Can HBOT Reduce Breast Cancer Treatment-Related Lymphedema?

Teas J, Cunningham JE, Cone L, Jansen K, Raghavan SK, Nitcheva DK, Xie D, Butler WM.

Department of Health Promotion Education and Behavior, Arnold School of Public Health, University of South Carolina and the South Carolina Cancer Center, Columbia, South Carolina, USA. jane.teas@palmettohealth.org

Abstract

OBJECTIVE:

Arm lymphedema after surgery or radiation for breast cancer is common, causing pain and limitation of activities. Previous reports of hyperbaric oxygen (HBO) therapy for breast edema led us to consider the use of HBO therapy for arm lymphedema.

METHODS:

Ten healthy postmenopausal women (age 58 +/- 5.7 years) with persistent (9.4 years +/- 9.1 years) arm lymphedema following breast cancer surgery and radiation (n = 10) plus chemotherapy (n = 7) received 20 HBO treatments (90 minutes at 2.0 ATA five times a week for 4 weeks). End points included changes in upper extremity volume, platelet counts, plasma levels of vascular endothelial growth factor (VEGF), and lymph angiogenic-associated vascular endothelial growth factor-C (VEGF-C). Lymphedema volume (LV) was defined as the volume of the unaffected arm subtracted from the volume of the affected arm.

RESULTS:

We observed a 38% average reduction in hand lymphedema (-7.4 ml, 11.6 SD, range -30-+8 ml, p = 0.076, 95% confidence interval -15.7-0.9 ml) at the end of HBO, which was independent of changes in body weight. For those who benefited (n = 8), the reduction was persistent from the end of treatment to a final measurement an average of 14.2 months after the last HBO treatment. However, total LV did not change significantly. VEGF-C increased from baseline (p = 0.004) before treatment 20, suggesting HBO had begun to stimulate this growth factor.

CONCLUSIONS:

Future studies should explore the effects of a greater number of HBO treatments on lymphedema, with more patients.

Cancer and HBOT

Discussing patient histories is an essential part of communication. In addition, we have more science to support oxygen therapy than any other intervention in medicine. Why increasing the inspired partial pressure a small amount over what is routinely used should be regarded as snake oil is beyond me and shows the fundamental ignorance of our profession. It is NOT quackery.

There is no evidence that cancer is activated by HBO indeed the first post WW 2 use of HBO was as an adjunct to radiotherapy in which high tissue tensions increase the kill rate. There was a trial published from a London medical, school about 5 years ago on the value of HBOT in glottic cancer.

Philip James M.D.
Wolfson Hyperbaric Medicine Unit
University of Dundee

Cancer and HBOT

A review of the most recent literature involving increased pressure oxygen and Head and Neck cancer in irradiated patients not only displays no evidence of cancer growth enhancement but rather shows a reduced incidence of cancer recurrence. While increased pressure oxygen should not currently be considered as an anti-neoplastic agent, the preponderance of data suggests that cancer, past or present, should not be a contraindication to the use of increased pressure oxygen.

Breathe well and stay healthy,

Michael Capria

Ref: Marx RE: Radiation Injury to tissue. In: Hyperbaric Medicine Practice. Kindwall EP (Ed). Best Publishing Company. Flagstaff (AZ) 1994. Chapter 23, 498-503.

Williams RB, et al.: Effect of hyperbaric oxygen on induced colon cancer in rats. Proceedings of the 25th Annual Meeting of the Association for Academic Surgery 1991.

Feldmeier JJ, et al.: Does hyperbaric oxygen have a cancer-causing or promoting effect? A review of the pertinent literature. Undersea and Hyperbaric Medicine 1994;2(4):467-475. Granstrom G: Tumor recurrence and development of new head and neck cancers after HBO2-treatment, a prospective clinical study. Proceedings: Int. Joint Meeting on Hyperbaric and Underwater Medicine 1996, Milan:47-60

Immune System Blamed for Cancer

The Immune System may Help to Create Tumors.
Hyperbaric Oxygen Reduces Inflammation and Restores Circulation

Long-term over-activation of the immune system may be the single most important cause of cancer, say experts. When the immune system goes into over-drive it leads to inflammation of the tissues.

Many scientists agree that this inflammation may play a role in the Development of cancer. An inflamed tissue is a melting pot of cancer-causing molecules.

Professor Angus Dalgleish However, a new report suggests that the Importance of this role may have previously been under-estimated.

The authors argue that long-standing over-activation of the immune system is the key event in the genesis of many forms of the disease.

The research could herald an entirely new approach to both preventing and treating cancer. Drug therapy.

It raises the prospect that some existing anti-inflammatory drugs - currently front-line treatments for conditions like arthritis and inflammatory bowel disease - could be used to keep cancer at bay.

According to conventional wisdom, cancer has a variety of causes.

But Dr Ken O'Byrne, of the University of Leicester, and Professor Angus Dalgleish of St George's Hospital in London argue that many of these factors work in the same way - by switching on the immune system for too long.

Dr O'Byrne said: "One of the biggest mysteries of cancer is why the body allows cells to build up cancerous mutations, when it has an immune system that ought to stop this from happening.

"But we think that when the immune system overcooks, perhaps because of long-term exposure to an infection or carcinogenic chemical, it loses its ability to fight disease and instead may actually begin to nurture and protect young cancer cells.

"If we could calm the immune system down with certain anti-inflammatory drugs, we might be able to reduce the rates of many common cancers. Kicked into action"

This review makes a fascinating case for the link between exhausted immunity, chronic inflammation and cancer Dr Mary Berrington Tissues become inflamed when the immune system is kicked into action by injury, infection or an allergic reaction.

White blood cells and molecules involved in the immune response are produced to fight off infection and aid the healing process.

However, the same molecules that stimulate the regeneration of damaged tissues may also play a part in the birth of cancer and accelerate its growth and spread.

The researchers argue that continually switching on the immune system encourages cancer in a number of ways:

- Immune cells that would normally kill developing cancer cells can be switched off.
- Immunity for healthy cells can be spread to cancer cells too.
- Blood vessel growth is stimulated, providing nutrition for cancer cells
- Many immune system molecules are extremely chemically reactive, and may actually cause cancerous mutations by attacking DNA.

The researchers believe that nearly all carcinogens work by over-cooling the immune system. For instance, tobacco smoke can cause long-term inflammation.

They also believe that cancer might cause inflammation too, thus creating the conditions needed to boost the growth and spread of the disease.

Professor Dalgleish said: "An inflamed tissue is a melting pot of cancer-causing molecules, so what better way for a cancer cell to give itself a helping hand that by learning to copy those very same conditions?

"Of course this means that some anti-inflammatory pills might not only help in preventing cancer, but in treating the disease too."

Dr Mary Berrington, Science Information Manager for The Cancer Research Campaign, said: "This review makes a fascinating case for the link between exhausted immunity, chronic inflammation and cancer.

"It's essential that we look at all the evidence, although much of it at the moment is circumstantial."

The report is featured in the British Journal of Cancer.

Hyperbaric Oxygen: Does it Have a Cancer Causing or Growth Enhancing Effect?

Fifth Consensus Conference of the European Committee for Hyperbaric Medicine with the European Society of Therapeutic Radiology and Oncology

October, 2001

Lisbon Portugal

John J. Feldmeier, D.O.
Professor and Chairman
Radiation Oncology Department
Medical Director
Hyperbaric Medicine
Medical College of Ohio

I. Introduction:

The first reported concern that hyperbaric oxygen might have cancer growth enhancing effects appeared in a paper by Johnson and Lauchlan in 1966.1 These authors published their experiences in irradiating 25 patients with Stage III or IV Cervical Cancer utilizing hyperbaric oxygen as a radiosensitizer. The authors reported a more frequent than expected incidence of metastases and a pattern of metastases that appeared to be unusual. One patient is reported to have developed an esophageal metastasis. This first publication was subsequently followed by a number of larger human trials wherein hyperbaric oxygen was used as a radiosensitizer. Additionally, a number of animal trials have been published specifically to address the issue of hyperbaric oxygen's effect on primary tumor and metastatic growth. Several in vitro studies are also in the literature which address these concerns. This issue is still of concern to some2 and is the topic of this paper to be presented at the joint ECHM and ESTRO Consensus Conference on the role of hyperbaric oxygen in the treatment of radiation-induced injury in normal tissues.

Certainly, it is a reasonable concern that a therapeutic modality which is recommended as an adjunct to healing and is administered to promote proliferation of fibroblasts, epithelial cells and blood vessels in a wound could also lead to proliferation of malignant cells and angiogenesis in the tumor as well. The assumption that since cellular and vascular proliferation are promoted by hyperbaric oxygen in a healing wound that it will necessarily have the same effect in a tumor, though understandable at first glance, is also fairly naïve since it fails to recognize the important differences that exist between the complex physiology of wound healing and the equally complex and unique pathophysiologies of malignant transformation, tumor growth and metastases.

I will approach this important discussion by reviewing the published pre-clinical studies (animal and in vitro) followed by the results of clinical publications which ultimately are the most important. I will also discuss some of the mechanisms whereby hyperbaric oxygen could be postulated to have malignant growth potentiating effects and hopefully refute such putative effects. I will emphasize the discussion of tumor angiogenesis since recent concerns about the potential for hyperbaric oxygen to enhance malignant growth have been most frequently related to hyperbaric oxygen's effect as an inducer of angiogenesis. Other possible mechanisms of carcinogenesis and malignant growth enhancement will include discussions of a possible direct effect on cancer growth, immune suppression, free radical formation and mutagenesis. The discussion will also deal broadly and simultaneously with the concerns of enhanced carcinogenesis and enhanced metastatic growth although the author recognizes that important differences exist in the pathophysiology of each of these entities.

II. Pre-clinical Studies:

The effect of hyperbaric oxygen on tumor cells in cell culture and tumor growth in animal models have been studied in many publications. In terms of a potential impact on initiating or enhancing malignant growth, these publications can be divided into the following categories: 1. Papers addressing the direct effect of hyperbaric oxygen on cell growth in culture; 2. The effects of hyperbaric oxygen on immune competency; 3. The effects of hyperbaric oxygen on free radical formation; 4. The effects of hyperbaric oxygen on mutagenesis (generally as a result of free radical formation); and 5. Animal models of tumor growth and metastases.

1. Direct Effects on Cells in Cell Culture:

Kalns3 and associates have reported the effects of hyperbaric oxygen on the growth of two prostate cancer cell lines in cell culture. In this study, both cell lines had their growth suppressed after exposure to 3.0 ATA 100% oxygen for 90 minutes relative to normobaric controls by 8.1% and 2.7% respectively.

Feldmeier4 and associates in abstract form have reported a dose dependent reduction of numbers of colonies of B16 (amelanotic melanoma) cells grown cell culture by increasing pressures or times of exposure to hyperbaric oxygen. In this study, cells exposed to hyperbaric oxygen were also less likely to adhere to fibronectin substrata suggesting decreased metastatic potential since the ability of cells to adhere to vascular endothelium is a prerequisite for successful metastasis.

The studies cited above demonstrate an inhibitory direct effect on tumor cell growth in cell culture and suggest an effect which may decrease metastatic potential. A caution should properly be applied in interpreting the results of both of these reports in that the oxygen tensions experienced by the cells in culture are much higher than those cancer cells would experience in vivo in either an animal model or in human subjects in clinical trials.

2. Hyperbaric Effects on Immune Competence:

Cancer incidence and progression are known to increase in individuals chronically immune suppressed. A number of publications report immune suppression by hyperbaric exposures mostly in animal models and mostly as a result of extreme exposures in terms of pressure and time of exposure. In 1997, Xu5 and colleagues in a murine trial have shown a decrease of some lymphocyte subpopulations in the spleen and thymus after exposure to hyperbaric oxygen, but no delay in T cell response to Con A was observed. Brenner and associates6 have recently reported depression of several immune parameters including a weakening of response to antigens, a slowing of allograft rejection and a weakening of autoimmune response after hyperbaric exposures. They suggest that such effects are offset by acclimatization. Feldmeier and associates7 have reported no effects on a broad range of immune parameters in healthy human volunteers exposed to a typical course of clinical hyperbaric oxygen.

The above studies do not consistently demonstrate a frequency or degree of immune suppression, which is likely to potentiate malignant growth. The study by Brenner suggests that adaptation does occur in human subjects. Even if prolonged extreme hyperbaric exposures are immune suppressive, it is likely that the intermittent nature of clinical hyperbaric oxygen wherein the patient is only exposed to increased oxygen tensions for 90 to 120 minutes does not overwhelm the influences of the other 22 to 22 and ½ hours that the patient lives at normoxic and normobaric conditions

3. Hyperbaric Oxygen Effects on Free Radical Generation:

Free radicals are known to contribute to the development of a number of degenerative and deleterious conditions including cancer. Several recent studies suggest that exposure to hyperbaric oxygen does not necessarily lead to increased free radical damage. Kaelin and associates8 have shown a significant increase in the activity of the free radical scavenger superoxide dismutase in animals exposed to hyperbaric oxygen. Zamboni and his collaborators9 failed to demonstrate signs of increased free radical damage by hyperbaric exposure in an animal model of reperfusion injury. On the other hand, Monstrey et al10 showed an increase in soft tissue damage in a model of Adriamycin extravasation in animals exposed to hyperbaric oxygen both before and after the extravasation. The authors attribute this additional damage to increased free radical activity Elayan and associates11 showed no evidence of increased levels of 2,3-dihydroxybenzoic acid (a surrogate measure of free radical generation) in Sprague-Dawley rats exposed to hyperbaric oxygen at 3.0 ATA.

The available scientific information does not conclusively demonstrate an increase in free radical damage induced by hyperbaric oxygen. Again the intermittent nature of the hyperbaric exposure probably reduces the effects of any

increase in reactive oxygen species. Adaptive mechanisms, which lead to an increase in free radical scavengers, seem to also reduce the deleterious effects of any additional free radical generation.

4. Mutagenesis and Subsequent Carcinogenesis:

Several authors have voiced concerns about mutagenesis and resultant carcinogenesis caused by free radical generation as a result of hyperbaric oxygen exposure. In 1985, Ceruti12 discussed the carcinogenic effects of prooxidants including hyperbaric oxygen. This paper presents no first hand evidence of a carcinogenic or mutagenic effect of hyperbaric oxygen but instead discusses the known effects of oxygen active oxygen species (free radicals) and assumes that hyperbaric oxygen exposure will necessarily result in increased free radical damage including mutation and carcinogenesis. Interestingly, several of the author's key references were not reports of true hyperbaric exposure but instead prolonged exposure to increased concentrations of oxygen at ground level.13,14 The author extrapolates the results and makes the assumption that such observations would be the case even more so at hyperbaric pressures. Similar reasoning had suggested that hyperbaric oxygen was contraindicated in ischemia-reperfusion injuries since it was assumed that exposure to hyperbaric oxygen under these circumstances would lead to increased free radical generation and resultant damage. Investigators demonstrating beneficial effects of hyperbaric oxygen in iscemia-reperfusion injury including the induction of free radical scavengers as already discussed above have refuted this rationale. A group from the University of Ulm have studied the effects of hyperbaric oxygen on mutations in the leukocytes of healthy human volunteers exposed to 2.5 ATA.15 In this study and follow on studies, there were no changes seen in levels of 8-Ohguanine (one of the major DNA modifications induced by reactive oxygen species).15,16 Also no induction of mutations at the HPRT locus were detected. This too is a standard test for mutagenesis. DNA damage was demonstrated by the comet assay and mutations were demonstrated in the mouse lymphoma assay (MLA). The authors suggest that mutations observed due to hyperbaric exposures are clastogenic, i.e. the result of DNA strand breaks.

There is no doubt that reactive oxygen species can under some circumstances cause mutations which may lead to carcinogenesis. The available information cited above does not give consistent evidence for hyperbaric induced mutagenesis. Some in vitro studies do show mutagenesis in cells in cell culture. Again we should observe the caution that oxygen levels achievable in cell cultures are much higher than those achievable in vivo. Furthermore, in vitro studies and in vivo studies which only involve a single exposure or a short course of exposure may not allow for the development of protective mechanisms such as the induction of free radical scavengers including superoxide dismutase. Also, as before, the intermittent rather than continuous exposure of patients to hyperbaric oxygen is likely to permit repair of many of the DNA breaks that may result during the clinical hyperbaric treatment. A publication by Bruyninckx and associates17 in 1978 discusses that oxygen levels that are mutagenic in sensitive cells in cell culture may be physiologic in humans bringing into question cell culture studies that show mutagenesis due to hyperbaric oxygen exposure in terms of their carcinogenesis in human subjects.

5. Animal Studies of Tumor Growth and Metastasis:

In response to Johnson and Lauclan's1 publication, a number of researchers set out to investigate the effects of hyperbaric oxygen exposure on animals with transplanted, induced or spontaneous tumors. Table 1 lists those animal studies specifically designed to answer the issue of whether hyperbaric oxygen exposure of these animals led to enhanced growth of the dominant tumor mass or of resultant metastases. The first of these studies was published in 1966 and the last in 2001. A total of 17 publications are briefly summarized in the Table 1.18-34 Fifteen of the 17 studies show no increase in primary or metastatic growth. Two studies that show evidence of enhanced growth are mixed in their results. The paper by Shewell and Thompson26 shows an increase in the rate of lung metastases for spontaneous mammary tumors in mice while in the same study transplanted tumors had identical rates of growth and metastases in the control and hyperbaric groups. The increase in incidence of lung metastses in the spontaneous tumor group does not achieve statistical significance. In the paper by McMillan et al29 with an anthracene induced tumor in a hamster

cheek pouch model, animals exposed to hyperbaric oxygen had fewer but larger tumors. In an almost identical model, Marx and Johnson27 showed a delay in the development of cancers in animals exposed to hyperbaric oxygen. Six of these studies in Table 1 actually show some evidence of decreased tumor growth or metastases in animals exposed to hyperbaric oxygen. Mostly this decrease is seen as a trend and generally not in a statistically or clinically significant fashion. Please note that the Table legend identifies those studies with an enhancing, an inhibitory, a neutral or a mixed result.

Taken on the whole, these animal studies demonstrate no worse than a neutral effect by hyperbaric oxygen on the growth of induced, transplanted and spontaneous tumors and their secondary metastases. It is important to note that a broad range of tumor types and histologies were investigated in these studies. The tumors studied include squamous cell carcinomas, adenocarcinomas (mammary tumors), melanomas, leukemias and sarcomas. Some have suggested that hyperbaric oxygen may stimulate growth in one tumor histology and not another. The consistent results in a broad spectrum of tumor types fails to support this belief.

III. Human Studies:

Fifteen clinical reports are given in Table 2.1,35-48 These list the publications from which we can analyze the effects of hyperbaric oxygen on recurrence or metastases in patients exposed to hyperbaric oxygen. Twelve of the 15 publications come from studies published to report the efficacy of hyperbaric oxygen as a radio-sensitizer. The study by Van Den Brenk et al35 compared outcome in a group of head and neck cancer patients radiosensitized by hyperbaric oxygen and compared this to outcome in a historic control group. Also the study by Denham45 and associates compared patients irradiated under hyperbaric conditions to historic controls. Likewise, the original publication by Johnson and Lauchan1 was not a controlled trial. The remainder of the radio-sensitization studies were randomized and controlled. These studies were not specifically designed to address the issue of the effect of hyperbaric oxygen on primary growth or metastasis. The focus of our review in table 2 centers on incidence of metastases and survival of the patients since the control or growth of the primary tumor was impacted by the radiation, which the patient received as the primary endpoint of these studies. Destruction of the primary tumor was consistently improved in the hyperbaric group compared to the air controls. Often, this improvement in local control did not translate into a survival advantage for the patients. Ten of these 12 studies are clearly either neutral or advantageous in terms of patient survival or incidence of metastases. The original paper by Johnson and Lauchan1 that first voiced concerns of enhanced tumor growth under hyperbaric conditions is refuted by a larger experience in cervical cancer by the same author.37 The report by Cade35 and associates is a mixed study wherein the hyperbaric group radio-sensitized for lung cancer had no increased metastases; whereas, the bladder cancer patients receiving hyperbaric oxygen had increased metastases. The patients in the control and hyperbaric groups were not well matched.

There were increased numbers of patients in the hyperbaric group with advanced stage and more aggressive histologies. Outcome of treatment for patients with bladder cancer is substantially worse for advanced and poorly differentiated tumors. Most of the trials of hyperbaric radio-sensitization involve patients with squamous cell cancers of the head and neck or cervix. These patients were favored for enrollment into these trials because local control is often tantamount to cure since neither tumor commonly metastasizes until quite late in its course.

The other 3 studies present anecdotal experiences in patients with a history of malignancy who undergo a course of hyperbaric oxygen as treatment for radiation injury or non-healing wounds. One is a report of 3 patients with paralysis secondary to spinal cord injury who had had HBO2 for pressure ulcers and were found to have urothelial tumors which progressed rapidly after discovery.45 Two of the 3 patients had indwelling catheters for many years. The authors discuss long term usage of catheters for bladder drainage as a risk factor for urothelial tumors. The authors also report that another 113 patients with spinal cord injury were given hyperbaric oxygen at their facility for various reasons and that none of these patients developed malignancy. Bradfield and associates47 in 1996 reported 4 head and neck patients

with advanced head and neck cancer who were treated with hyperbaric oxygen for radiation injury and had recurrence and rapid progression of their malignancies thereafter. All 4 patients had originally presented with advanced cancers. Two had already had recurrence before hyperbaric oxygen Another patient had his irradiation delayed by 6 months after surgery as a result of pneumonia. Delayed initiation of radiation as an adjunct to surgery is well known to increase the likelihood of recurrence.

Finally, Marx48 has reported his follow-up of 245 patients who received hyperbaric oxygen for radiation injury. He compares this to another group of 160 patients treated by him for radiation injury but who did not receive hyperbaric treatments. Recurrence was decreased in the hyperbaric group from 19.6% compared to 28% in the non-hyperbaric group.

Those studies listed in Table 2 that report enhanced or accelerated tumor or metastatic growth after hyperbaric oxygen include a total of 72 patients. Those studies which show a neutral or tumor suppressive effect include more than 3,000 patients. The weight of clinical evidence available to us fails to give convincing support to concerns that hyperbaric oxygen enhances malignant growth.

IV. Angiogenesis

1. Introduction:

The coordinated steps needed for angiogenesis in wound healing and tumor growth are very complex and not yet completely understood. Recent medical discoveries begin to elucidate these very involved processes. This discussion is meant to present a synopsis of the presently understood mechanisms and to consider the effects of hyperbaric oxygen on tumor angiogenesis based on what we know and what we can postulate based on indirect evidence. Before we begin, stop to consider that angiogenesis is not only important in tumor growth and wound healing but also in myocardial ischemia and diabetic retinopathy. There is no ground swell of concern that hyperbaric oxygen is pathologically increasing angiogenesis in diabetic retinopathy or therapeutically enhancing angiogenesis in coronary artery disease. I suggest from the outset that each of these entities represents at least in part a unique pathophysiology with commonalties but also with important differences.

2. A Primer of Tumor Angiogenesis:

Tumor angiogenesis has become a very hot topic in Oncology over the past few years with the somewhat delayed popularization of the work of Judah Folkman, M.D. from Harvard. Since 1971 Dr. Folkman49 has proposed that tumor angiogenesis plays a key role for tumor growth and metastasis and that anti-angiogenic therapies should be pursued as strategies in the control and treatment of cancers. His work is now widely accepted in principle, and there are currently a number of different anti-angiogenic factors under study in Phase I, II and III clinical trials.50 These trials are directed at blocking tumor angiogenesis at multiple points along an involved and complex cascade of events that must come together to allow tumor angiogenesis to successfully progress. Without angiogenesis, tumor growth is restricted to 1 to 2 mm3 and metastases will not grow. (Dr.Folkman51 has estimated that every endothelial cell supports as many as 100 tumor cells).

3. Steps in the Angiogenesis Process: For tumor angiogenesis to occur a number of coordinated steps must successfully occur.52

Initially the basement membrane of existing blood vessels must be broken down along with their extracellular matrix. These actions are mediated by a class of enzymes called matrix metalloproteinases (MMP's). This breakdown of the basement membrane allows new branches to form off an existing blood vessel.

Andothelial cells must divide to form vascular tubules branching off from existing blood vessels. This process of endothelial cell division is regulated by a complex balance between growth factors and inhibitory factors. Once these endothelial cells have begun to proliferate, they must come together to form a closed tube.

i. Over a dozen growth factors have been identified which increase proliferation, survival and motility of endothelial cells. VEGF (Vascular endothelial growth factor) appears to have the most cell specific effect on endothelial cell mitosis. Acidic and basic fibroblast growth factors (aFGF and bFGF), epidermal growth factor (EGF), interleukin-8, and tumor necrosis factor alpha also play a prominent role. Endothelial surface proteins such as alphav, beta3 integrin and E-selectin increase the motility and survival of endothelial cells.
ii. Another group of circulating factors has also been identified which inhibit endothelial cell mitosis and motility. These include angiostatin, endostatin, interferons alpha and beta, platelet factor 4 (PF4), and thrombospondin-1. Several antagonists of the matrix metalloproteinases have also been identified. These include TIMP-1, TIMP-2 and TIMP-3 (tissue inhibitors of metalloproteinase).
iii. A final group of factors regulates the re-establishment of the basement membrane for the newly formed vascular tubules. These are not as well studied but are known to include the angiopoietins (ang-1 & ang-2).
iv. A group of receptors on the endothelial cells has also been identified with which both the inhibitory and angiogenic factors interact. These also represent potential targets for disruption of angiogenesis.

4. Summary of Tumor Angiogenesis:

The process of tumor angiogenesis is complex involving multiple discrete steps. Each of these may offer a separate potential strategy for disrupting the complex system of tumor vasculature and thus destroying a tumor or at least inhibiting its growth.

5. Two Compartment Model of a Tumor:

Dr.Folkman53 has suggested that in regard to angiogenesis, a tumor can be considered as composed of 2 compartments: 1) The tumor cell compartment and 2) the endothelial cell compartment. Each compartment is highly interdependent and each offers opportunities for therapeutic intervention.

i. The predominant environment of the tumor cell compartment is hypoxic, acidotic and hypoglycemic. Cancer cells are rapidly dividing and their hypermetabolic activity in a poorly vascularized region leads to anaerobic glycolysis with glucose depletion and lactic acid production. The elaboration and release of mitogenic growth factors including VEGF and bFGF occurs in this compartment. Hypoxia is known to upregulate the release of VEGF. These growth factors in turn stimulate a rapid proliferation of endothelial cells.
ii. Endothelial cells release growth factors including PDGF, interleukin-6 and IGF-1 (Insulin-like growth factor). These growth factors in turn stimulate proliferation and/or motility of tumor cells.

6. Angiogenesis in Wound Healing: the Role of Oxygen, A Brief Review

Wound healing like tumor angiogenesis requires complex multi-step interactions between cells, growth factors and the extracellular matrix. Angiogenesis is a major component of the wound healing process.54

The Process of Wound Healing: Dr. Knighton55 has suggested that the healing wound can also be approached as a 2 Compartment Model:

The wound space is the first compartment and comprises the regulatory compartment. Here, the environment is hypoxic, acidotic, hyperkalemic and hypercarbic. At the edge of the wound near the last perfused capillary, oxygen tensions are in the range of 40mmHg and go to 0 to 15mmHg at the center of the wound. In this hypoxic environment from the regulatory compartment a number of growth factors are elaborated that lead to angiogenesis.

i. These growth factors can be grouped into 3 major categories:
    a. Mitogens which signal cells to proliferate.
    b. Chemoattractants which lead cells including macrophages to migrate.
    c. Transforming growth factors which change the cellular phenotype. Many growth factors are both mitogens and chemoattractants.
ii. The mitogens include platelet derived growth factor (PDGF), epidermal growth factor (EGF) and several angiogenesis factors including acidic and basic fibroblast growth factors (aFGF and bFGF). In the wound space compartment, hypoxia and lactic acid stimulate both growth factor production and macrophage migration. In short order after wounding, macrophages are attracted into the wound space where they perform a dual role: 1) They engulf and destroy bacteria and other cellular debris in the wound and 2) They release many growth factors including angiogenesis factors. Just as in tumors, these factors must encourage endothelial cell migration, proliferation and basement membrane matrix production after new vascular tubes are formed.
iii. The chemoattractants include complement C5a which is chemotactic for neutrophils and PDGF which is chemotactic for fibroblasts.
iv. The final group of growth factors are the transforming growth factors. These growth factors are believed to stimulate production of matrix molecules, i.e. collagen and glycosoaminoglycans. In certain concentrations, they may inhibit fibroblast mitoses.

The second compartment in the 2 compartment model is the Responder Compartment which is composed of vascularized connective tissues and replaces the wound space as the wound heals. Here oxygen plays a crucial role in collagen synthesis, hydroxylation and cross linking. Oxygen is also necessary for epithelization.

7. Oxygen and Tumor Angiogenesis: What We Know and What We Can Surmise

Basic Principles: The similarities between tumor angiogenesis and wound healing are striking. Since we actively promote hyperbaric oxygen in part to promote angiogenesis as a component of successful wound healing, should we be concerned that it might also enhance angiogenesis in cancers? Should we refuse to treat a patient with cancer or even a remote history of cancer because we might activate an inactive cancer or its dormant metastases? These are valid questions, and though all of the mechanisms by which hyperbaric oxygen might enhance tumor angiogenesis are not known, the information that is available strongly suggests that hyperbaric oxygen is not likely to enhance tumor angiogenesis. In fact, we do know that tumor cells which grow and survive in hypoxic regions of the tumor are more aggressive, more prone to metastasis and more resistant to treatment. What are the specific considerations?

i. At this point in time, we only partially understand the mechanisms by which angiogenesis is enhanced by oxygen and shut down at the completion of wound healing. Well-oxygenated wounds do not have their healing accelerated by hyperbaric oxygen. The growth of malignancies including angiogenesis continues regardless of oxygen status. In other words, tumor angiogenesis is very different from angiogenesis in normal healing wounds at least in some very important ways.
ii. The intermittency of hyperbaric oxygen which increases oxygen tensions optimally to the range of 30 to 40 mmHg to stimulate collagen synthesis, hydroxylation and cross linking appears to be the key in HBO2 as an adjuvant to healing in chronic hypoxic wounds. No similar mechanisms have been identified in tumor stroma formation.
iii. Angiogenic growth factors elaborated in the wound require hypoxia and lactic acid.54 Some have suggested that macrophages, a major source of angiogenic factors in wounds, will continue to use anaerobic pathways of glycolysis even in the presence of oxygen at least for some time.54 It is widely accepted that normal levels of oxygen attained once the wound is healed and vascularized are the signal to discontinue further angiogenesis.54 It is likely that prolonged exposures to hyperbaric oxygen even if tolerable to the patient would have negative effects and ultimately inhibit healing. Consider the following quote from Davis et al56, 1988: Periodic elevation

of PO2 in relatively ischemic wounds has powerful effects on wound dynamics both by enhancing leukocyte bacterial killing and by providing fibroblast-collagen support for capillary angiogenesis factor provided by hypoxic macrophages during the 20-22 hours a day that wound PO2 drops to hypoxic levels."

Angiogenesis in wounds differ from cancers in several ways:

i. A wound necessarily involves negative space. Even in an approximated surgical wound, the healing process must generate new tissue to occupy this negative space. Tumors generally arise in space already occupied by existing tissues and are characterized by invasiveness. For tumors to grow they must release collagenases to dissolve basement membranes and dissolve normal tissue into which the cancer population of cells can invade and proliferate. Tumors are known to co-opt existing vessels and it is likely that they also co-opt pre-existing stroma.52 This obviates or at least reduces the need to generate collagen and other connective tissues de novo.
ii. The substance of the healed wound, i.e. the supporting connective tissues and the overlying epithelium are unlike malignant tumors in that their continued proliferation past healing is regulated by various feedback signals including contact inhibition.54 In the healed wound unbridled growth is not supported; whereas, it is the nature of malignant cell division that it does not respond to feedback signals from other cells and tissues and that its growth continues unabated.53
iii. Tumor vasculature is not well organized and does not conform to normal patterns (artery-arteriole-capillary-venule-vein).57 Tumors often contain giant capillaries and arteriovenous shunts without intervening capillaries. Blood sometimes flows from one vein to another. Leaks in these vessels often occur contributing to the well known and frequent phenomenon of peritumoral edema. In other words, tumor angiogenesis does not undergo maturation and integration with pre-existing vasculature in the same fashion as a successfully healed wound.

What is known about Tumor Angiogenesis/Growth/Metastasis and Oxygen

i. Hypoxia has been shown to be an intense stimulus for angiogenesis.54-56
ii. VEGF (Vascular Endothelial Growth Factor) has its elaboration and release upregulated by hypoxia.58-62 Numerous publications have demonstrated the increase of VEGF with hypoxia.58-VEGF is released by the tumor cell itself.52
iii. Interleukin-8 release is increased by hypoxia63 This phenomenon has been demonstrated in human glioblastoma cells in culture. IL-8 has been shown to have angiogenic properties in this model.
iv. PEDF (Pigment Epithelium Derived Factor) an angiogenic inhibitor is down regulated by hypoxia and upregulated by hyperoxia64. This effect was demonstrated in human retinoblastoma cells in culture.
v. Large scale DNA overreplication and gene (oncogene) amplification occurs in hypoxic regions of tumors.65 The frequency of mutations in tumor cells in hypoxic conditions was five fold those cells cultured in normoxic conditions. Teicher66 has suggested that the genetic instability demonstrated by tumor cells in hypoxic regions is likely to result in the development of drug resistance.
vi. Hypoxia selects for tumor cells with diminished potential for apoptosis.67 Apoptosis or programmed cell death is felt to be an important protection against malignancy since malignant cells become immortal and continue to divide indefinitely. Graeber et al67 have shown that hypoxia causes defects in apoptosis in oncogenically transformed Rat1 fibroblasts grown in tissue culture.
vii. Hypoxic tumors are resistant to radiation and some chemotherapy agents.66 Since the 1950's we have known that tumors with large populations of hypoxic cells are resistant to cell kill by ionizing radiation.68 More recent studies have shown that many chemotherapeutic agents have their efficacy reduced in areas of hypoxia. Teicher et al69 reported that 3 discrete types of chemotherapies exist in regard to their killing of cells related to the oxygen status of those cells. Type 1 agents are those which demonstrate diminished cell kill in regions of hypoxia; Type 2 agents selectively kill hypoxic cells; Type 3 chemotherapies kill cancer cells equally well in hypoxic and normoxic environments. Type 1 drugs include Bleomycin, Procarbazine, Actinomycin-D and

Vincristine. Rice et al70have reported that hypoxia leads to resistance to Methotrexate by enhancing the frequency of dihydrofolate reductase gene amplification in Chinese hamster ovary cells.

viii. Hypoxia has been shown to predict for tumor aggressiveness and metastatic potential. Hoeckel and associates71 have shown that patients with cervical cancer with significant regions of hypoxia have decreased survival. Gatenby et al72 have reported a higher likelihood of metastases in patients with hypoxic squamous cancers. Brizel and his associates73 reported that patients with larger fractions of hypoxic cells in their soft tissue sarcomas had worse survival and more common metastases than those who had higher oxygen levels in their tumors. For survival the break point was 10 mmHg and for metastases the favorable group had median oxygen values greater than 20 mmHg while the unfavorable group had oxygen levels less than 7.5 mmHg.

8. Summary of Considerations Related to Angiogenesis:

Many similarities exist between tumor and wound angiogenesis. Many important differences exist as well. Both require hypoxia for the release of angiogenic growth factors. In wounds, oxygen is needed for its immune effect and for the support it provides for fibroblastic proliferation, collagen release, hydroxylation and cross-linking. Oxygen is also needed for epithelization.54 Cancers co-opt blood supply initially from surrounding structures and may co-opt stroma as well.57 Certainly, those who have intensely studied tumor angiogenesis have not identified collagen production or release as part of the complex series of events needed to successfully generate tumor angiogenesis. Epithelial coverage is not a major component of cancer growth though it is vital for wound healing. Often cancers become ulcerated and do not have an epithelial cover. The preponderance of known characteristics of tumors shows with consistency that hypoxic tumor cells elaborate angiogenesis factors, grow more aggressively, throw off more metastases and are subject to decreased apoptosis and increased genetic instability and therefore increased drug resistance. Hypoxic cells are resistant to irradiation and some chemotherapies. Most importantly, the vast majority of published clinical experience and animal studies specifically designed to answer this issue show that neither the primary tumor nor metastatic deposits grow more aggressively when hyperbaric oxygen has been administered.

V. Final Conclusions:

The available published evidence strongly suggests that intermittent hyperbaric oxygen has no enhancing effect of cancer primary or metastatic growth. Likewise, there is no credible evidence that hyperbaric oxygen is an initiator or promotor of cancer de novo. Ample pre-clinical and clinical information have been reviewed. Animal studies specifically designed to study the impact of hyperbaric oxygen on malignant tumor growth and metastasis conducted from 1966 to 2001 fail in an overwhelming fashion to demonstrate a tumor growth enhancing effect. While 3 clinical publications entailing 72 patients suggest a possible cancer or metastases promoting effect, large numbers of mostly controlled studies including over 3,000 patients enrolled in trials designed to investigate hyperbaric oxygen as a radio-sensitizer demonstrate either a neutral or cancer inhibitory effect. Dr. Marx has followed 405 patients treated for delayed radiation injury and observed a decreased incidence of recurrence in those patients treated with hyperbaric oxygen. The possibility that significant immune suppression, free radical induced damage or mutations leading to carcinogenesis is likely to enhance malignant growth in hyperbaric patients is not well supported by the reviewed literature. Finally, contentions that tumor angiogenesis is likely to be promoted by hyperbaric oxygen in the same fashion that angiogenesis is promoted in non-healing hypoxic wounds fail to recognize the unique nature of those processes in these very different physiologic and pathophysiologic systems. Most recent evidence supports the findings that tumors which thrive in hypoxic environments are more prone to a rapid aggressive course including resistance to treatment, increased incidence of metastases, decreased cell death due to apoptosis and a higher likelihood of tumor lethality.

The author proposes that patients for whom hyperbaric oxygen treatments are likely to be useful for the treatment of radiation injuries should not have this therapy denied to them because of unsubstantiated fears that hyperbaric oxygen might cause a higher likelihood of tumor recurrence or metastases.

References

1. Johnson RJR, Lauchlan SC. Epidermoid carcinoma of the cervix treated by 60Co therapy and hyperbaric oxygen. Proceedings of the third international congress on hyperbaric medicine. 1966;648-652.
2. Feldmeier JJ, Heimbach RD, Davolt DA, Brakora MJ. Hyperbaric oxygen and the cancer patient: A survey of practice patterns. Undersea Hyper Med 1993;20(4):337-345.
3. Kalns J, Krock L, Piepmeier E. The effect of hyperbaric oxygen on growth and chemosensitivity of metastatic prostate cancer. Anticancer Res 1998;18:363-367.
4. Feldmeier JJ, Onoda JM, Bossung DE, Court WS, Alecu R. Effect of Hyperbaric oxygen on cancer cell metastatic potential and proliferation.(abs) Undersea Hyper Med 1997;24(supl):125.
5. Xu X, Yi H, Suzuki H, Kobayashi S, takahashi H, Nakashima I. Differential sensitivities to hyperbaric oxygen of lymphocyte subpopulations of normal and autoimmune mice. Immunology Letters 1997;59:79-84.
6. Brenner I, Shephard RJ, Shek PN. Immune function in hyperbaric environments, diving and decompression. Undersea Hyper Med 1999;26:27-39.
7. Feldmeier JJ, Boswell RN. Brown M, Shaffer P. The effects of hyperbaric oxygen on the inununological status of healthy human subjects. In: Kindwall EP. ed. Proceedings of the eighth international congress on hyperbaric medicine. San Pedro, CA: Best Publishing Co, 1987:41-46.
8. Kaelin CM, Im MJ, Myers RAM, Manson PN, Hoopes JE. The effects of hyperbaric oxygen on free flaps in rats. Arch Surg 1990; 125:607-609.
9. Zamboni WA, Roth AC, Russel RC, NemiroffPM, Casas L, Smoot EC. The effects of acute hyperbaric oxygen therapy on axial pattern skin flap survival when administered during and after total ischemia. J Reconstr Microsurg 1989; 5:343-347.
10. Monstrey SJ, Mullick P, Narayanan K, Ramasastry SS. Hyperbaric oxygen therapy and free radical production: an experimental study in doxorubicin (Adriamycin) extravasation injuries. Annals of Plastic Surgery 1997;38(2): 163-168.
11. Elayan IM, Axley MJ Prassad PV, Ahlers ST Auker CR. Effect of hyperbaric oxygen treatment on nitric oxide and oxygen free radicals in rat brain. Journal of Neurophysiology 2000;83(4):2022-2029.
12. Ceruti PA. Prooxidant states and tumor promotion. Science 1985;227(4685):375-381.
13. Heston WE, Pratt AW. Effect of concentration of oxygen on occurrence of pulmonary tumors in strain A mice. J Nat Cancer Inst 1959;22:707-717.
14. Sturrock JE, Nunn JF. Chromosomal damage and mutations after exposure of Chinese hamster cells to high concentrations of oxygen. Mutation Res 1978;57:27-33.
15. Dennog C, Gedik C, Wood S, Speit G. Analysis of oxidative DNA damage and HPRT mutations in humans after hyperbaric oxygen treatment. Mutation Research 1999;431(2):351-359.
16. Rothfuss A, Merk O, Radermacher P, Speit G. Evaluation of mutagenic effects of hyperbaric oxygen (HBO) in vitro II. Induction of oxidative DNA damage and mutations in the mouse lymphoma assay. Mutation Research 2000;471: 87-94.
17. Bruyninckx WJ, Mason HS, Morse SA. Are physiologic oxygen concentrations mutagenic? Nature 1978; 274: 606-607.
18. McCredie JA, Inch WR, Kruen J, Watson T A. Effects of hyperbaric oxygen on growth and metastases of the C3H BA tumor in the mouse. Cancer 1966; 19:1537-1542.
19. Suit HD, Smith J, Suchato C. Effect of daily exposure to high pressure oxygen on tumor growth. Am J Roentgenol1966; 97:1019-1022.
20. DeCosse 11, Rogers LS. Effect of hyperbaric oxygen and cancer chemotherapy on growth of animal tumors. Cancer Res 1966; 26:287-291.
21. Johnson RE, Kagan AR, Bryant TL. Hyperbaric oxygen effect on experimental tumor growth. Radiology 1967; 88:775-777.

22. Dettmer CM, Kramer S, Gottlieb SF, Aponte GE, Driscoll MA. The effect of increased oxy- gen tensions upon animal tumor growth. JNCI 1968; 41:804-810.
23. Evans JC. Metastasis following radiotherapy in hyperbaric oxygen Radiol 1971; 22:538-540.
24. Feder B B, Stein JJ, Smith TK, Schaeflein JW, Boutelle JL, Conroy RM. The effect of hyperbaric oxygen on pulmonary metastases in C3H mice. Radiology 1968; 90: 1181-1184.
25. Johnson RJR, Wiseman N, Lauclan SC. The effect of hyperbaric oxygen on tumor metastases in mice. Clin Radiol 1971; 22: 538-540..
26. Shewell J, Thompson SC. The effect of hyperbaric oxygen treatment on pulmonary metastasis in the C3H mouse. Eur J Cancer 1980; 16:253-259.
27. Marx RE, Johnson RP. Problem wounds in oral and maxillofacial surgery; the role of hyperbaric oxygen. In: Problem Wounds-The Role of oxygen. JC Davis and TK Hunt (Eds.) New York, Elsevier, 1988; Chapter 4: 107-109.
28. Frid IA, Sapov IA, Katyshev AV, Lupanov AI, Rudakov VF, Semiachkina SO, Shul'ga NI. Effects of hyperbaric oxygenation on tumor growth. Vopr Onkol 1989; 35(8): 970-973.
29. McMillan T, Calhoun KH, Mader JT, Stiernberg CM, Rajarman S. The effect of hyperbaric oxygen on oral mucosal carcinoma. Laryngoscope 1989; 99:241-244.
30. Mestrovic J, Kousta D, Gosovic S, Denoble P, Radojkovic M, Angjelinovic S, Basic I, Marusic M. Suppression of rat tumor colonies in the lung by oxygen at high pressure is a local effect. Clin Exp Metastasis 1990; 8(2): 113-119.
31. Headley DB, Gapany M, Dawson DE, Kruse GD, Robinson RA, McCabe BF. The effect of hyperbaric oxygen on growth of human squamous cell carcinoma xenografts. Arch Otolaryngol Head Neck Surg 1991; 117(11): 1269-1272.
32. Sklizovic D, Sanger JR, Kindwall EP, Fink JG, Grunert BK, Campbell BH. Hyperbaric oxygen therapy and squamous cell carcinoma cell line growth. Head Neck 1993; 15 (3): 236-240.
33. Lyden E Granstrom G, Cvetkovska E, Nilsson J, Westin T, Edstrom S. Cell proliferative modulation of MCG 101 sarcoma from mice exposed to hyperbaric oxygenation. Undersea Hyperb Med 1997; 24: 123-129.
34. Takiguchi N, Saito N, Nunomura M, Kouda K, Oda K, Furuyama N, Naksjima N. Use of 5-FU plus hyperbaric oxygen for treating malignant tumors: evaluation of antitumor effect and measurement of 5-FU in indivdual organs. Cancer Chemother Pharmacol 2001; 47(1): 11-14.
35. VandenBrenk HAS, Madigan JP, Kerr RC. An analysis of the progression and development of metastases in patients receiving x-radiation in hyperbaric oxygen. Clin Radiol 1967; 18:54-61.
36. Cade IS, McEwen JB. Megavoltage radiotherapy in hyperbaric oxygen. Cancer 1967; 20:817-821.
37. Johnson RJR, Walton RJ. Sequential study of the effect of the addition of hyperbaric oxygen on the 5-year survival rates of carcinoma of the cervix treated with conventional radiation fractions. Am J Roentgenol Radium Ther Nucl Med 1974; 120:111-117.

38. Henk JM, Kunkler PB, Smith CW. Radiotherapy and hyperbaric oxygen in head and neck cancer: final report of first controlled clinical trial. Lancet 1977; July:101-103.
39. Henk JM, Kunkler PB, Smith CW. Radiation therapy and hyperbaric oxygen in head and neck cancer: interim report of second clinical trial. Lancet 1977; Ju1y:104-108.
40. Bennett MB, Sealy R, Hockly J. The treatment of stage III squamous cell carcinoma of the cervix in air and in hyperbaric oxygen. In: Smith G, ed. Proceedings of the sixth international congress on hyperbaric medicine. Scotland: Aberdeen University Press, 1977:247-252.
41. Perrins DJD, Wiernik G. Controlled trials in carcinoma of the bladder. In: Smith G, ed. Proceedings of the sixth international congress on hyperbaric medicine. Scotland: Aberdeen University Press, 1977:253-258.
42. Watson ER, Halnan KE, Dische S, et al. Hyperbaric oxygen and radiotherapy: a medical research council trial in carcinoma of the cervix. Br J Radiol 1978; 51: 879-887.

43. Dische S. Hyperbaric oxygen. The medical research council trials and their clinical significance. Br J Radio11979; 51:888-894.
44. Brady LW, Plenk HP, Hanley JA, Glassburn JR, Kramer S, Parker RG. Hyperbaric oxygen therapy for carcinoma of the cervix stages IIB, IlIA, IIIB, and IV A. Results of a randomized study by the radiation therapy oncology group. Int J Radiat Oncol Biol Phys 1981; 7: 991-998.
45. Eltorai I, Hart GB, Strauss MB, Khonsari F, Montroy RE. Does hyperbaric oxygen provoke an occult carcinoma in man? In: Kindwall EP, ed. Proceedings of the eighth international congress on hyperbaric medicine. San Pedro, CA: Best Publishing, 1987:18-29.
46. Denham W, Yeoh EK, Ward GG, Ahmad AS, Harvey NDM. Radiation therapy in hyperbaric oxygen for head and neck cancer at Royal Adelaide Hospital-1964-1969. Int J Radiat Oncol Biol Phys 1987; 13: 201-208.
47. Bradfield JJ, Kinsella JB, Mader JT, Bridges EW, Calhoun KH. Rapid progression of head and neck squamous carcinoma after hyperbaric oxygen. Otolaryngol Head Neck Surg 1996; 114: 793-797.
48. Marx RE. Radiation injury to tissue. In: Kindwall EP, Whelan HT (eds) Hyperbaric Medicine Practice (Second Edition). Flagstaff, AZ: Best Publishing Co., 1999; 720.
49. Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med 1971; 285: 1182-1186.
50. Jones, PH and Harris, AI. The Current Status of Clinical Trials in Anti-angiogenesis PPO Updates, Principles and Practice of Oncology 2000; 14(1):1-9.
51. Folkman, J. Fighting Cancer by Attacking its Blood Supply. Scientific American, September 1996, 150-154.
52. Folkman,J. Tumor angiogenesis In: Cancer Medicine 4th Edition Holland, Frei, Bast, Kufe, Morton and Weichselbaum eds, Williams&Wilkins, Baltimore, 1997, 181-204.
53. Folkman,J. Antiangiogenic Therapy In: Cancer: Principles and Practice of Oncology, Devita, VT, Hellman, S, Rosenberg, S eds. Lippincott-Raven, Philadelphia, 1997:3075-3085.
54. Hunt TK. The physiology of wound healing. Annals of Emergency Medicine 1988; 17: 1265-1273.
55. Knighton,DR. Mechanisms of Wound Healing In: Hyperbaric Medicine Practice, Kindwall, EP ed., Best, Flagstaff, 1995, 119-140.
56. Davis, JC, Buckley CJ, Barr PO. Compromised Soft Tissue Wounds:Correction of Wound Hypoxia In:Problem Wounds:The Role of Oxygen, Davis, JC and Hunt, TK eds. Elsevier, New York, 1988, 143-152.
57. Connolly JL, Scnitt SJ, Wang HH, Dvorak AM, Dvorak HF. Principles of cancer pathology. In: Cancer Medicine 4th Edition Holland, Frei, Bast, Kufe, Morton and Weichselbaum eds, Williams&Wilkins, Baltimore, 1997, 533-555.
58. Shweiki D, Itin A, Soffer, Keshet E. Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis, Nature, 1992;359:843-848.
59. Minchenko A, Bauer T, Salceda S, Caro J. Hypoxic stimulation of vascular endothelial growth factor expression in vitro and in vivo, Lab Invest, 1994;71:374-379.
60. Mulkhapadhyay D, Tsiokas L, Zhou X-MZ, Foster D, Brugge JS, Sukahatme VP. Hypoxic induction of human vascular endothelial growth factor through c-Src activation. Nature 1995;375:577-581.
61. Leith JT, Michelson S. Secretion rates and levels of vascular endothelial growth factor in clones of HCT-8 human colon tumour cells as a function of oxygen concentration. Cell Prolif 1995; 28: 415- 430.
62. Chiarotto JA and Hill RP. A quantitative analysis of reduction in oxygen levels required to induce up-regulation of VEGF mRNA in cervical cancer cell lines, British Journal of Cancer, 1999; 80(10):1518-1524.
63. Desbaillets I, Diserens A, Tribolet N, Hamou M, Van Meir EG. Regulation of interleukin-8 expression by reduced oxygen pressure in human glioblastoma. Oncogene 1999; 18: 1447-1456.
64. Dawson DW, Volpert OV, Gillis P, Crawford SE, Xu H-J, Benedict W, Bouck NP. Pigment epithelium-derived factor: a potent inhibitor of angiogenesis. Science 1999;285:245-248.
65. Reynolds TY, Rockwell S, Glazer PM. Genetic instability induced by the tumor microenvironment, Cancer Research 1996;56:5754-5757.

66. Teicher BA. Physiologic mechanisms of therapeutic resistance: blood flow and H ypoxia. Hematology/Oncology Clinics of North America 1995;9:475-506.
67. Graeber TG, Osmanian C, Jacks T, Housman DE, Koch CJ, Lowe SW, Giaccia AJ. Hypoxia-mediated selection of cells with diminished apoptotic potential in solid tumors. Nature, 1996;379:88-91.
68. Churchill-Davidson I. The oxygen effect in radiotherapy-historical review. Front Radiat Ther Onc 1968; 1:1-15.
69. Teicher BA, Lazo JS, Sartorelli AC. Classification of antineoplastic agents by their selective toxicities toward oxygenated and hypoxic cells. Cancer Research 1981; 41: 73-81.
70. Rice GC, Hoy C, Schimke RT. Transient hypoxia enhances the frequency of dihydrofolate reductase gene.amplification in Chinese hamster ovary cells, Proc Natl Acad Sci, 1986;83:5978-5982.
71. Hoeckel M, Knoop C, Schlenger K, Vorndran B Knapstein PG, Vaupel P. Intratumoral pO2 predicts survival in advanced cancer of the uterine cervix. Oxygen Transport to Tissue XV. Vaupel P (ed.) Plenum Press, New York. 1994: 445-450.
72. Gatenby RAA, Kessler HBB, Rosenblum JSS, Coia LRR, Moldofsky PJJ, Hartz WHH, Broder GJJ. Oxygen distribution in squamous cell carcinoma metastases and its relationship to outcome of radiation therapy, Int J Radiat Oncol Bio Phys 1988;14:831-838.
73. Brizel DM et al. Tumor oxygenation predicts for the likelihood of distant metastases in human soft tissue sarcoma, Cancer Research, 1996;56:941-943.

Cancer and Hyperbaric Oxygen Therapy. Green is the medical Color for Oxygen!

A study of the effect of Hyperbaric Oxygenation of Yoshida Sarcoma: Especially on its Influence on the Generation Time.
Osada, T. Nagoya J. Med. Sci. 31, 1968: 243-276.
“HBO at 3 ATA suppressed the mitosis of its cells and potentiated the mitosis suppression by alkylating agents and impairment of DNA synthesis; HBO has an additive effect to chemotherapeutic agents.”

Oxygen Poisoning and Tumor Growth.
Campbell, J.A. Br. J Expl. Path. 18; 1937: 191-197.
"Tumors in rodents were not altered.”

Hyperbaric Oxygen in Experimental Cancer in Mice.
Kluft, O., Boerema, I. Cl. Appl. of Hyperbaric Oxygen. Cited by McCredie, 1966.
“Growth of an allogenic tumor in the mouse was inhibited. Distant metastases were decreased.”

Effects of Hyperbaric Oxygen on Growth and Metastses of the C3HBA Tumor in the Mouse
McCredie, J.A., Inch, W.R., Kruuv, J., Watson, T.A. . Cancer, 19; 1966; 1537-1542.
”Found no effect on tumor growth nor on the incidence of lung metastases. "The results suggest that the clinical use of HBO is unlikely to increase the rate of cancer growth or the incidence of metastases."

The Effect of Hyperbaric Oxygen on Pulmonary Metastases in C#H Mice.
Feder, B.H., Stein, J.J., Smith, T.K., Schaeflein, J.W., Boutelle, J.L., Conroy, R.M. Radiology, 90:6, 1968: 1181-1184.
”HBO does not enhance the growth rate of distant metastases from C3H implanted tumor.”

Effects of Breathing Gases Containing Oxygen and Carbon Dioxice at 1 and 3 Atmospheres Pressure on Blood Flow and Oxygenation of Tumors.
Kruuv, J., Inch, W.R., McCredie, J.A. Can. J. Physiol. Pharmacol., 45; 1967: 49-56.
”Oxygenation was often improved in the anoxic areas of the tumor in animals breathing O2 at 1 ATA and almost all those at 3 ATA”

Effecto of Duration of Breathing 95% Oxygen plus 5% Carbon Dioxide Before X-irradiation on Cure of C3H Mammary Tumor
Inch, W.R., McCredie, M.A., Sutherland, R.M. Cancer, 25:4; 1970; 926- 931.
“Increased X-Ray Therapy Cure Rate Combined with O2 inhalation.”

Hyperbaric Oxygen and Radiotherapy: A medical research council trial in carcinoma of the cervix
Watson, E.R., Halnan, K.E., Dische, S., Sanders, M.I., Cade, I.S., McEwen, J.B., Wiernik, G., Perrins, D.J., Sutherland, I. .Br. J. Radiol., 51:611, 1978: 879-887.
“Favorable synergistic action of HBO and radiotherapy especially in cancer of the cervix and the head and neck but not the bladder.”

Carcinoma of cervix with severe anemia: Treatment by radiotherapy without blood transfusion using hyperbaric oxygen.
Dische, S., Hewitt, H.B. Br. J. Radiol, 45:539, 1972: 848-850.
“Reported on the use of HBO and radiotherapy on recurrent cancer of the colon and rectum with symptomatic improvement in some cases.”

Does Hyperbaric Oxygenation provoke an Occult Carcinoma in Man?
Ward, et al. Cited by EItorai, I. et al Proceedings of the Eighth International Congress on Hyperbaric Medicine. 1987.
”HBOT was beneficial to cancers in certain cites when combined with radiation, viz.: larynx, salivary glands, tongue, palate, floor of mouth”

High-dose effects in the treatment of carcinoma of the bladder under air and Hyperbaric Oxygen Conditions.
Kirk, J., Wingate, G.W., Watson, E.R. Clin. Radiol. 27:2, 1976: 137-144.
“One third of patients with cancer of the bladder with radiotherapy under HBOT showed high dose effects.”

Radiotherapy and Hyperbaric Oxygen in head and neck cancer. Final report of first controlled clinical trial.
Henk, J.M., Kunkler, P.B., Smith, C.W. Lancet, 2:8028, 1977: 101-103.
“Survival and local recurrence-free rates significantly higher in head and neck cancer when given radiotherapy under HBO.”

Henk, J.M., Smith, C.W. Radiotherapy and Hyperbaric Oxygen in Head and Neck Cancer.
Interim report of 2nd clinical trial. Lancet, 2:8029, 1977: 104-105
Survival and local recurrence-free rates significantly higher in head and neck cancer when given radiotherapy under HBOT.

Does Hyperbaric Oxygenation Provoke an Occult Carcinoma in Man?
Eitorai, I. et al. Proceedings of the Eighth International Congress on Hyperbaric Medicine. 1987.
“HBOT plays some role in sensitizing certain tumors to radiotherapy.”

Hyperbaric Oxygen— An Effective Tool to Treat Radiation Morbidity in Prostate Cancer

Radiother Oncol 2001 Nov;61(2):151-6 (ISSN: 0167-8140)
Mayer R; Klemen H; Quehenberger F; Sankin O; Mayer E; Hackl A; Smolle-Juettner FM
Department of Radiotherapy, University Medical School of Graz, Auenbruggerplatz 32, A-8036 Graz, Austria.

PURPOSE:

We report the results of hyperbaric oxygen therapy (HBO) used in the treatment of radiation cystitis and proctitis following irradiation of prostate cancer.

MATERIALS AND METHODS:

Between June 1995 and March 2000, 18 men (median age 71 years) with radiation proctitis (n=7), cystitis (n=8), and combined proctitis/cystitis (n=3) underwent HBO therapy in a multiplace chamber for a median of 26 sessions (range 2-60). The treatment schedule (2.2-2.4 atmospheres absolute, 60 min bottom time, once-a-day, 7 days a week) was set at a lower limit of 20 sessions; the upper limit was left open to symptom-related adjustment. Prior to HBO treatment, RTOG/EORTC late genitourinal (GU) morbidity was Grade 2 (n=3), Grade 3 (n=6) or Grade 4 (n=2); modified RTOG/EORTC late gastrointestinal (GI) morbidity was either Grade 2 (n=4) or Grade 3 (n=6).

RESULTS:

Sixteen patients underwent an adequate number of sessions. RTOG/EORTC late GU as well as modified GI morbidity scores showed a significant improvement after HBO (GI, P=0.004; GU, P=0.004; exact Wilcoxon signed rank test); bleeding ceased in five out of five patients with proctitis and in six out of eight patients with cystitis; one of those two patients, in whom an ineffective treatment outcome was obtained, went on to have a cystectomy.

CONCLUSIONS:

HBOT treatment seems to be an effective tool to treat those patients with late GI and GU morbidity when conventional treatment has led to unsatisfactory results. Particularly in patients with radiation cystitis, HBOT should not be delayed too long, as in the case of extensive bladder shrinkage improvement is hard to achieve.

Successful Treatment of Radiation-Induced Brain Necrosis by Hyperbaric Oxygen Therapy

Neurol Sci 2003 May 15;209(1-2):115-7 (ISSN: 0022-510X)
Kohshi K; Imada H; Nomoto S; Yamaguchi R; Abe H; Yamamoto H
Department of Neurosurgery, School of Medicine, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, 807-8555, Kitakyushu, Japan.

We describe a 68-year-old man who underwent Hyperbaric Oxygen (HBOT) therapy to manage radiation necrosis of the brain, which developed after two treatments with stereotactic radiosurgery (SRS) to the same lesion. The necrosis was subsequently treated with steroids alone for 2 months; however, he progressed clinically and radiographically. Improvement again was noted with the reinstitution of HBO therapy.

This case suggests that HBO therapy is an important therapeutic option in the treatment of brain radiation necrosis caused by SRS.

New Strategy for Attacking Brain Tumors

The Cincinnati Post (Cincinnati, OH); 6/18/2004; Wood, Roy

The concept of increasing atmospheric pressure to heal ailments dates to the 1600s.

Now, University of Cincinnati researchers and doctors at University Hospital are studying the use of hyperbaric chambers for treating brain tumor patients suffering potentially fatal side effects from brain radiation therapy.

"These patients don't have a whole lot of options," says Dr. Laurie Gesell, director of the Division of Hyperbaric Medicine in the UC's Department of Emergency Medicine, who's leading the study.

"They have a devastating disease, they have a brain tumor, which has significant morbidity associated with it," she said. "They then get treated aggressively to try to treat that horrific disease.

"They end up with a complication that can have just as much significant morbidity or mortality as the disease itself."

Gesell is working with University Hospital's new Brain Radionecrosis Center, the only facility in the country participating in the two-year, $450,000 study. It's funded by the National Cancer Institute, through the National Institutes of Health.

Gesell explains the problem this way.

When patients are diagnosed with brain tumors, typical treatment includes radiation therapy, chemotherapy, or surgery.

That often leads to a usually treatable brain radiation injury.

Soft-tissue injury to the brain begins with swelling that sometimes disappears without treatment. So when it's first diagnosed, doctors might just watch it, Gesell says.

If patients start showing clinical symptoms, they're put on steroids.

"If the steroids don't control the progressive injury pattern, the dose of the steroids will increase and increase and increase," Gesell says.

"But there are complications and side effects from the steroids, which can be just as devastating for individuals' health," she said.

"If the steroids don't work in controlling this disease, the only thing really left out there as a standard of care is to go in and surgically cut out that portion of the brain.

"But lots of brain tumors are in areas where you can't do surgery because they're too far down or in areas where it's too risky to do surgery."

Furthermore, the incidence seems to be increasing because of the aggressiveness with which doctors are trying to treat brain tumors, she says.

Although more study needs to be done to determine how many people develop side effects from brain radiation therapy, about 200,000 people a year in the United States are diagnosed with either primary or secondary brain tumors, says Gesell.

"Physicians have become more aggressive in treating these brain tumors in order to get better outcomes for their patients," Gesell says.

"That also means that the incidence of problems and complications from the radiation has also increased."

Knowing that hyperbaric oxygen treatment is the standard of care for conditions such as carbon monoxide poisoning, hard-to-heal wounds, crush injuries, decompression sickness and a host of other conditions, doctors at University began using hyperbaric treatments on the patients with the conciliation -- known as brain radionecrosis -- about six years ago.

The treatment involves placing the patient in a pressure chamber and having the patient breathe pure oxygen at a pressure similar to being under 33 to 66 feet of seawater, Gesell says. Each treatment lasts 1 1/2 hours.

Treatments are repeated every day for one to three months.

Preliminary results are promising, Gesell says. In many patients, damaged tissues have been healed completely.

In about 86 percent of cases, doctors were able to stabilize or decrease the steroids dosage. In some cases, patients even were able to stop taking steroids.

MRIs showed that the disease had stabilized or improved in 78 percent of patients, Gesell says.

Armed with the results, doctors applied for the funding for the current study.

Doctors believe the pure oxygen at increased pressure causes new blood vessels to grow in injured tissue, but no one is sure exactly how, says Gesell.

Gesell and her team of researchers at UC and the Neuroscience Institute set up the Brain Radionecrosis Center to study not only how well hyperbaric oxygen therapy works, but also the mechanism that enables it to work.

Her collaborators in the research are Christopher Lindsell of the Institute for Health Policy and Health Services Research at UC; Dr. Ronald Warnick, a neurosurgeon with the Mayfield Clinic and the Neuroscience Institute and professor of neurosurgery at UC; and Dr. John Breneman, a neuro-radiologist with institute and professor of radiation oncology and neurosurgery at UC.

The initial study, known as a pilot trial, will involve only 30 patients, but researchers have already been receiving calls from all over the nation, Gesell says.

If the treatment proves to be as effective as preliminary findings indicate, the team expects to expand its study into a multi-center trial involving a large number of patients.

That ultimately could lead to the establishment of hyperbaric oxygen therapy as the main treatment for patients with brain radionecrosis.

Chemo Brain Response To HBOT

William S. Maxfield, MD, FACNM
National Hyperbarics, Inc.
34918 US Hwy. 19 North
Palm Harbor , Florida 33684

A 56-year old woman was diagnosed in 1993 with breast cancer. She had a lumpectomy followed by six weeks of radiation therapy and six months of chemotherapy with Cytoxan, methotrexate, and fluorocuracil. Tamoxifen therapy was given for five years. Shortly after starting chemotherapy, she noted a gradual and progressive memory impairment with confusion, poor ability to recall recent events and understand information provided to her. She had a tendency to misplace her possessions and lost interest in many of the activities she had participated in previously, including playing bridge. Her reading comprehension deteriorated and she no longer was able to cook many of the dishes that she had prepared in the past. Because of the cognitive defect, she had to stop working in 1996. The patient was evaluated for HBOT on 04-05-02 . She received 20 treatments of hyperbaric oxygen therapy (HBOT) for 1 hour at full pressure of 1.5 ATA. At her last evaluation on 07-08-02 , the patient reported that there had been significant improvement in her memory and she was no longer in a “fog”. There was significant improvement in her ability to analyze and think out tasks that she needed to perform which she could not do before HBOT. Due to her memory improvement she has been able to return to work for the first time in six years

Fish Oil Helps Cancer Patients

May prevent weight loss and wasting in those with disease

WEDNESDAY, Sept. 10 (HealthDayNews) -- Fish oil may help prevent cachexia, the severe wasting and weight loss experienced by people with some types of advanced cancer, says a British study in the current issue of Gut.

Cachexia, a result of changes in metabolism and loss of appetite, is a major factor in the illness and death of patients with advanced cancer.

This study included 200 people with pancreatic cancer. A high-calorie, high-protein supplement was given to 105 of the patients, while 95 of them received an energy-dense, high-protein supplement enriched with omega 3 essential fatty acid and vitamins E and C. Each group drank 480 milligrams a day for eight weeks.

Omega 3 essential fatty acids are found in fatty fish such as salmon and herring.

Before the study, the patients had lost about 17 percent of their body weight and were losing more than 3 kilograms of weight a month. After eight weeks of taking the supplements, weight loss had stopped in both groups.

When they examined the data more closely, the researchers found a direct and significant association between the amount of weight and muscle bulk gained and the amount of fish oil supplement consumed by patients.

This association was not found in the patients taking the supplement without the fish oil.

Patients taking the fish oil supplement also reported a much improved quality of life.

The authors write that further research is necessary to confirm their findings.

Scan Detects Oxygen Levels in Tumors

April 23 (HealthDay News) -- New research suggests that scientists are close to developing a simple way to measure oxygen levels in tumors, giving doctors a heads-up about what kind of treatment is best for individual patients.

The findings fit into an emerging trend of individualized treatment for patients with cancer instead of treating people the same way, said Dr. Mark Dewhirst, a professor of radiation oncology at Duke University Medical Center.

"If successful, [the trend] will revolutionize the way that we treat cancer," said Dewhirst, who co-wrote a commentary accompanying the new study, published April 22 in the Journal of Clinical Investigation.

Scientists began realizing the important role of oxygen in tumors about 50 years ago, said study co-author James Mitchell, branch chief of radiation biology at the U.S. National Cancer Institute's Center for Cancer Research. The scientists discovered that tumors with higher concentrations of oxygen were more susceptible to radiation, he said.

"Radiation damages cells by causing damage to DNA, and one particular type of damage renders the DNA molecule non-reparable," Mitchell said. But less oxygen in the tumor allows tumor cells to survive more easily by making the DNA destruction process more difficult, he said.

According to Dewhirst, the same is true for chemotherapy drugs, which also don't work as well when tumors have less oxygen.

Lower levels of oxygen create other problems, Dewhirst. "One would think at first that lack of oxygen would make tumors unhealthy and easy to kill," he said. "But actually, the opposite happens -- tumor cells that lack oxygen become more aggressive and more difficult to kill."

Tumors with lower oxygen levels even spread more easily through the body, he said.

Doctors can check oxygen levels in patients by inserting a needle. But doctors can't insert needles into some patients, and. in others, it's difficult to insert the needle deep enough, Mitchell said.

In the new study, the researchers tested a scanning technique called pulsed electron paramagnetic resonance imaging and used it in tandem with magnetic resonance imaging. The study authors said they were able to successfully measure oxygen levels in tumors in mice by using the non-invasive technology.

"The imaging that is described in this study provides all of the information necessary to evaluate oxygen levels in tumors as well as to examine underlying causes for the lack of oxygen," Dewhirst said. "The fact that all of the imaging is completely non-invasive provides the ability to perform this measurement more than once, (meaning) this could be used to monitor the effectiveness of cancer therapy."

There are caveats, however. The research hasn't reached the human testing level yet, and it may not work in people. "Scaling up the method to make it suitable for use in humans will be a significant challenge, but not impossible," Dewhirst said.

For now, the plan is to launch more studies with animals to see if the technique works as a way to test cancer drugs.

SOURCES: Mark W. Dewhirst, DVM, Ph.D., Gustavo S. Montana professor of radiation oncology and professor of pathology and biomedical engineering, Duke University Medical Center, Durham, N.C.; James Mitchell, Ph.D., branch chief, radiation biology, Center for Cancer Research, U.S. National Cancer Institute, Bethesda, Md.; April 22, 2008, Journal of Clinical Investigation

Hyperbaric Oxygenation - New Strategy for Attacking Brain Tumors

The concept of increasing atmospheric pressure to heal ailments dates to the 1600s.

Now, University of Cincinnati researchers and doctors at University Hospital are studying the use of hyperbaric chambers for treating brain tumor patients suffering potentially fatal side effects from brain radiation therapy.

"These patients don't have a whole lot of options," says Dr. Laurie Gesell, director of the Division of Hyperbaric Medicine in the UC's Department of Emergency Medicine, who's leading the study.

"They have a devastating disease, they have a brain tumor, which has significant morbidity associated with it," she said. "They then get treated aggressively to try to treat that horrific disease.

"They end up with a complication that can have just as much significant morbidity or mortality as the disease itself."

Gesell is working with University Hospital's new Brain Radionecrosis Center, the only facility in the country participating in the two-year, $450,000 study. It's funded by the National Cancer Institute, through the National Institutes of Health.

Gesell explains the problem this way.

When patients are diagnosed with brain tumors, typical treatment includes radiation therapy, chemotherapy or surgery. That often leads to a usually treatable brain radiation injury. Soft-tissue injury to the brain begins with swelling that sometimes disappears without treatment. So when it's first diagnosed, doctors might just watch it, Gesell says.

If patients start showing clinical symptoms they're put on steroids. "If the steroids don't control the progressive injury pattern, the dose of the steroids will increase and increase and increase," Gesell says. "But there are complications and side effects from the steroids, which can be just as devastating for individuals' health," she said. "If the steroids don't

work in controlling this disease, the only thing really left out there as a standard of care is to go in and surgically cut out that portion of the brain.

"But lots of brain tumors are in areas where you can't do surgery because they're too far down or in areas where it's too risky to do surgery."

Furthermore, the incidence seems to be increasing because of the aggressiveness with which doctors are trying to treat brain tumors, she says.

Although more study needs to be done to determine how many people develop side effects from brain radiation therapy, about 200,000 people a year in the United States are diagnosed with either primary or secondary brain tumors, says Gesell.

"Physicians have become more aggressive in treating these brain tumors in order to get better outcomes for their patients," Gesell says.

"That also means that the incidence of problems and complications from the radiation has also increased."

Knowing that hyperbaric oxygen treatment is the standard of care for conditions such as carbon monoxide poisoning, hard-to-heal wounds, crush injuries, decompression sickness and a host of other conditions, doctors at University began using hyperbaric treatments on the patients with the conciliation -- known as brain radionecrosis -- about six years ago.

The treatment involves placing the patient in a pressure chamber and having the patient breathe pure oxygen at a pressure similar to being under 33 to 66 feet of seawater, Gesell says. Each treatment lasts 1½ hours. Treatments are repeated every day for one to three months.

Preliminary results are promising, Gesell says. In many patients damaged tissues have been healed completely.

In about 86 percent of cases, doctors were able to stabilize or decrease the steroids dosage. In some cases, patients even were able to stop taking steroids.

MRIs showed that the disease had stabilized or improved in 78 percent of patients, Gesell says. Armed with the results, doctors applied for the funding for the current study.

Doctors believe the pure oxygen at increased pressure causes new blood vessels to grow in injured tissue, but no one is sure exactly how, says Gesell.

Gesell and her team of researchers at UC and the Neuroscience Institute set up the Brain Radionecrosis Center to study not only how well hyperbaric oxygen therapy works, but also the mechanism that enables it to work.

Her collaborators in the research are Christopher Lindsell of the Institute for Health Policy and Health Services Research at UC; Dr. Ronald Warnick, a neurosurgeon with the Mayfield Clinic and the Neuroscience Institute and professor of neurosurgery at UC; and Dr. John Breneman, a neuroradiologist with institute and professor of radiation oncology and neurosurgery at UC.

The initial study, known as a pilot trial, will involve only 30 patients, but researchers have already been receiving calls from all over the nation, Gesell says.

If the treatment proves to be as effective as preliminary findings indicate, the team expects to expand its study into a multi-center trial involving a large number of patients.

That ultimately could lead to the establishment of hyperbaric oxygen therapy as the main treatment for patients with brain radionecrosis.

Bends Cure Could Aid Cancer Women

By Jane Elliott
BB News health reporter

Decompression chambers, used to treat deep-sea divers with the bends, could hold the key to relieving a painful side effect of breast cancer.

Experts believe lymphoedema - severe swelling in the arm following surgery andradiotherapy - could be alleviated by breathing in pure oxygen.

A trial funded by Cancer Research UK is now looking for 63 women to test their theory.

Previous trials have already produced promising results.

Five years ago Shirley Fenton, 66, from Buckfastleigh, in Devon, took part in the pilot trial, led by the Royal Marsden Hospital and The Institute of Cancer Research.

Progress

She said: "The swelling in my arm has reduced by 10% and the arm has softened quite a lot.

"Before there was no give in it. Now there is no difference to the other side.

"I had swollen fingers that I used to call my sausage fingers, but now I can get my rings on."

“We were breathing pure oxygen ”

Shirley Fenton

Shirley first had breast cancer when she was a young mother of 34.

She had a lumpectomy and radiotherapy, but her lymph nodes were not removed.

Seventeen years later she had another unrelated breast cancer. Again she had a lumpectomy and radiotherapy, but this time surgeons also removed her lymph nodes.

A few years later she started to suffer from a terrible swelling in her arm.

"I did not know what was happening. My arm started to swell up. But I did not let it stop me doing anything and I would still play golf with this enormous arm."

Because Shirley and her contemporaries were the first wave to have their lymph nodes removed, there were few support systems in place - and cancer experts were not as aware as they are today about the symptoms and side effects.

When she was first diagnosed with lymphoedema she was simply given a sleeve, like a stocking for varicose veins, to reduce her swelling.

Later she was told about massage that could help drain the excess fluid.

But she said that because she had the condition for so long, many regarded her as someone whose condition could merely be maintained rather than improved.

Trial

When she heard about the six-week trial in the hyperbaric unit, which helps treat divers suffering from the bends, she agreed to take part.

"We were breathing pure oxygen.

"And then after 90 minutes we would start to decompress. It was like being in an aeroplane, because your ears pop.

"It was an experience I would not have missed for anything. I found it very enlightening."

The treatment, called hyperbaric oxygen therapy (HBO), will be available in Hull, Plymouth, Gosport and Leytonstone.

Professor John Yarnold, a consultant at the Royal Marsden Hospital, is leading the trial.

He said he hoped to show that HBO treatment could permanently reduce swelling.

“This complication has been assumed to be inevitably progressive and irreversible ”

Professor John Yarnold

"Patients cured of breast cancer by treatments that include radiotherapy to the armpit may be left with a life-long legacy of arm swelling.

"This is thought to be due to narrowing of lymphatic vessels that drain tissue fluid out of the arm, rather in the same way that veins drain blood.

"Narrowing of these channels is caused by scarring (fibrosis) stimulated by the radiotherapy. A very similar syndrome can develop after surgery to the armpit.

"For many decades, this complication has been assumed to be inevitably progressive and irreversible, but our recent research suggests that the condition might be improved by high-pressure oxygen therapy.

"Our current clinical trial aims to test the findings of an earlier pilot study, which reported worthwhile improvements in a proportion of patients who had had radiotherapy up to 30 years ago."

He added: " If the present trial confirms our earlier findings, this will certainly change the way we think about lymphoedema as well as, hopefully, changing the lives of patients living with this condition.

"As part of the trial, we are keen to investigate possible mechanisms by which high-pressure oxygen might improve lymphoedema.

"One of the ideas we are looking into is that high-pressure oxygen may stimulate the growth of new lymphatic channels as well as lead to a reduction in scar tissues surrounding existing lymphatic channels in the armpit."

Volunteers

Two thirds of volunteers recruited to the trial will receive 90 minutes of HBO therapy, five days a week for six weeks.

They will wear a large transparent dome over their heads that supplies pure oxygen through tubes and during this time they will be able to read or talk normally.

The remaining third of volunteers will receive standard care for lymphoedema including bandaging, exercise and massage.

Professor Robert Souhami, at Cancer Research UK, said: "Current therapies for lymphoedema aim to control the symptoms rather than treating the cause.

"There are encouraging signs that hyperbaric oxygen therapy might be an effective treatment and this trial will provide stronger evidence."

Women wishing to check if they are eligible for the study should contact Mrs Lone Gothard, Research Coordinator on 020 8661 3460 or visit the cancer trials database on Cancer Research UK's patient information website.

Hyperbaric Oxygen as a Chemotherapy Adjuvant in The Treatment of Osteosarcoma

Source from Oncology Reports: November 2009, Volume 22 Number 5, Pages 1045 - 1050
Affiliations: Department of Orthopaedic Surgery, Kagoshima Graduate School of Medical and Dental Sciences, Kagoshima 890-8520, Japan

Although hyperbaric oxygen has been shown to enhance the efficacy of radiotherapy and chemotherapy for the treatment of several malignant tumors, the impact of hyperbaric oxygen on osteosarcoma has not yet been demonstrated. In this study, we investigated the efficacy of hyperbaric oxygen alone and in combination with an anti-cancer drug as an adjuvant to chemotherapy. In vitro, highly metastatic murine osteosarcoma cell lines were exposed to hyperbaric oxygen and cell viability was examined. Hyperbaric oxygen alone significantly suppressed cell proliferation, and hyperbaric oxygen plus carboplatin exhibited significant synergism in suppression of cell proliferation. In vivo, C3H mice were subcutaneously inoculated with osteosarcoma cells and divided into four groups: control, hyperbaric oxygen, carboplatin, and carboplatin plus hyperbaric oxygen. After 5 weeks, increase in both tumor volume and number of lung metastases was significantly suppressed in the hyperbaric oxygen group. Concomitant hyperbaric oxygen clearly enhanced the chemotherapeutic effects of carboplatin on both tumor growth and lung metastasis in osteosarcoma-bearing mice. Moreover, mortality in the carboplatin plus hyperbaric oxygen group was significantly lower than in the other three groups. These findings suggest that hyperbaric oxygen plus carboplatin combination therapy could be an appropriate therapeutic regimen for the treatment of patients with osteosarcoma.

Hyperbaric Oxygen Therapy Enhances Radiation & Chemotherapy

Oncol Rep. 2009 Nov;22(5):1045-50.
Hyperbaric oxygen as a chemotherapy adjuvant in the treatment of osteosarcoma.
Kawasoe Y, Yokouchi M, Ueno Y, Iwaya H, Yoshida H, Komiya S.
Department of Orthopaedic Surgery, Kagoshima Graduate School of Medical and Dental Sciences, Kagoshima 890-8520, Japan.

Abstract

Although hyperbaric oxygen has been shown to enhance the efficacy of radiotherapy and chemotherapy for the treatment of several malignant tumors, the impact of hyperbaric oxygen on osteosarcoma has not yet been demonstrated. In this study, we investigated the efficacy of hyperbaric oxygen alone and in combination with an anti-cancer drug as an adjuvant to chemotherapy. In vitro, highly metastatic murine osteosarcoma cell lines were exposed to hyperbaric oxygen and cell viability was examined.

Hyperbaric oxygen alone significantly suppressed cell proliferation, and hyperbaric oxygen plus carboplatin exhibited significant synergism in suppression of cell proliferation. In vivo, C3H mice were subcutaneously inoculated with

osteosarcoma cells and divided into four groups: control, hyperbaric oxygen, carboplatin, and carboplatin plus hyperbaric oxygen. After 5 weeks, increase in both tumor volume and number of lung metastases was significantly suppressed in the hyperbaric oxygen group. Concomitant hyperbaric oxygen clearly enhanced the chemotherapeutic effects of carboplatin on both tumor growth and lung metastasis in osteosarcoma-bearing mice. Moreover, mortality in the carboplatin plus hyperbaric oxygen group was significantly lower than in the other three groups.

These findings suggest that hyperbaric oxygen plus carboplatin combination therapy could be an appropriate therapeutic regimen for the treatment of patients with osteosarcoma.

Hyperbaric Oxygen Therapy for Cancer

Hyperbaric Oxygen Therapy – HBO or HBOT – has its fans as an aid in Cancer Treatment.

The argument runs that using a Hyperbaric Chamber (which is designed to increase blood oxygen levels and is proven to work in this way with a number of illnesses), will overcome one of the main influences of cancer: Namely, that cancer exists in a low-oxygen environment and plentiful oxygen can kill it off.

But is it really an alternative cancer cure, or a very promising complementary cancer therapy? It is already used to good effect when used with radiotherapy where it reduces tissue damage and side-effects. Other cancer centres use it to improve the uptake of chemotherapy drugs. Here we look at the use of Hyperbaric Oxygen and cancer in a little more detail.

What is Hyperbaric Oxygen Treatment?

HBOT chambers to treat deep sea divers suffering from decompression sickness (‘the bends’) were first developed by the military in the 1940’s. Pilots who climb or lose altitude too quickly and miners who surface too quickly may also experience this condition.

Decompression sickness involves a dangerous loss of oxygen in the blood stream and can be both painful and fatal.

By the 1960’s it was realised that HBOT might be appropriate to other conditions and illnesses and it was used for example for carbon monoxide poisoning cases and other oxygen-depletion scenarios such as gangrene. It was thus shown to increase, not just blood oxygen levels, but tissue oxygen and improve tissue healing.

There are now many other illnesses and conditions for which the idea of increasing cellular oxygen load is accepted as having significant benefits - for example ulceration (caused by radiotherapy, diabetes and so on), brain damage after accidents and plastic surgery. And, in some countries, cancer.

Otto Warburg

In 1931 Otto Warburg won a Nobel prize for explaining that oxygen was the enemy of the cancer cell – it kills them. Indeed cancer cells thrive in an environment where oxygen is depleted.

Since that time many alternative cancer experts have pondered over ways of delivering oxygen to cancerous tissue in the hope of killing the cancer cells and restoring the tissue to a normal state. In our interview with Dr Contreras of The Oasis of Hope Hospital in Mexico, he told us how they were using a form of dialysis to deliver ozone to the tissues. (Note - while oxygen is a double atom molecule O2, ozone is a triple atom molecule O3). He claimed that the system was in early stages of development, but did seem to extend the lives of cancer patients already tested, by months if not by years. Today there are well respected centres operating inside the USA that use ozone to treat cancer, as a part of their offering.

Oxygen is a drug!

Believe it or not but oxygen has officially been declared a drug by the FDA in America who have stated that it must not be prescribed to treat anything other than those illnesses approved and for which there is 'evidence'. For example, decompression sickness, anaemia, gangrene, skin grafts, soft tissue damage, burns, abscess in the head or brain, osteomyelitis. In effect, they have banned the use of Hyperbaric Oxygen to treat cancer. But then in 2011, they have taken steps to ban the use of intravenous vitamin C compounds, which can also increase cell oxygen levels! They don´t seem to want you oxygenating your cancer cells at all. Will eating glutathione-rich vegetables be banned next?

HBO as a Complementary Therapy for cancer

i) Radiotherapy

HBOT is currently used with cancer patients to reduce inflammation in bones and adjacent tissues where radiotherapy may cause damage - it seems to have an ability to reduce secondary radiation damage after radiotherapy. For example a study (HYPON) showed that the use of HBOT could reduce jaw bone damage in patients given radiotherapy for head and neck cancers. Radiotherapy damages surrounding tissues, not just cancer cells. Other uses include the regeneration of blood vessels - blood supplies may be restricted to tissues and bones by the harmful action of radiotherapy; and oxygen treatment can help significantly. It has also been shown to help reduce secondary problems with both pelvic and bowel cancer. These effects are acknowledged in the UK and have been added to the repertoire of orthodox medicine. At the end of this article you will see that the Royal Marsden are asking for recruits to their phase III clinical trial - it´s for people who experienced side effects after radiation for pelvic cancer.

ii) Lymphoedema

There is also evidence that HBOT may help people with lymphoedema following breast cancer and lymph nodule surgery. Quite simply, oxygen therapy aids healing and patients in research talk of reduced swelling and less pain, with a softening of the damaged tissue.

What happens during HBOT?

People can be 'treated' individually or in groups depending upon the size of the chamber. Inside, the pure oxygen is administered at pressures 1.5 to 3 times normal atmospheric pressure. Treatment time is usually about 90 minutes and only cotton clothing may be worn. There are treatment centres throughout the UK – you might contact the British Hyperbaric Association.

Side effects may include claustrophobia, fatigue, headaches, ear problems and nausea. It is occasionally possible the myopia (short sightedness) occurs, and people with lung disease may experience a collapsed lung, heart patients may have symptoms worsened. It is not recommended for pregnant women.

Cancer patients taking drugs such as doxorubicin, cisplatin or bleomycin are advised not to use HBOT.

HBO as an alternative cancer treatment

Oxygen therapy, ozone therapy, the use of hydrogen peroxide and even the simple ingestion of more foods containing glutathione all have one aim: To deliver more oxygen to the mitochondria inside the cell. It is the mithochondria (the power stations) that cease their normal job of burning carbohydrate in the presence of oxygen to produce energy (the Krebs Cycle), instead producing energy by burning glucose in the absence of oxygen. This typifies a cancer cell.

While the theory is great, the research to date has often been anecdotal and patchy. The primary problem, as Contreras told me, is the delivery system. Increasing the oxygen levels in the blood does not necessarily increase them in the cells.

There are studies involving mice who have been induced with cancer to give them oral mucosal carcinoma. Hyperbaric oxygen reduced the level of cancer, preventing some mice developing the disease. However, in some cases where the mice already had the disease, oxygen seemed to make matters worse. (The effect of hyperbaric oxygen therapy on oral mucosal carcinoma; Terry McMillan, Karen Callhoun et al).

Patients with brain tumours may well derive benefit. Treatment using HBO with brain damage has definitely shown promise, and this has now been extended to brain cancer. In a 2006 Clinical Trial in Japan, brain tumour patients receiving radiotherapy and chemotherapy experienced longer survival times and reduced side effects when using HBO. (Ogawa et al). In 2007 a second clinical trial showed extended survival times with reduced side effects using HBO with just radiotherapy in glioma patients (Kohshi et al). Now (July 2011) researchers at the Long Island Brain Tumour Centre are try to replicate those studies again in a Phase II clinical trial with gliomas. (Ed: How many do you need?)

Researchers at the University of Washington and Washington State University have shown that the herb artimisinin, or Wormwood, kills a cancer cells in conjunction with Hyperbaric Oxygen in early research in the 1990's. They describe wormwood as an important antimalarial drug.

Wormwood acts by reacting with iron in a cell to form a free-radical which kills the cell. Malaria parasites and cancer cells are high in iron.

New research in 2011 on a culture of leukaemia cells has shown that wormwood acts to kill about 15 per cent of cancer cells in the laboratory experiments. And they found almost the same 15 per cent figure when using HBO. Combining the two treatments say a 38 per cent reduction in cancer growth. Professor of bioengineering, Henry Lai said "We only measured up to 48 hours. Over longer time periods we expect the synergistic effects to be even more dramatic."

Importantly, there are a number of cancer centres in Germany that currently use Hyperbaric Oxygen Therapy to treat cancer, sometimes as a single stand-alone therapy, but more usually in conjunction with other treatments, including either complementary therapies or chemotherapy. And, they claim excellent results.

Trawling the web I found quotes such as:

"I utilize mild Hyperbaric Therapy (mHBT) in all stages of cancer; upon detection, as well as pre and post surgery, pre, post and during chemo and radiation. In fact if chemotherapy is used in conjunction with mHBT, the chemotherapy dose must be reduced. The mHBT will potentate any primary cancer treatment. mHBT is the best cancer prevention and cancer remission therapy out there, bar none." US Doctor, Bergeron, Rhett, MD

"By increasing the oxygen environment to the cancer cells, it makes them less virulent and in many instances destroys them. (Yutsis, Pavel I., MD, Oxygen to the Rescue)

The Final Word

Consistently, in my research on HBOT, I have found articles talking excellent theory, but little hard research evidence in practice. This is not to say I am a doubter, I am not. But it is one thing telling me that oxygen kills cancer cells in my Oxford University Lectures, and another thing developing the delivery systems that can actually do it. Maybe Hyperbaric Oxygen is that delivery system. I acknowledge that there are centres in Germany claiming excellent results, there are cancer experts in the USA lauding its potential and I do have sympathy with the argument that oxygen treatment is unpatentable so if you could cure people of cancer by putting them in an oxygen chamber a lot of 'Pharma' companies would go bust. I would just like to see some numbers now please.

Hyperbaric Oxygen Therapy clearly provides real benefits as a complementary therapy when used with radiotherapy and lymphoedema. And, there is no doubt that the logic and even the science is great in theory that this really could be a

major cancer treatment in the coming years. The great thing is that we know Hyperbaric oxygen is a healing treatment - there is already significant evidence for a variety of illnesses. And we know that it is an ´all-over-body treatment, just as cancer is an ´all-over-body´ disease. It already has staunch supporters in countries like Germany and Japan.

You should keep an open mind on Hyperbaric Oxygen Therapy and explore developments.