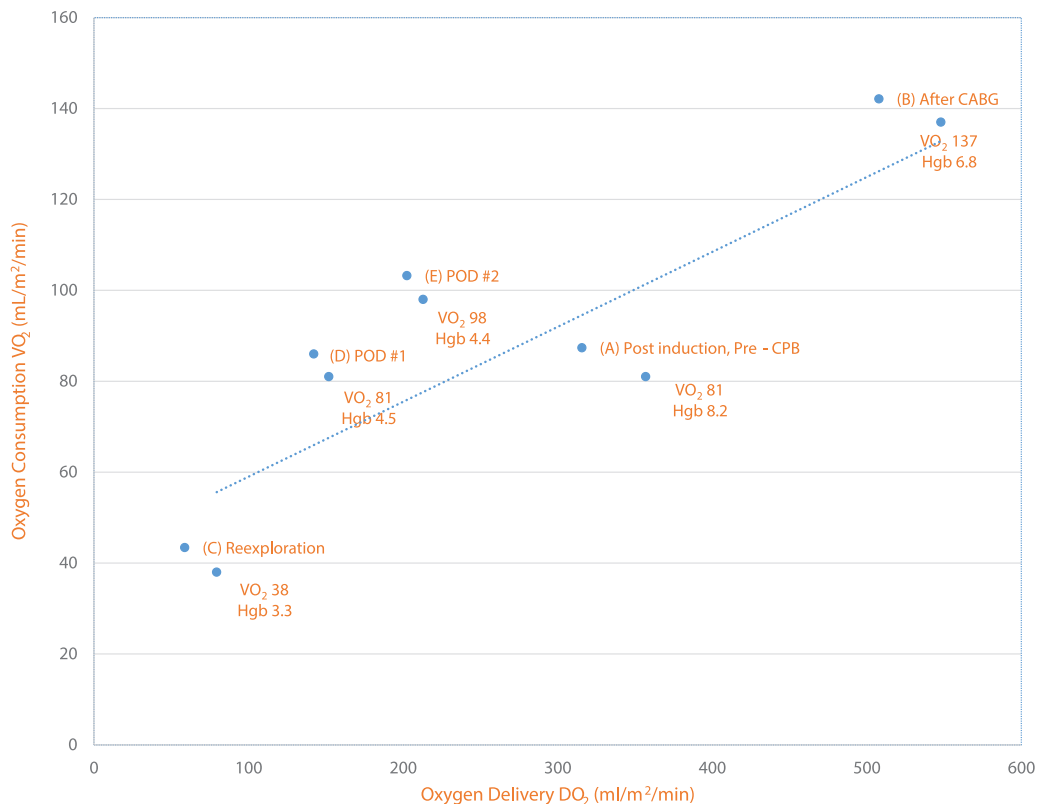
Figure 1. Relationship between oxygen delivery (Do_2) and oxygen consumption (Vo_2). CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; Hgb = hemoglobin; POD = postoperative day.

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/m^2/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/m^2/min).[2] Our patient, however, tolerated a much lower Do_2 of 2.1 mL/kg/min (79 mL/m^2/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/m^2/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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