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Hyperbaric Oxygen Therapy and Hereditary Spherocytosis: Report of 2 Cases

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Wirjosemito SA, Touhey JE. Hyperbaric oxygen therapy and hereditary spherocytosis: report of 2 cases. J Hyper Med 1988; 3(1):45–50.—Two patients with hereditary spherocytosis were treated with hyperbaric oxygen (HBO) for refractory leg ulcers. No hemolytic complication occurred. These patients also had a defective leukocyte-adherence function, resulting in repetitive bouts of skin and subcutaneous infections. The mechanism whereby HBO induces hemolysis involves generation of hydrogen peroxide, which cleaves the double bonds of erythrocyte membrane unsaturated fatty acids. In addition, hydrogen peroxide negatively affects the cation transport mechanism of the cell membrane, thus producing osmotic lysis. The "older" erythrocytes are more vulnerable to lysis by hydrogen peroxide than the young group. The lysis has been demonstrated in vitamin-E-deficient animals. The protective effect of vitamin E is due to its unique structure, which traps the oxygen radicals of hydrogen peroxide. Although uncommon, vitamin E deficiency in humans can occur in gastrointestinal malabsorption syndrome (steatorrhea), abetalipoproteinemia, and some premature infants. Recent findings of increased deformability in erythrocytes exposed to HBO may indicate a salutary effect of HBO on the red cells of hereditary spherocytosis, which are more rigid and less deformable than normal. If, for an associated condition, a patient with hereditary spherocytosis must be treated with HBO, close monitoring of the hemogram, hemolysis parameters, and vitamin E level is warranted. Supplemental vitamin E may be indicated.

congenital spherocytosis, hyperbaric oxygen

Introduction

Hyperbaric oxygen (HBO) has been established as an adjunctive treatment in selected wound healing problems. Among the relative contraindications to its use is congenital (hereditary) spherocytosis. The increased osmotic fragility of the erythrocytes may predispose these patients to hemolysis under HBO conditions (1). Two cases of congenital spherocytosis, a father and daughter, were treated with HBO in our facility for their chronic refractory leg ulcers. No overt hemolytic complications occurred. We present a discussion on the effects of HBO on normal red blood cells (RBC), and on RBCs of congenital spherocytosis, followed by suggested guidelines in the event such a patient must be treated with HBO.

Case 1

A 34-yr-old Hispanic male was referred to the USAF Hyperbaric Center at Brooks Air Force Base, TX, for the adjunctive HBO treatment of 2 chronic ulcers of the right lower leg. Each was approximately 3 × 5 cm in size, and had not healed despite 7 to 8 mo. of several different modalities of treatment. His pre-HBO transcutaneous oxygen tension measurements at 1 atmosphere absolute (ATA) are shown in Table 1. The daily HBO treatments at 45 fsw, for 90 min (three 30 min O_2 breathing cycles, with two 10-min air breaks) were well tolerated, but unfortunately the patient opted to withdraw from treatment after a total of 13 dives. He was subsequently diagnosed as having hereditary spherocytosis with leukocyte adherence defect, manifested by frequent bouts of skin and subcutaneous infections. During the HBO treatment there was no evidence of hemolytic complication. His hemoglobin and hematocrit remained stable. Subsequent follow-up by correspondence revealed his wound was progressing well and finally healed completely.

Case 2

A 15-yr-old Hispanic female, the daughter of case 1, also known to have hereditary spherocytosis and leukocyte adherence defect, was referred for HBO treatment because of a chronic left lower leg ulcer which resulted from a minor trauma sustained 8 mo. previously. Her pre-HBO transcutaneous oxygen tension measurements are shown in Table 2. Due to her elevated transcutaneous oxygen tension level and that hereditary spherocytosis was a relative contraindication for HBO therapy, she was not accepted for the treatment. Later, debridement and skin grafting were performed. The patient

Table 1: Pre-HBO Transcutaneous Oxygen Tension Measurements, Case 1

Location	Room air, mmHg	100% O_2, mmHg
Adjacent to ulcers	43	256
Opposite leg (control)	49	230

Table 2: Pre-HBO Transcutaneous Oxygen Tension Measurements, Case 2

Location	Room air, mmHg	100% O_2, 1 ATA, mmHg
Proximal to ulcer	73	432
Distal to ulcer	100	626
Chest (control)	90	533

became septicemic, the graft was rejected, and the donor site deteriorated. She had a long, difficult recovery. At the time of discharge, her wound was improving. On subsequent follow-up, however, the wound showed regression of healing, with extensive eschar and areas of hypertrophic granulation. She was referred back for adjunctive HBO therapy. This time, she was accepted with close monitoring of her hemoglobin, hematocrit, reticulocyte count, and serum hemoglobin level for possible hemolytic complication. No evidence of hemolysis occurred, and the monitoring was terminated after 2 wk of HBO treatment. The wound was finally healing well enough to accept skin grafts, which took completely. The donor sites were much improved at the time of discharge.

Discussion

The hemolytic effect of HBO on RBC has been known for many years. Studies using vitamin E (tocopherol)-deficient mice exposed to HBO at 4 ATA demonstrated that excess hydrogen peroxide was produced, resulting in peroxidation of membrane lipids, ultimately causing hemolysis (2–7). In chow-fed (chow containing adequate vitamin E) animals, lipid peroxidation did not occur (8).

Two mechanisms are possible whereby hydrogen peroxide produces hemolysis (2, 3, 5, 7): a) Primary (direct) effect in which peroxidation of membrane lipids involves breaking up of the double bonds in unsaturated fatty acid chains ("deacylation"), particularly of phosphatidyl-ethanolamine (which contains mostly unsaturated fatty acids). This results in anatomical defects in the cell membrane, altering the permeability of the cell, causing hemolysis. The saturated fatty acid chains have been shown to be unaffected. b) Secondary effect of lipid peroxides involves damage to RBC proteins, enzymes, and metabolic pathways, as demonstrated by the inhibition of sulfhydryl-bearing enzyme glyceraldehyde-3-phosphate dehydrogenase in humans, and decreased activity of erythrocyte acetylcholinesterase in dogs exposed to HBO. Glyceraldehyde-3-phosphate dehydrogenase is involved directly in ATP formation. Decreased ATP formation results in the failure of cation transport mechanism, causing osmotic lysis.

According to Hochstein (9), a normal RBC is protected from lipid peroxidation by an existing antioxidant mechanism consisting of the free GSH (reduced glutathione) of the cell; sulfhydryl compounds of the cell membrane, and vitamin E. The membrane sulfhydryl compounds, including GSH, are also destroyed by the peroxidation, aggravating the ongoing lysis, by two probable mechanisms (3): sulfhydryl depletion increases membrane permeability, producing hemolysis; and the loss of those sulfhydryl groups attached to the double bonds of fatty acids exposes these bonds to further rupture by lipid peroxidation.

Thus, we see the crucial role of vitamin E in providing protection against peroxidation (3, 4). This protective mechanism has been described by Jacob

and Lux (3). A portion of alpha tocopherol (main congener of vitamin E) is a long chain fatty acid soluble in the lipid milieu of membranes; the rest of the molecule is an aromatic, substituted phenol, which, due to its unsaturated, resonating structure, can "trap" free radicals from hydrogen peroxide or its breakdown products. Consequently, in the absence of vitamin E, hydrogen peroxide is free to react with other double bonds in RBC membranes, cleaving the fatty acids at the sites of unsaturation. The RBCs most susceptible to the damage from lipid peroxidation are of the older group, whereas the younger RBCs and reticulocytes are more resistant (3, 9). These young cells have been shown to have a much better ability to repair the damage by incorporating plasma fatty acids into membrane phosphatidyl-ethanolamine, called "reacylation" (Fig. 1).

In humans, tocopherol deficiency occurs infrequently in the following conditions (3, 10):

a. Gastrointestinal malabsorption syndromes (steatorrhea). Due to its solubility in fat, vitamin E may be depleted by this route. A moderate decrease in ^{51}Cr-labeled red cell survival (half-lives, 8–15 d) has been demonstrated.
b. Abetalipoproteinemia, a rare malabsorption entity where the bizzarely shaped acanthocyte has been found to be peroxide-sensitive.
c. Premature infants with moderate hemolytic anemia and pyknocytosis.

Mengel et al. (11) reported a case of hemolytic anemia 2 d after exposure to HBO (2 ATA). They found that the patient's RBC resembled that of vitamin-E-deficient mice in terms of its in vitro sensitivity to hydrogen peroxide. Kann et al. (10) postulated that this was a form of delayed oxygen toxicity. Stocks

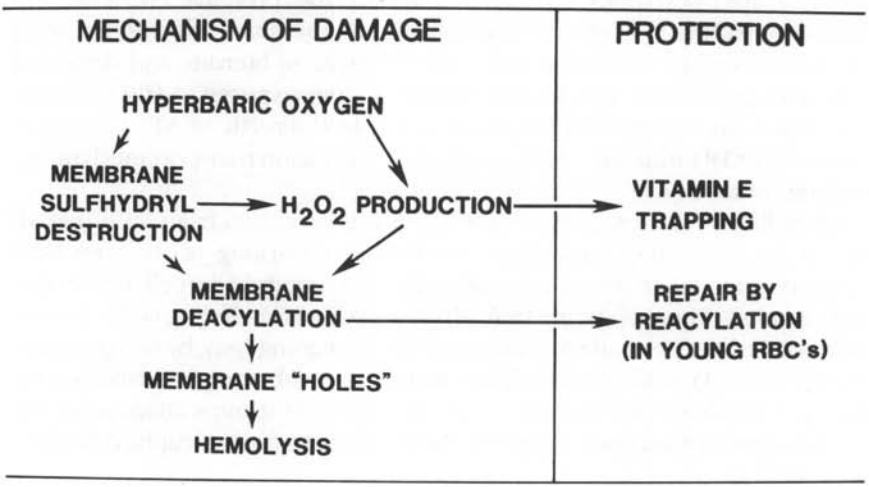

FIG. 1—Schematic representation of the mechanism of peroxide hemolysis and protection. Modified from (3).

et al. (12) measured in vitro susceptibility of RBC to lipid peroxidation based on the breakdown of oxidized fats to malonyldialdehyde (MDA). The MDA formation was normal in 4 patients with congenital spherocytosis, suggesting no hemolysis occurred.

The exact abnormality of RBC in congenital spherocytosis is unknown. The RBCs of these patients have less lipid per cell and less surface area per lipid than normal. No evidence exists of abnormal surface thiol activity inasmuch as studies have failed to show differences in the depth and mobility of sulfhydryl groups of the spherocytes from normal RBCs. The RBCs of patients with congenital spherocytosis demonstrate abnormal membrane permeability to sodium, in that more energy is required for their ion pumps to maintain cell integrity. The cells seemed to be less pliant and deformable, thus predisposing them to sequestration in the spleen. Recent studies revealed that some abnormality in the cytoskeleton of RBC in hereditary spherocytosis exists due to defective phosphorylation by membrane kinases of spectrin, a structural protein important for maintaining cytoskeletal rigidity. This abnormality contributes to the spherical shape and rigidity of the cell (13, 14).

Mathieu et al. (15) have demonstrated increased RBC deformability in patients undergoing HBO therapy. This deformability was thought to be due to changes in either the function of membrane ion exchangers or the phosphorylation of spectrin. The increased RBC deformability may exert a favorable outcome of HBO treatments in patients with congenital spherocytosis (Mathieu, personal communication).

The type of leukocyte dysfunction described in our cases has been studied by Anderson et al. (16). The oxidative activity of the patients' leukocytes during phagocytosis was diminished due to an abnormal granulocyte-particle interaction rather than to defective intracellular microbicidal capacity. This evidence was shown by the absence in these patients of deep-seated granulomatous infections characteristic of patients with chronic granulomatous disease or other disorders of leukocyte oxidative metabolism.

Our 2 patients might have been isolated, unusual cases, for HBO cannot be safely administered to every patient with congenital spherocytosis due to varieties within the disease itself. However, there are instances where HBO may be the only effective treatment modality. In such cases, certain precautions are warranted to minimize potential risks. The following guidelines are recommended in the management of patients with congenital spherocytosis, who, because of the presence of an associated condition, must receive HBO treatment:

1. Close monitoring of hemogram; suspect hemolysis for all reductions in values.
2. During the first 2 wk of HBO therapy, monitor serum hemoglobin and reticulocytes; afterward, repeat for any reduction in hemoglobin or hematocrit.

3. Ensure adequate nutrition, especially vitamin E intake. Supplemental tocopherol may be indicated in gastrointestinal malabsorption syndromes. Baseline serum tocopherol level may need to be obtained.
4. Avoid HBO therapy, if at all possible, in patients with active hemolysis.

References

1. Kindwall EP. Hyperbaric medicine procedures. Milwaukee, WI: St. Luke's Hospital, 1984.
2. Carolla RL, Mengel CE, Husney RM. Effect of in vivo hyperoxia on erythrocyte fatty acid composition. Aerosp Med 1968; 39:1290–1293.
3. Jacob HS, Lux SE IV. Degradation of membrane phospholipids and thiols in peroxide hemolysis: studies in vitamin E deficiency. Blood 1968; 32(4):549–567.
4. Johnson WP, Jefferson D, Mengel CE. In vivo hemolysis due to hyperoxia: role of H_2O_2 accumulation. Aerosp Med 1972; 43(9):943–945.
5. Mengel CE, Kann HE Jr. Effects of in vivo hyperoxia on erythrocytes. III. In vivo peroxidation of erythrocyte lipid. J Clin Invest 1966; 45(7):1150–1158.
6. Mengel CE. The effects of hyperoxia on red cells as related to tocopherol deficiency. Ann NY Acad Sci 1972; 203:163–171.
7. Kann HE Jr., Mengel CE. Mechanisms of erythrocyte damage during in vivo hyperoxia. In: Proceedings of third international conference on hyperbaric medicine. Washington, DC: National Academy of Sciences, National Research Council; 1966:65–72.
8. Carolla RL, Brubaker LH, Mengel CE. Age of red blood cells destroyed by in vivo hyperoxia. Aerosp Med 1974; 45(11):1273–1275.
9. Hochstein P. Antioxidant mechanism and hemolysis associated with lipid peroxidation. In: Proceedings of third international conference on hyperbaric medicine. Washington, DC: National Academy of Sciences, National Research Council; 1966:61–64.
10. Kann HE, Mengel CE, Clancy WT, Timms R. Effects of in vivo hyperoxia on erythrocytes. VI. Hemolysis occurring after exposure to oxygen under high pressure. J Lab Clin Med 1967; 70(1):150–157.
11. Mengel CE, Kann HE, Heyman A, Metz E. Effects of in vivo hyperoxia on erythrocytes. II. Hemolysis in a human after exposure to oxygen under high pressure. Blood 1965; 25(5):822–829.
12. Stocks J, Kemp M, Dormandy TL. Increased susceptibility of red-blood-cell lipids to autoxidation in haemolytic states. Lancet 1971; 7693:266–269.
13. Jandl JH, Cooper RA. Hereditary spherocytosis. In: Williams, Beutler, Erslev, Lichtman, eds. Hematology, 3rd ed. New York: McGraw-Hill Book Co.; 1983:547–553.
14. Valentine WN. Hereditary spherocytosis. In: Stein JH, ed. Internal medicine. Boston: Little, Brown & Co., 1983:1559–1561.
15. Mathieu D, Coget J, Vinckier L, Saulnier F, Durocher A, Wattel F. Red blood cell deformability and hyperbaric oxygen therapy. Med Subaquatique Hyperbare 1984, 3:100–104. English translation by the Translation Branch, USAF SAM/EDI, School of Aerospace Medicine, Brooks Air Force Base, TX.
16. Anderson DC, Schmalsteig FC, Finegold MJ, et al. The severe and moderate phenotypes of heritable Mac-1, LFA-1 deficiency: their quantitative definition and relation to leukocyte dysfunction and clinical features. J Infect Dis 1985; 152(4):668–689.

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