

Use of hyperbaric oxygen in rheumatic diseases: case report and critical analysis

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Hyperbaric oxygen has been used in patients with rheumatic disease for many years without reports of untoward or unusual complications for a variety of non-rheumatic indications. Recent evidence that hyperbaric oxygen inhibits the actions of certain cytokines, acts as an immune modulator and may help cognitive dysfunction has resulted in a re-examination of its potential role in rheumatic diseases. A case report of a lupus/scleroderma crossover patient is presented whose cognitive dysfunction improved after hyperbaric oxygen therapy. The history of hyperbaric oxygen and its physiology are related, along with a focused review of its effects on the immune and central nervous systems. Areas which might warrant further consideration by rheumatologists are outlined, as well as areas of concern.

Keywords: hyperbaric oxygen: scleroderma: rheumatic diseases

Introduction

Hyperbaric oxygen therapy is defined as the subjecting of patients to pure oxygen breathing at ambient temperatures which are greater than normal atmospheric pressure. Although concepts of hyperbaric oxygen therapy were first employed in 1662, its modern use other than for decompression dates from 1956 when hyperbaric oxygen was used to perform cardiac surgery in Holland.¹ Mechanically, the most common applications of hyperbaric oxygen are to dissolve air or gas emboli and treat divers with 'bends' or decompression sickness.

New insights into the biochemical and immune interactions of hyperbaric oxygen have increased interest in its potential applications over the past decade. The United States Medicare system has approved hyperbaric oxygen for 14 different indications ranging from acute carbon monoxide intoxication, gas gangrene and osteoradionecrosis to acute peripheral arteriolar insufficiency. Over the past 20 years, patients with a variety of conditions, especially multiple sclerosis, have reported cognitive improvements after undergoing hyperbaric oxygen. One lupus/scleroderma crossover patient whose case is reported here, underwent hyperbaric oxygen therapy specifically for cognitive impairment and experienced subjective and objective improvement. Her case is presented and our concepts of hyperbaric oxygen and the immune and central nervous systems are reviewed.

Case report

A 53-year old Caucasian woman flight attendant who was in her usual state of health until 1979 when she underwent thyroidectomy and inadvertent parathyroidectomy for Graves' disease. In February 1980 her Heyer-Schulte saline breast implants (placed in 1977 for cosmetic purposes) were replaced with Cox-Uphoff silicone prostheses. She was

well until 1986 when she presented to UCLA Medical Center with subcutaneous edema, Raynaud's phenomenon, sclerodactyly, inflammatory arthritis and erythematous rashes. A work-up demonstrated an ANA of 1:40 (speckled), elevated sedimentation rates (averaging in the high 30s), and persistently decreased IgA levels. She was diagnosed as having a lupus/scleroderma crossover, although the possibility of eosinophilic fasciitis was considered. (It was ultimately ascertained that she occasionally took L-tryptophan to sleep after long flights.) No disease modifying therapy was given; supportive diuresis and nonsteroidal anti-inflammatory agents were prescribed. Over the following 7 years, her ANA rose to 1:1280 (homogeneous), a positive IgG anticardiolipin antibody was found, and her course was complicated by pericarditis and supraventricular tachyarrhythmias. The latter two items were felt to be suggestive of cardiac scleroderma: anti RNP was negative and her inflammatory arthritis subsided, sclerodactyly worsened and brawny subcutaneous edema persisted. By 1990, she was no longer able to work and went on disability. In 1991 she was explanted with subjective improvement in her musculoskeletal pains. Although she had intermittent myofascial tender points in her upper back and neck area, the ACR criteria for fibromyalgia were never fulfilled. Sinus surgery performed in 1993 incidentally revealed silicone granulomas in her sinuses. The patient began complaining of cognitive dysfunction and extreme fatigue by 1990 which did not improve with explantation. An MRI scan of the brain in 1993 showed left parieto occipital deep white matter perivascular changes. Her medications at the time included thyroid, estrogen/progesterone hormonal replacement and vitamin D. On 7 January 1994 a SPECT scan demonstrated evidence for moderate and extensive temporal, parietal, frontal (more than two standard deviations below normal) and mild occipital and cerebellar (1.5 standard deviations below normal) hypoperfusion. She underwent 15 treatments over 3 weeks of hyperbaric oxygen with 1.5 atmospheres for 30 mm at a free-standing facility without complication in February 1994. Immediately afterwards, her cognitive abilities subjectively improved. She applied for reinstatement with her airline and took a 3-week in-flight retraining course, graduating at the top of her class. Nine months later, on 11 October the SPECT scan was repeated at the same facility. The original abnormalities were still present, but an overall 3-6% improvement of tracer distribution was evident. In the left occipital lobe and left and right superior parietal lobes, approximately 12% improvements were noted. At that time her ANA was 1:1280 (homogeneous), Westergren sedimentation rate 5 mm/h, and she was a senior flight attendant on the Los Angeles-Hong Kong route for her airline, making three round trips a month.

Discussion.

Several of our patients with lupus have undergone hyperbaric oxygen for osteomyelitis over the years without problems, and a few reported a slight decrease in their lupus activity and improved ability to think clearly. The case presented is the first where dramatic cognitive improvements were purported, although detailed cognitive-related objective testing other than SPECT scanning was not performed before and after treatment. She presented with an unusual and perhaps unique combination of features that could be consistent with silicone adjuvant arthropathy, eosinophilic myalgic syndrome, Graves' disease, systemic lupus erythematosus and scleroderma. Although it is possible

that the timing of her cognitive improvements and hyperbaric oxygen were coincidental, it is our belief that this case warrants further examination of the potential use of hyperbaric oxygen in rheumatic diseases.

*What is hyperbaric oxygen therapy and how is it administered?*²⁻⁴

At one atmosphere, patients with a normal hemoglobin (15 g/dl) can theoretically transport about 20 ml of oxygen 100 ml of blood (95% as oxyhemoglobin and 5% in solution), but this actually decreases by two thirds after passing through the capillaries. The ability of a gas to dissolve into liquid is dictated by its index of solubility, partial pressure and temperature (Henry's General Gas Law). With hyperbaric oxygen, enough molecular oxygen can be dissolved into a patient's blood stream to satisfy all metabolic requirements. For example, breathing 100% oxygen at 1, 2 or 3 atmospheres results in 2, 4 and 6 ml of oxygen in solution per 100 ml of blood, respectively. Patients are usually treated with 1.2-3.0 times atmospheric pressure for 30-90 min which is equivalent to the pressure that a diver is exposed to at a depth of between 5 and 20 metres underwater.

The cost of hyperbaric oxygen ranges from \$200 to \$500 per treatment and a course of therapy ranges from 15 to 40 treatments (\$3,000-\$20,000). Hyperbaric oxygen can be administered in a variety of pressure chambers: large multiplace units where six or more patients are treated at the same time; smaller one or two place chambers which are also pressurized with air and patients breathe oxygen through aviation-type masks, or hoods; and smaller single place chambers which are pressurized with oxygen and no mask system is needed.

What are the physiologic actions of hyperbaric oxygen therapy?

Increased oxygen tension has profound effects on the body's metabolism and cellular milieu. By preserving ATP in cell membranes it decreases edema and is particularly useful in burn patients. Hyperbaric oxygen promoted capillary angiogenesis, decreases leukocyte adhesion and platelet aggregation to capillary walls after trauma, increases the ability of white blood cells to engage in microbial killing, increases tissue levels of superoxide dismutase and increases collagen and fibroblast formation.^{5,6} Hyperbaric oxygen decreases blood flow to tissues while increasing their oxygen tension. Clinically, it has been used to promote wound healing, especially to ischemic areas. Other physiologic effects include a 10-20% reduction in cardiac output due to slowing the heart rate.⁷

How does hyperbaric oxygen affect the immune system?

Healthy volunteers given hyperbaric oxygen have a significant increase in CD8 levels and decrease in CD4 levels. This is associated with a rise in the number of HLA-DR antigen bearing cells, with a transient increase in monocytes.⁸ These changes are observable for a little over 24 h.

CD3 levels, B cell and natural killer cell values do not change. Similar findings have been found in normal mice in two separate studies.⁹⁻¹⁰ Interestingly, the administration of hyperbaric oxygen to NZB or MRL/lpr mice suppressed immunoglobulin production by spleen cells.⁹ Long-term hyperbaric oxygen delayed the development of proteinuria, facial erythema and lymphadenopathy in MRL/lpr mice. Inamoto *et al* showed that hyperbaric oxygen has immunosuppressive properties modulated by decreasing interleukin 1 and prostaglandin E2 production, but interleukin 6 production was not altered.¹¹

How does hyperbaric oxygen affect the central nervous system?

Studies of hyperbaric oxygen on the central nervous system show that at tensions of 1.2-1.5 atmospheres absolute (ATA), it decreases blood flow by 1-20% (mean of various studies is about 10%).² Other physiologic changes occur. These include greater permeability of the blood-brain barrier to medications and increased oxygen tensions to tissues that far outweigh the net effects of mild vasoconstriction. The deformability of erythrocytes is increased resulting in improved oxygen transportation in the microvasculature circulation and lactate removal.¹² Hyperbaric oxygen stimulates the metabolism of nerve cells deprived of oxygen. As early as the 1960s, Meijne reported cognitive improvements in patients to performing mathematical calculations and demonstrated increased typewriter skills after hyperbaric oxygen.¹³ An area of controversy among hyperbaricists concerns the possibility that once 1.5 ATA is exceeded, anaerobic metabolism is favored and thus cognitive skills do not improve as well as they would at lower pressures. Di Sabato *et al*¹⁴ performed a controlled study (with sham hyperbaric controls) on patients with cluster headaches. The dramatic improvements were attributed to vasoconstriction, decreased edema, increased serotonin synthesis and decreased cerebral hypoxia. Additionally, in the central nervous system hyperbaric oxygen decreases adrenaline and monoamine oxidase levels as well as promoting axonal regeneration.¹⁵

Hyperbaric oxygen for multiple sclerosis and other autoimmune diseases

As hyperbaric oxygen decreases demyelination from perivascular edema, over 6000 patients with multiple sclerosis have undergone this therapy in the past 10 years. A published trial by *The New England Journal of Medicine* suggesting improvement with hyperbaric oxygen in 40 patients in 1983 stimulated considerable interest.¹⁶ However, it was evident that even though hyperbaric oxygen increased helper T lymphocyte levels, patients liked the treatment and reported subjective improvements (especially in sense of well-being, cognition and bladder function), four separate placebo-controlled double-blind trials failed to demonstrate any objective benefits of using the Kurtzke Disability Status Scale or any other parameters.¹⁷⁻²⁰ This was also confirmed in a 22 institution multicenter registry of 312 patients followed for 2 years.²¹

Occasionally patients with other rheumatic syndromes and associated complications have been held to respond to hyperbaric oxygen. Aseptic necrosis complicating systemic lupus, for example, appears to be worthy of greater scrutiny.²² Abstracts and

presentations at seminars and meetings on hyperbaric oxygen claim benefits for pneumatosis cystoides intestinalis in scleroderma, livedo reticularis with vasculitis and Raynaud's phenomenon. Articles have appeared advocating hyperbaric oxygen for Crohn's disease and cyclophosphamide-associated hemorrhagic cystitis.^{23,24}

How safe is hyperbaric oxygen?

Hyperbaric oxygen is generally quite safe, but serious complications can occur.²⁵ Absolute contraindications to hyperbaric oxygen include pregnancy, underlying malignancy, untreated pneumothorax, concomitant therapy with doxorubicin, cis-platinum or disulfiram. Special considerations need to be taken into account if the patient has upper respiratory tract infections or chronic sinusitis (which make clearing the ears and sinuses problematic), low seizure thresholds (with high fevers or epilepsy), emphysema with CO₂ retention (which suppresses breathing), and congenital spherocytosis (hemolysis can result). The most common complication of hyperbaric oxygen is barotrauma to the ears and sinuses caused by pressure changes, which has been reported in about 5%. Occurring in 0.1-5% of patients are hypersensitivity reactions, confinement anxiety, central nervous system oxygen toxicity, pulmonary oxygen toxicity and temporary changes in eyesight. To minimize risks, patients are advised to have an ear, nose and throat examination by the treating physician before therapy, not to drink alcohol or take any medication for 4 h prior to treatment, and to wear cotton clothing.

Is there a potential role for hyperbaric oxygen in rheumatic diseases?

Very little is known about the influence of hyperbaric oxygen on the immune system. Animal models of autoimmune disease and normal mice are conducive to hyperbaric oxygen studies. Hyperbaric oxygen might be useful in combination with other therapeutic modalities. Further study is needed in these areas before proceeding to human trials. Nevertheless, anecdotal testimonials that hyperbaric oxygen helps people think more clearly should be taken seriously and ultimately subjected to a prospective trial.

Systemic lupus erythematosus (SLE) is an autoimmune disorder that afflicts several hundred thousand Americans. Nearly half manifest similar cognitive deficits that do not respond to Corticosteroids.²⁶ In the past few years, the development of single photon emission computerized tomography (SPECT) has shown hypoperfusion abnormalities bitemporally and bifrontally in patients with SLE and, incidentally, with fibromyalgia/chronic fatigue syndromes.²⁷⁻²⁹

Hyperbaric oxygen is a well characterized, old technology whose immunomodulatory properties and effects on cognition have never been adequately studied. Although relatively expensive, this reasonably safe procedure might have potential heretofore unrealized applications to patients with rheumatic disease.

References

- 1 Meijne NG. The history of hyperbaric oxygen. In: NG Meijne (ed.) *Hyperbaric Oxygen and its Clinical Value*. Springfield. IL: C Thomas.1970: 3-10.
- 2 Fischer D *et al*. *Handbook of Hyperbaric Oxygen Therapy*. Geneva: Springer Verlag. 1989.
- 3 Bakker DJ. Hyperbaric oxygen therapy: past, present and future indications. *Adv Exp Med Biol* 1992; 317: 95-105.
- 4 NHLBI Workshop Summary. Hyperbaric oxygen therapy. *Am Rev Respir Dis* 1991;144:1414-1421.
- 5 Kindwall EP. Hyperbaric oxygen: more indications than many doctors realise. *Br Med J* 1993; 307: 515-516 (editorial).
- 6 Kaelin CM *et al* The effects of hyperbaric oxygen on free flaps in rats. *Arch Surg* 1990; 125: 607-609.
- 7 Committee Report on Hyperbaric Oxygen Therapy. Publication no. 3OCR (HBO) 1989. revised edition. Undersea and Hyperbaric Medical Society, Bethesda. MD. USA.
- 8 Bittennan N *et al* Effect of a single exposure oxygen on blood mononuclear cells in human subjects. *Undersea Hyper Med* 1993; 20:194-204.
- 9 Saito K *et al* Suppressive effect of hyperbaric oxygen on immune responses of normal and autoimmune mice. *Clin Exp Immun* 1991;86: 322-327.
- 10 Gadd MA *et al*. Effect of hyperbaric oxygen on murine neutrophil and T lymphocyte functions. *Crit Care Med* 1991 18: 974-979.
- 11 Inamoto Y *et al* Effect of hyperbaric oxygen on macrophage function in mice. *Biochem Biophys Res Commun* 1991; 179: 886-891.
- 12 Neubauer RA. Gottlieb SF. Miala A Jr. Identification of hypometabolic areas in the brain using brain imaging and hyperbaric oxygen. *Clin Nuc Med* 1992; 17: 477-481.
- 13 Meijic NG. The influence of high nitrogen tensions on workers in compressed air. In: NG Meijne (ed.) *Hyperbaric Oxygen and its Clinical Value*. Springfield IL: C Thomas. 1970: 84-93.
- 14 Di Sabato *et al*. Hyperbaric oxygen therapy in cluster headache. *Pain*,1993; 52: 243-245.
- 15 Fischer D *et al*. Hyperbaric oxygen in disorders of the nervous system.In: Fischer D (ed) *Handbook of Hyperbaric Oxygen Therapy*. Geneva: Springer 1989:135-149.

- 16 Fisher BH, Marx M, Reich T. Hyperbaric oxygen treatment of multiple sclerosis: a randomized and placebo controlled double-blind Study. *N Engl J Med* 1983;308: 181-186.
- 17 Wiles CM *et al.* Hyperbaric oxygen in multiple sclerosis: a double blind trial. *Br Med J* 1986; 292: 367-371.
- 18 Barnes MP *et al.* Hyperbaric oxygen and multiple sclerosis: short-term results of a placebo-controlled, double-blind trial. *Lancet* 1985; 1:297-300.
- 19 Wood J *et al.* A double-blind trial of hyperbaric oxygen in the treatment of multiple sclerosis. *Med J Aust* 1985; 143: 238-240.
- 20 Harpur GD *et al.* Hyperbaric oxygen therapy in chronic stable multiple sclerosis: double-blind study. *Neurology* 1986; 36: 988-991.
- 21 Kindwall EP *et al.* Treatment of multiple sclerosis with hyperbaric oxygen. Results of a national registry. *Arch Neur* 1991; 48:195-199.
- 22 Marx RE, Johnson RP Studies in the radiobiology of Osteoradionecrosis and their clinical significance. *Oral Surg Oral Med Oral Pathol* 1987; 64: 379-390.
- 23 Brady CE, Cooley BI, Davis JC. Healing of Severe perianal and cutaneous Crohn's disease with hyperbaric oxygen. *Gastroenterology* 1989;97: 756-760
- 24 Hader JE *et al.* Hyperbaric oxygen treatment for experimental cyclophosphamide-induced hemorrhagic cystitis. *J Urol* 1993; 149:1617-1621.
- 25 KK Jain (ed). *Textbook of Hyperbaric Medicine*. Lewiston, NY: Hogart & Huber, 1992.
- 26 Wallace DJ, Metzger *et al.* Systemic lupus and the nervous system. In Wallace DJ, Han BH (eds), *Dubois' Lupus Erythematosus*, 4th end. Philadelphia, PA: Lea & Febiger. 1993; 370-385.
- 27 Rubbert A *et al.* Single photon emission computed tomography analysis of cerebral blood flow in the evaluation of central nervous system involvement in patients with systemic lupus erythematosus. *Arthritis Rheum* 1993; 36:1253-1262.
- 28 Ichise M *et al.* Assessment of regional cerebral perfusion by ^{99m}TcHMPAO SPECT in chronic fatigue syndrome. *Nuc Med Comm* 1992;13: 767-772.
- 29 Goldstein JA *et al.* The assessment of vascular abnormalities in late life chronic fatigue syndrome by brain SPECT: comparison with late life major depressive disorder. *J Chr Fatigue Syndrome* 1995;1: 55-79.