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Hyperbaric Oxygen Reverses Organ Dysfunction in Severe Anemia

*J. Eric Greensmith, M.D., Ph.D.**

HIGH oxygen content within the plasma that can supplement, or even supplant, the hemoglobin-bound oxygen can be achieved by use of hyperbaric oxygen administration. In 1960, Boerema *et al.*[1] exsanguinated pigs and then "reanimated" them by treatment in a hyperbaric chamber. Forty years later, hyperbaric therapy can be life saving when used as temporizing or definitive therapy in cases of severe anemia when transfusion is difficult to achieve or refused.

Case Reports

Case 1

A 20-yr-old woman with a history of dysfunctional uterine bleeding underwent control of erratic and heavy menstrual bleeding *via* synthetic estrogen–progesterone hormonal therapy. The patient discontinued taking the medication and subsequently experienced 7 days of severe dysfunctional uterine bleeding.

At admission to another hospital, while in the supine position, the patient had a heart rate of 88 beats/min and a blood pressure of 125/81 mmHg. While in an upright position, she reported "dizziness and a pounding head," with a heart rate of 120 beats/min and a blood pressure of 145/78 mmHg. Hemoglobin and hematocrit concentrations were 5.3 g/dl and 15%, respectively. Because of the patient's religious prohibition against transfusion, therapy was limited to 25 mg conjugated estrogens and volume resuscitation with 2 l normal saline solution and 500 ml hetastarch. There was no record of oxygen administration. She was transferred to our institution, and her hemoglobin and hematocrit concentrations were 3.5 g/dl and 10%, respectively. She was administered a second dose of intravenous estrogens. A Foley catheter was inserted through the cervical os into the uterine cavity and inflated to tamponade uterine bleeding. At arrival to the surgical intensive care unit, she was pale and asthenic, without pain or discomfort. She was administered humidified oxygen *via* face mask. Over the next 2 h at rest, her heart rate was 120–134 beats/min, and her blood pressure was 110–141/47–62 mmHg, but she reported retrosternal chest pressure that was not radiating (fig. 1A). Twelve-lead electrocardiography (ECG) showed ST-segment changes in V1–V3 that were consistent with myocardial ischemia.

Because of her refusal to be administered blood or blood components, the patient underwent hyperbaric therapy at 2.4 absolute pressure in atmospheres (ATA) with an inspiratory oxygen fraction (F_{IO_2}) of 1.0. After 3 min at 2.4 ATA, the patient's chest pressure and ECG changes resolved (fig. 1B). The patient continued to be pain free for 127 min at 2.4 ATA and during the 5 min of an "air break" when F_{IO_2} was 0.21 at 2.4 ATA (this is a standard practice to minimize the chance of oxygen toxicity seizures). After completion of a 120-min period of pressurization, supplemental oxygen was removed, and the chamber returned to 1 ATA over 7 min, with the patient's F_{IO_2} at 0.21. At 1.5 ATA, the patient reported severe substernal chest pressure with recurrence of the ECG ST-segment depression in lead II (fig. 1C). The chamber underwent repressurization to 2.4 ATA with an F_{IO_2} of 1.0. Within 3 min, the chest pressure and ECG abnormality resolved.

Five milligrams of morphine was titrated intravenously. The patient remained alert and cooperative. The second return to 1 ATA was slowed to 0.03 ATA/min. Depressurization was accomplished with an F_{IO_2} of 1.0. Angina or ECG changes did not recur (fig. 1D). The patient was returned to the intensive care unit.

The patient was treated using hyperbaric therapy eight more times, initially twice a day, and later once a day. She continued to receive oxygen *via* a high-flow face mask when she was at 1 ATA with an F_{IO_2} of 1.0 administered *via* hood in the hyperbaric chamber with appropriate air breaks. During the third hyperbaric treatment, the patient reported a new type of chest discomfort: a burning sensation that was made worse during administration of hyperbaric therapy. She also experienced a sharp burning sensation during breathing, and a dry nonproductive cough developed. The patient had a high F_{IO_2} for more than 72 h, ranging from an F_{IO_2} of 1.0 at 2.4 ATA in the hyperbaric chamber to an F_{IO_2} of 0.7 during use of the face mask at 1 ATA in the intensive care unit. A clinical diagnosis of oxygen-associated pulmonary toxicity was determined. The patient was administered 800 mg vitamin E by mouth twice daily, and all symptoms resolved during the ensuing 24 h, despite continued exposure to high concentrations of oxygen.

Each day after presentation, the patient appeared to be more animated. The patient was allowed to stand and perform simple exercises in the hyperbaric chamber while at 2.4 ATA with an F_{IO_2} of 1.0. She had no further angina and ECG was normal. No effort was made to have her exercise at 1 ATA. The patient was administered 300 units/kg erythropoietin daily, folate, cyanocobalamin, and oral iron. A hematocrit concentration evaluated on hospital day 5 was 16%. Her reticulocyte count was 274.2 thousand/mm^3 (normal, 16–100). The patient continued to improve, with no further angina pectoris; she was transferred from the intensive care unit on hospital day 6 and discharged from the hospital on day 8. Eighteen days after admission, hemoglobin

* Assistant Professor.

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Address reprint requests to Dr. Greensmith: Department of Anesthesia, The University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, Iowa 52242–1009. Address electronic mail to: je-greensmith@uiowa.edu.

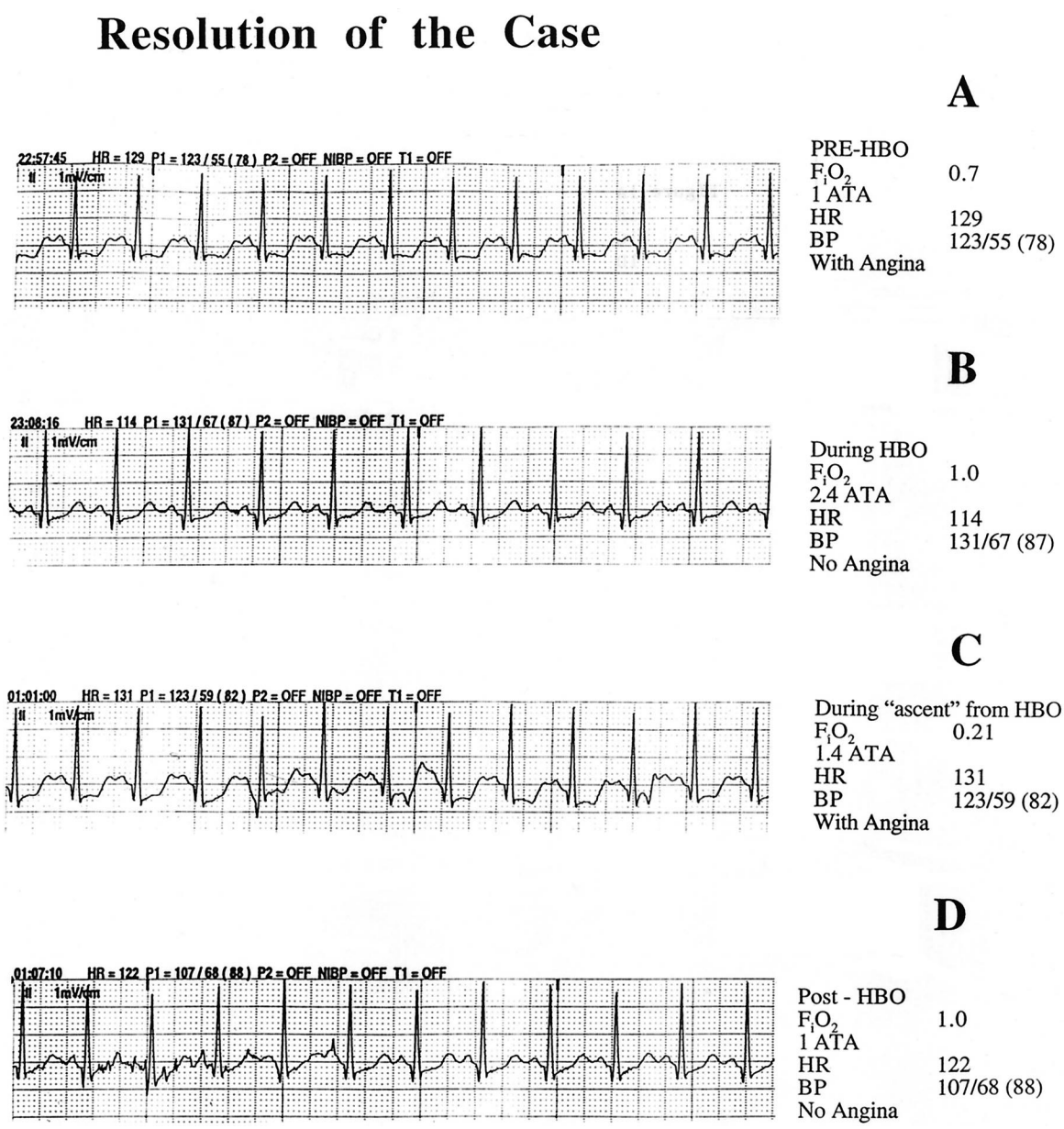

Fig. 1. Standard lead II electrocardiogram during four points in the clinical course of patient 1. (*A*) Prehyperbaric oxygen (HBO) ST-segment depression while experiencing angina pectoris. (*B*) Resolution of ST-segment depression and angina during hyperbaric oxygen treatment at 2.4 ATA. (*C*) Abrupt recurrence of ST-segment changes and angina during rapid ascent with an F_{IO_2} of 0.21. (*D*) Slow ascent to 1 ATA while breathing, with an F_{IO_2} of 1.0. No ST-segment depression or symptoms.

and hematocrit concentrations increased to 8.4 g/dl and 29.2%, respectively. Troponin I levels 4 days after admission were within normal limits. The patient reported easy fatigability, but there was no clinical evidence of neurologic sequelae.

Case 2

A 45-yr-old woman presented to a community hospital with mental status changes and a hematocrit concentration of 12.8% 15 days after an apparently uncomplicated vaginal delivery of a neonate and postpartum bilateral tubal ligation. Medical history included calcific aortitis of unknown origin that necessitated aortic valve replacement and right internal mammary artery bypass 6 yr previously. The patient was prescribed warfarin for her aortic valve prosthesis, which was suspended after her pregnancy was diagnosed. Anticoagulation was maintained with use of subcutaneous heparin. After vaginal delivery of a neonate and postpartum tubal ligation, warfarin anticoagulation was resumed. Prothrombin time was 112 s, with an international normalized ratio of 9.9. During previous aortic valve replacement surgery, the patient underwent transfusion, and an erythrocyte antibody (anti-c) was reported to have developed.

At arrival in the intensive care unit, hemoglobin and hematocrit concentrations were 2.6 g/dl and 9%, respectively. Initial blood lactate concentration was 7.4 mEq/l. The patient was administered oxygen *via* face mask. While undergoing assessment for hyperbaric therapy, the patient had a tonic clonic seizure and became unresponsive. She underwent ventilation *via* mask, with an F_{IO_2} of 1.0, and was trans-

ported rapidly to the hyperbaric chamber. The chamber was compressed to 2.4 ATA, and ventilation was maintained *via* a mask, with an F_{IO_2} of 1.0. Within 5 min at 2.4 ATA, the patient regained consciousness and became ebullient. Central venous partial pressure of oxygen (P_{VO_2}) was 186 mmHg.

The patient was administered a total of 14 units of fresh frozen plasma and 8 units of packed erythrocytes. This large-volume infusion caused congestive heart failure, as evidenced by rales, an S3, and tachypnea that necessitated tracheal intubation and sedation with the patient remaining at 2.4 ATA. Posttransfusion hemoglobin concentration was 9.4 g/dl, and the international normalized ratio decreased to 1.9. Lactate decreased to 1.9 mEq/l (normal, 0.5–2.2). The chamber was decompressed, and exploratory laparotomy was performed; 3 l liters blood was found in the peritoneal cavity. No further blood or blood component administration was necessary, and the patient was discharged on postoperative day 12 without apparent sequelae.

Discussion

This case report describes our attempts to avoid morbidity and mortality in young women with profound blood loss anemia. Transfusion of erythrocytes was the medical therapy of choice, but this was limited by patient consent and by difficulties in crossmatching in the respective cases. Hyperbaric oxygen therapy maximized plasma-dissolved oxygen, pending an increase in oxygen-carrying capacity.

At 1 atm of ambient pressure, blood with a hematocrit concentration of 43.5%[2] that is fully saturated with oxygen contains approximately 19 ml oxygen/dl blood, with dissolved oxygen contributing less than 2% of the total blood–oxygen content.

With a hemoglobin concentration of 3.0 g/dl, total blood–oxygen content while breathing room air decreases to 4.1 ml oxygen/dl blood, with dissolved oxygen representing 7% of blood–oxygen content. Because sustained oxygen extraction from hemoglobin exceeds 60% in only the most dire circumstances,[3,4] a more realistic estimate of oxygen available for biologic consumption is 2.5 ml oxygen/dl blood. The 0.3 ml/dl of dissolved oxygen is approximately 10% of the available oxygen.

At 2.4 ATA with an F_{IO_2} of 1.0, the arterial partial pressure of oxygen approaches 1,600 mmHg,[5] and dissolved oxygen content is approximately 4.8 ml oxygen/dl blood, which is a quantity sufficient to supply the majority of metabolic oxygen requirements. Total blood oxygen content with a hemoglobin concentration of 3.0 g/dl is approximately 8.7 ml oxygen/dl blood. Using 60% as a maximal value for sustained hemoglobin-bound oxygen extraction, the biologically useful oxygen content is 7.1 ml oxygen/dl blood. Sixty-seven percent of the usable oxygen is from the dissolved oxygen.

Survivors have been reported to have had hemoglobin concentrations comparable with our patients' anemic states. Lichtenstein *et al.*[6] described combined deep sedation, neuromuscular blockade, hemodilution, and cooling to a core body temperature of 29°C to reduce oxygen consumption 57% below baseline in a 37-yr old Jehovah's Witness with a hematocrit concentration of 4%.

Myking and Schreiner[7] treated a middle-aged woman with idiopathic hemolytic anemic crisis and mental status changes of syncope, urinary incontinence, paresthesia, disorientation, and stupor when the patient's hemoglobin concentration nadir was 3 g/dl. All symptoms were interrupted with use of hyperbaric oxygen therapy, and this relief persisted for several hours after each hyperbaric treatment.

Amonic *et al.*[8] reported the case of a 26-yr-old male Jehovah's Witness who refused transfusion despite a bleeding gastric lesion and who had a hemoglobin concentration of 2.2 g/dl and evidence of congestive heart failure, myocardial ischemia, and cerebral insufficiency. The patient was treated at 2 ATA with an F_{IO_2} 1.0 in 6-h cycles over the following 3 days. The patient was discharged 16 days after surgery, with a hematocrit concentration of 26%.

Recently, a similar case to ours was reported.[9] A 38-yr-old Jehovah's Witness experienced a placental abruption and bled, causing the hemoglobin concentration nadir to reach 2 g/dl. Despite tracheal intubation, sedation, and neuromuscular blockade to minimize oxygen consumption, a metabolic acidosis and subsequent ECG changes suggestive of myocardial ischemia developed; cardiac output was $7.6\,l \cdot min^{-1} \cdot m^{-2}$ with epinephrine support. Hyperbaric oxygen was administered for 90 min at 2 ATA and was associated with a reduced heart rate and cardiac output and with resolution of ischemic ECG changes and metabolic acidosis. Hyperbaric treatments were discontinued 16 days postpresentation, when the hemoglobin concentration was 3.6 g/dl and the patient was asymptomatic.

In our cases, the lower limits of hemoglobin concentration, consistent with myocardial sufficiency in the one case and cerebral sufficiency in the other case, were identified, and the decrement in oxygen delivery was rectified with use of hyperbaric oxygen therapy. In the second case, a central P_{VO_2} was 186 mmHg, which suggested that a surfeit of oxygen dissolved in the patient's plasma, and the hemoglobin-bound oxygen was unused (mixed venous oxygen saturation = 100%).

The oxygenation effects of hyperbaric oxygen are ephemeral; the tissue partial pressure of oxygen (p_{O_2}) has been reported to remain elevated for minutes to hours after the hyperbaric exposure.[10] For the second patient, transfusion effected the cure. This raises the question: why did the first patient, who refused transfusion, have no reported recurrences of hypoxia after removal from the hyperbaric environment. One possibility is that the ECG changes and symptoms the patient experienced before hyperbaric treatments represented an accumulation of anaerobic metabolic products and stresses that were cleared after sufficient oxygen was supplied. Periodic hyperbaric oxygen therapy may have prevented reaccumulation of metabolites to the threshold for symptoms. Furthermore, hyperbaric oxygen ther-

apy has been associated with a decrease in sympathetic tone and a lower heart rate, both of which would be beneficial in the presence of myocardial ischemia.[11] Heart rates during periods of angina in the chamber (129 and 131 beats/min) were increased relative to heart rates when angina was absent (114 and 122 beats/min).

The only other intervention in addition to slowing of the pressurization during hyperbaric oxygen therapy and maintaining an F_{IO_2} of 1.0 was the administration of morphine. Morphine decreases oxygen consumption 9–21% in critically ill patients, depending on the level of oxygen consumption.[12] Morphine may have decreased the metabolic oxygen consumption enough that the patient was able to meet this reduced level of oxygen consumption.

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