Hyperbaric oxygen for delayed radiation injuries.

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INTRODUCTION

Based on distinctions in their pathophysiologies, radiation complications should be divided into acute and delayed. Acute complications are generally cellular and mucosal and are caused by direct damage to cellular DNA with resultant cell death. These are usually self-limited and generally not dose limiting. Late radiation damage is primarily vascular and stromal.[1] Late complications are the most dreaded and determine the limits of tolerable radiation doses. The tolerance to radiation varies considerably from organ system to organ system. For years radiation oncologists and pathologists have felt that the mechanisms of early and late damage are completely unrelated. Although there are distinctions and identifiable differences in the nature and site of injury, we are beginning to appreciate that late radiation damage actually begins at the initiation of treatment. An increase in various biochemical substances including fibrogenetic cytokines are identifiable from the onset of treatment.[2] These have been associated with late radiation damage and their serial assays may allow for prophylactic interventions. An elevation of those cytokines, which lead to damage or conversely a depression of protective cytokines may identify a group of patients at high risk for late radiation damage. This early identification of those at risk prior to manifestations of frank radiation damage may permit prophylactic intervention. An exciting potential area for further research will include the application of hyperbaric oxygen during this latent period after radiation but before expression of the clinically expressed damage. Certainly, if such a group of reliable predictive assays can be identified, other therapeutic strategies to prevent radiation damage will also undergo investigation.

To date hyperbaric oxygen (HBO_2) has been a very successful therapeutic modality for delayed radiation injury. It has also been shown to be useful in a prophylactic intervention in several circumstances. A recent systematic review by Feldmeier and Hampson, summarizes 74 publications that report the results of hyperbaric oxygen for a wide range of soft tissue and bony necrosis. This review was conducted in an evidence-based fashion. All but seven papers are positive in terms of their therapeutic effect. Most of the negative reports are in neurologic injury where, especially in the CNS, injuries have been refractory to virtually all interventions. The application of HBO_2 has had its earliest and best-studied application in mandibular osteonecrosis. HBO_2 is an effective treatment modality for radiation necrosis because, at least in part, the pathophysiology of this process is vascular and stromal secondary to obliterative endarteritis. HBO_2 has been shown to induce neovascularization in this hypoxic milieu and to reduce fibrosis in irradiated tissues.

Molecular oxygen available simultaneously with ionizing radiation is the most potent radiation sensitizer known. The first interactions of radiation and HBO_2 were based on this observation. Mostly during the 1960's and early 1970's, HBO_2 was used as a radiosensitizer for

external beam radiation, and numerous clinical trials were conducted whereby patients with malignancies were irradiated while at pressure in monoplace HBO_2 chambers. Although many of these trials showed improved local control of cancers, especially in head and neck cancers and cervical cancer, this improvement did not generally translate into improved cure rates, and the practice of HBO_2 radio-sensitization for external beam irradiation has been largely abandoned.[3]

The Etiology of Radiation Necrosis or Late Radiation Injury and the Rationale for HBO_2.

Late radiation changes are characterized by fibrosis and endarteritis. If nutrient blood vessels are significantly narrowed and if inadequate O_2 is available to meet metabolic demands frank aseptic necrosis occurs.[1]

The development of radiation-induced endarteritis requires time to become established. Clinically we see a latent period of months to years before these changes result in necrosis. The process can be set off by trauma to the tissues such as dental extraction or surgical incision.

HBO_2 has been shown to induce neovascularization and reduce fibrosis in radiated hypoxic tissues. Marx[4] has shown an increase in vascular density and cellularity in histologic specimens of tissues before hyperbaric oxygen compared to specimens taken from the same site after hyperbaric treatments just prior to mandibular reconstruction. Marx[5] has also shown an improvement in sequential transcutaneous oxygen measurements in patients undergoing hyperbaric oxygen for mandibular necrosis. Feldmeier[6-8] and his co-workers have shown decreased stromal fibrosis by morphometric collagen assay and functional compliance measurements in a murine model of radiation enteritis.

Site Specific Applications of Hyperbaric Oxygen to Delayed Radiation Injuries

Mandibular Necrosis

Prior to the 1970's, HBO_2 had been used with mixed success for mandibular radiation necrosis (ORN).

Beginning in the late 1970's Marx and Johnson and their co-workers while at Wilford Hall USAF Medical Center in collaboration with the USAF Hyperbaric Medicine Center at Brooks Air Force Base established a formal protocol for treatment and evaluation of mandibular necrosis.[9] The development of a "Staging" system led to a logical application of HBO_2 integrated with surgery. The specific recommendations for therapy followed quite logically from the assignment to a particular stage.

a. Stage I - Patients receive 30 HBO_2 treatments at 2.4 ATA for 90 minutes In these patients no more than minor debridement in the dental chair was felt to be necessary.
   (1) If response was good and exposed bone was covering, the patient continued for 10 more treatments.
b. Stage II - These were non-responders to the first 30 treatments in Stage I but in whom debridement rather than a discontinuity resection was felt to be appropriate. Debridement was not accomplished until 30 HBO_2 treatments are completed.
   (1) Post debridement ten additional treatments were given.
c. Stage III- These were non responders to Stage II treatment or those who present with cutaneous fistulae, pathologic fracture or resorption of the inferior cortical border of the mandible.

(1) 30 HBO_2 treatments given followed by resection with 10 post-op HBO_2 sessions.

(2) 10 weeks after resection reconstruction was accomplished followed by 10 post reconstructive HBO_2 sessions. Reconstruction involved the use of freeze-dried cadaveric bone used as a carrier tray for the patient's own corticocancellous bone harvested from the iliac crest.

(3) External jaw fixation was maintained for 8 weeks following the reconstruction.

With this protocol, success in mandibular reconstruction has been unexcelled even when compared to more surgically complex procedures such as microvascular anastomosis with free flaps. However, there is nothing to preclude the use of free flaps or myocutaneous flaps along with hyperbaric oxygen and it is always a good principle to combine optimal surgery with HBO_2 as an adjunct in improving the quality of tissues in the recipient bed.

Including the publications by Marx, a total of fourteen publications are available reviewing the experience of applying HBO_2 to mandibular necrosis[10-23]. One very small randomized controlled trial by Tobey et al[13] is positive. Only twelve patients were studied in this publication. These patients were randomized to 100% oxygen at 1.2 vs 2.0 ATA. The authors state that those patients treated at 2.0 ATA "experienced significant improvement" compared to the group receiving oxygen at 1.2 ATA. No details are given regarding randomization or outcome determination. In fact we cannot tell how many patients were assigned to each group. The study is randomized and doubly blinded in that neither the patient nor the clinician assessing the patient knew which therapy the patient was receiving

Other than the trial by Tobey, all of the rest of the publications present case series. Of the fourteen publications, only the report by Maier et al[21] fails to show an advantage for hyperbaric oxygen in the treatment of existing ORN. In this paper, none of the hyperbaric oxygen is given prior to surgery. Hyperbaric oxygen is part of the overall management only after an attempt is made at surgical correction. Marx has previously established the importance of pre-operative HBO_2 prior to surgical wounding in irradiated tissues. This principle has been widely accepted by those applying HBO_2 to the treatment of ORN.

If all of the cases are combined (excluding those reported by Tobey and noting that Marx's second report includes the fifty-eight patients reported earlier), we have a total of 371 reported cases of mandibular ORN. Improvement is reported in 310 cases or 83.6%. Resolution would certainly be a superior endpoint. However, especially in the earlier reports, hyperbaric oxygen was not combined with aggressive extirpation of necrotic bone or with surgical reconstruction of bony discontinuity. Certainly, Marx has reported the best results of any single author. Marx has identified the need for optimizing surgery and sequencing HBO_2 and surgery to include and emphasize the pre-surgical application of HBO_2. Marx reports 100% success, but his successful treatment includes mandibulectomy and reconstruction in 73% of his patients. Dr. Marx also sets high standards for successful intervention in those patients requiring mandibulectomy and reconstruction. Marx requires not only the successful re-establishment of bony continuity but also requires functional success in that these patients must be able to support a denture for cosmesis and mastication.

HBO_2 for Osteoradionecrosis Prophylaxis

A randomized trial by Marx et al.[24] compared penicillin to HBO_2 prior to dental extractions as prophylactic strategies to prevent mandibular radiation necrosis in heavily irradiated mandibles. With thirty-seven patients in each group, ORN occurred in 11/37 (29.9%) of penicillin group and only 2/37 (5.4%) in HBO_2 group.

This protocol randomized only patients with 6800 cGy or higher dose. The penicillin group received 1 million units of penicillin just prior to surgery followed by 500 mg penicillin p.o. Q.I.D. for 10 days. The HBO_2 group underwent 20 HBO_2 treatments prior to extractions and 10 HBO_2 treatments after extractions.

Two additional clinical series present their results in the prophylactic treatment of fifty-three additional patients. If we combine the patients from all three reports, we find an incidence of osteoradionecrosis (ORN) in 4.5% (4 of 90) of the HBO_2 prophylaxis group (2 of 37 Marx; 1 of 29 Vudiniabola[25]; and 1 of 24 David[23]). In Marx's control group, the incidence of osteoradionecrosis was 29.9% (11 of 37).

Laryngeal Necrosis

Fortunately, radiation-induced laryngeal necrosis is an uncommon complication. In a well designed radiation treatment course, its incidence should be less than 1%. Higher doses per treatment fraction, higher total doses and neutron irradiation increase the risk of laryngeal chondroradiation necrosis.

The effects of HBO_2 on chondroradiation necrosis of the larynx have been reported by three authors from three separate institutions.[26-28] The majority of these patients had severe (Chandler's Grade III or IV necrosis). Without hyperbaric oxygen treatment, the usual recommendation is laryngectomy for those patients in whom laryngeal edema is persistent. The rationale for this recommendation is that vast majority of patients with persistent edema have tumor, and even if they do not, salvage is not possible because no effective treatment had been known for laryngeal chondronecrosis. Symptoms of both laryngeal necrosis and tumor recurrence may include airway compromise, edema, fetid breath and production of necrotic debris. Biopsy in such patients may be subject to sampling error or may further exacerbate the necrotic process. Biopsy should be avoided or minimized if possible. Obviously, biopsy may be ultimately required to demonstrate or rule out tumor recurrence. If the results from these three trials are combined, only six of thirty-five patients treated with hyperbaric oxygen required laryngectomy. The rest maintained their larynx with most patients having good voice quality after HBO_2.

Other Soft Tissue Necrosis Injuries of the Head and Neck

Dr. Marx's chapter in the textbook, Hyperbaric Medicine Practice[29] reports his experience in a prospective controlled but not randomized study applying hyperbaric oxygen to soft tissue radionecrosis of the head and neck. Those patients who refused hyperbaric oxygen or for whom treatment was not practical due to having homes distant from a hyperbaric chamber or other financial reasons were assigned to the control group. These cohorts of patients were treated concurrently and all other aspects of their treatment were identical. In his report of 160 patients receiving hyperbaric oxygen in support of surgical resection or flap reconstruction in heavily irradiated patients comparing wound infection, wound dehiscence and delayed wound healing, Marx reports the incidence of complications in the HBO_2 group versus the control group in the following fashion: 1. Wound infection: 6% versus 24%; 2. Wound dehiscence: 11% versus 48%; and 3. Delayed wound healing: 11% versus 55%. Applying the Chi square test to these results we obtain P values of 0.004, less than 0.0001 and less than 0.0001 respectively for each of these outcome measures. These patients received twenty pre-operative HBO_2 treatments followed by ten post-operative treatments at 2.4 ATA.

In addition to the large controlled trial reported by Marx, there are three additional publications reporting case series in which hyperbaric oxygen has been applied to soft tissue radiation injuries of the head and neck (other than larynx).[30-32] These consistently report a

positive outcome in patients treated with HBO_2 for soft tissue radionecrosis of the head and neck. The case series by Davis et al[31] reports success in fifteen of sixteen patients treated for soft tissue radionecrosis of the head and neck. Many of these patients had large chronic soft tissue wounds as a result of their radiation injury. In 1997 Neovius[30] and colleagues reported a series of fifteen patients treated with hyperbaric oxygen for wound complications within irradiated tissues. They compared this group to a historical control group from the same institution. Twelve of the fifteen patients in the hyperbaric group healed completely with improvement in two and no benefit in one. In the control group only seven of fifteen patients healed. Two patients in the control group developed life-threatening hemorrhage and one of these did exsanguinate. Any practitioner experienced in caring for head and neck cancer patients has experienced at least one patient in his or her career that exsanguinated as the result of a soft tissue necrosis of the neck which progressed to erode into the carotid artery or other major vessel.

Chest Wall Necrosis

Radiation is a frequent modality applied to lung, breast, or esophageal cancers. Chest wall radiation necrosis occurs most frequently in breast cancer after mastectomy due to the need to treat skin and subcutaneous tissues to a relatively high dose since this tumor often recurs in the skin of the chest wall. HBO_2 in this setting has not been extensively reported.

Hart [11] has reported the use of hyperbaric oxygen as an adjunct to skin grafting in six patients with radiation injury of the chest wall with all patients experiencing graft take. Feldmeier and his colleagues[33] have reported a total of twenty-three cases of radiation necrosis of the chest wall: eight with soft tissue only necrosis and fifteen with a combination of bone and soft tissue necrosis. Resolution in those with soft tissue involvement only was 75% while those with a component of bone necrosis had resolution in 53%, and all of these patients required resection of necrotic bone. If bone is involved aggressive debridement to include resection of non-viable bone is required for good results

In a case report Carl and Hartmann[34] in 1998 published their results in treating a patient with long-standing symptomatic breast edema following lumpectomy and irradiation. The patient received fifteen, 90 minute HBO_2 treatments at 2.4 ATA. The patient had complete resolution of pain and edema.

Carl and his associates[35] in 2001 reported the outcome of 44 patients who suffered complications following lumpectomy and irradiation for early breast cancers. These patients were found to have pain, edema, fibrosis and telengectasias. Each patient experienced these complications in various combinations. The severity of symptoms was assessed a score for each patient based on a modified LENT-SOMA score. Only patients with at least grade 3 pain (persistent and intense) or a summed LENT-SOMA score of 8 were studied. Each patient was assessed a score from 1 to 4 in the severity of symptoms in the categories of pain, edema, fibrosis/ fat necrosis and telangectasia/erythema. Thirty-two patients agreed to undergo hyperbaric oxygen treatment while twelve women refused HBO_2 and constituted the control group. Hyperbaric oxygen treatments resulted in a statistically significant reduction in the post-treatment SOMA-LENT scores in women receiving hyperbaric oxygen compared to those who did not. Fibrosis and telangectasia were not reduced. Women in the control group continued to demonstrate symptoms at the completion of the trial with no improvement in pain or edema while seven women in the hyperbaric group had complete resolution of their symptoms at the end of the trial.

Radiation Cystitis

Several single institutional reports have shown efficacy in this rare disorder. Hemorrhagic cystitis secondary to radiation may require cystectomy if it does not respond to conservative measures such as instillation of formalin or alum. HBO_2 reports with serial cystoscopies and serial U.A.'s have shown resolution in a high percentage of cases. Success has varied from 60 to 95% and has been durable over time.

There are seventeen published reports detailing results of HBO_2 interventions in the treatment hemorrhagic radiation induced cystitis.[36-52] These publications are all case series. The report by Bevers et al[45], which includes the largest number of patients, was a prospective but not a controlled trial. In the final report by Weiss et al[47], the earlier patients reported by the same author were included. The second paper by Lee[42] reporting twenty-five patients includes the twenty patients previously reported by the same author. If we combine all those patients reported in these seventeen publications, we find a total of 190 patients treated with HBO_2 with 145 patients or 76.3% resolving when treated with hyperbaric oxygen.

Many of the patients reported in the hyperbaric experience had already failed conservative management including irrigation and the instillation of alum or formalin. Severe hemorragic radiation cystitis is unquestionably a life threatening and quality of life limiting disorder. Cheng and Foo[53] have reported their experience in managing nine serious refractory cases of hemorrhagic radiation cystitis without hyperbaric oxygen. Six patients were treated with bilateral percutaneous nephrostomies. Three patients required ileal loop diversions of their urinary stream. Four of nine (44%) patients ultimately died in spite of these aggressive treatments. Similarly, Sun and Chao[54] have reported a 3.7% mortality due to bladder injury in their review of 378 patients treated with radiation for cervical cancer.

A success rate of 76.3% with hyperbaric oxygen is all the more impressive when results with other more aggressive interventions are considered. It is also noteworthy that 16 of 17 publications are positive reports. These patients represent patients treated in several different countries on 3 different continents with consistent benefit seen in a large majority of patients in each study except that reported by Del Pizzo[46].

Radiation Enteritis /Proctitis

There are fourteen publications reporting experience in applying hyperbaric oxygen as treatment for radiation enteritis and proctitis.[55-68] The first paper is a case report detailing the successful treatment of a single patient with hemorrhagic proctitis. An additional eight case series reports have been published. Of the 114 cases reported in these nine publications, forty-one (36%) resolved and 68 (60%) improved after treatment with hyperbaric oxygen. In the report by Feldmeier et al, especially impressive was the resolution of fistulae in six of eight patients with only three requiring surgical closure. In the same report, only seven of twenty-six patients who healed required surgical debridement or surgical flaps or grafts.

The animal studies by Feldmeier[58,63] demonstrate a decrease in fibrosis and an improvement in compliance in the small bowel of animals receiving hyperbaric oxygen before frank necrosis was evident. In these studies enough time was allowed for the vascular changes and fibrosis associated with late radiation injury to be established prior to animal sacrifice. Characteristically, a latent period of several months to years is observed to occur between the completion of radiation and the clinical expression of radiation damage.

Miscellaneous Abdominal and Pelvic Injuries

Farmer and his colleagues[12] in 1978 as part of a report, which included radiation injuries to many sites, reported a single case of vaginal necrosis. This necrosis resolved with HBO_2. Williams and his associates[69] reported their results in treating 14 patients with vaginal radiation necrosis in 1992. Thirteen of fourteen patients had resolution of their necrosis with hyperbaric treatment. One patient required two courses of HBO_2. In 1996 Feldmeier and colleagues[59] reported a series of forty-four patients treated with various abdominal and pelvic injuries. The results from this report in treating small and large bowel injuries have already been discussed above. Twenty-six of thirty-one (84%) patients who experienced injuries to the abdominal wall, groin, perineum, vagina or pelvic bones and who received at least twenty hyperbaric treatments had complete resolution with treatment. This group included 6 patients with vaginal necrosis, all of whom experienced complete resolution with treatment. If we total the results reported in these three papers we find complete resolution in a variety of pelvic and abdominal soft tissue injuries in forty of forty-six patients (87%). All but one patient of the twenty-one reported in all three papers with soft tissue vaginal necrosis was treated successfully.

Extremities

Hyperbaric oxygen has also been reported as a useful therapy in radiation necrosis of the extremities. In the report previously discussed by Farmer and his colleagues[12] a single case of foot injury did not respond to hyperbaric oxygen. In a series published by Feldmeier and associates[70], seventeen patients with necrosis of the extremities treated with hyperbaric oxygen were reported. Sixteen of the seventeen patients had only soft tissue necrosis. Eleven of seventeen had resolution with HBO_2. If we restrict our analysis to those patients in whom follow-up was available and in whom there was no evidence of recurrent cancer, eleven of 13 (85%) had complete resolution.

Neurologic Radiation Injuries

There are fourteen publications wherein hyperbaric oxygen has been applied to radiation-induced neurologic injuries. [11, 71-83] These injuries include radiation myelitis of the spinal cord, radiation necrosis of the brain, optic nerve injury and brachial plexopathy.

Hart and Mainous[11] in 1976 reported five cases of myelitis treated with hyperbaric oxygen without significant improvement. Glassburn and Brady[71] have reported nine cases of myelitis in which patients received hyperbaric oxygen. Six of these nine patients improved, including improvement in motor function. In 2000 Calabro and Jinkins[79] reported a single case of transverse spinal myelitis in which the patient demonstrated progressive improvement including imaging documentation by MRI after treatment with hyperbaric oxygen. Feldmeier and his colleagues[75] have reported a statistically significant delay in the onset of transverse myelitis in mice who received hyperbaric oxygen after radiation but prior to the expression of spinal cord injury. There are no other known successful treatments for radiation induced transverse myelitis and the consequences of myelitis are permanent paralysis and loss of sensation below the level of involvement. The published experience reviewed above shows improvement in seven of fifteen patients treated with hyperbaric oxygen.

There are six published reports in which hyperbaric oxygen has been applied to the treatment of brain necrosis. In the publication by Hart and Mainous[11], a single case of brain necrosis is presented and this patient had improvement after treatment. In the paper by Chuba and associates[77], hyperbaric oxygen treatment led to temporary improvement initially in all ten pediatric patients treated. Ultimately, four of these patients died as a result of their malignancy. At the time of their publication, five of the surviving six patients had maintained the neurologic improvement. Leber and

colleagues[78]reported the use of hyperbaric oxygen in two patients with radiation necrosis after radiosurgery for arteriovenous malformations. After hyperbaric treatment, both patients had shrinkage of their lesions by imaging studies and one had complete resolution by serial MRI studies. The paper by Cirafisi and Verderamae[80] presents a case report of a single patient who failed to respond to hyperbaric oxygen. The patient had also failed to respond to steroids and anti-coagulants. Gesell and colleagues[82] have reported the largest experience to date in applying hyperbaric oxygen to the treatment of radiation-induced brain necrosis. These results were presented at the 2002 Annual Meeting of the Undersea and Hyperbaric Medical Society. After hyperbaric oxygen treatment seventeen of twenty-nine patients had an improved neurologic examination and in twenty of twenty-nine patients, it was possible to decrease steroid requirements. At the same meeting Dear and associates[83] presented their experience in treating twenty patients with radiation-induced brain necrosis. In eleven patients with Glioblastoma Multiforme, only one patient showed objective improvement. However, seven of these eleven patients were dead of tumor within a short time following hyperbaric oxygen and obviously had active tumor at the time of treatment. It is very likely that the presence of tumor contributed to the neurologic deficits manifested by these patients. It is a consistent observation that soft tissue necrosis lesions within previously irradiated fields will not heal if tumor is present in the wound or area of injury. In the other nine patients with other tumors reported by Dear, eight were subjectively improved and three had objective improvement. If we combine the results from these six publications, we find that twenty-nine of sixty-three (46%) patients reported had a positive therapeutic outcome with hyperbaric oxygen. No other treatments short of surgical resection of the necrotic focus have been effective.

There are four publications reporting the results in applying hyperbaric oxygen to the treatment of radiation induced optic neuritis. Again all four of these publications are case series including the single case report by Fontanesi.[74] Only four of the nineteen patients reported in these publications had visual improvement. Guy and Schatz[72] report in their series that hyperbaric oxygen must be initiated promptly. In their series, two patients had complete restoration of their sight when they began hyperbaric treatment within seventy-two hours of loss of their sight. The other two patients who had begun hyperbaric oxygen at two weeks and six weeks respectively after loss of vision had no improvement. In the paper by Borruat et al[76], a single patient with bilateral radiation-induced optic neuritis had complete resolution in the more recently affected eye and improvement but not resolution in the eye first affected. These results also suggest the importance of early intervention in order to obtain an optimal outcome. In this desperate circumstance where permanent blindness is likely to occur, a trial of hyperbaric oxygen intervention would appear to be justified based on humanitarian considerations. This therapy must be promptly initiated.

Finally, in regard to peripheral nerve injury treated by hyperbaric oxygen, we have the randomized controlled trial conducted by Pritchard and colleagues[81]. This study was designed to investigate the effect of HBO_2 in the treatment of radiation-induced brachial plexopathy. This trial is a negative study in that it fails to demonstrate a therapeutic ***improvement*** in neuropathy for patients receiving HBO_2. The median time from onset of symptoms until enrollment into the trial was eleven years. As noted above, in some neurologic disorders, a positive outcome for hyperbaric oxygen requires prompt intervention. Importantly and interestingly, patients in the hyperbaric arm did demonstrate less post study deterioration in neurologic function compared to the control group. This decrease in rate of deterioration was statistically significant. Six patients in the hyperbaric arm also experienced an unexpected reduction in symptomatic lymphedema of the affected arm.

The Issue of Carcinogenesis

An issue that frequently arises when considering a patient for hyperbaric oxygen who also carries a cancer diagnosis is what does HBO_2 do to growth or potential recurrence of the malignancy. In a publication from 1994, Feldmeier and his colleagues[84] reviewed the discoverable literature related to this issue. An overwhelming majority of both clinical reports and animal studies reviewed in this paper showed no enhancement of cancer growth. A small number of reports actually showed a decrease in growth or rates of metastases. In 2001 at the Consensus Conference jointly sponsored by the European Society of Therapeutic Radiology and Oncology (ESTRO) and the European Committee for Hyperbaric Medicine (ECHM), Feldmeier[85] updated this material. In this review, Feldmeier emphasized the differences known in tumor and wound healing angiogenesis. Each has similar but distinctly different processes operational. He showed that there are significant differences between tumors and wounds in the growth and inhibition factors, which modulate angiogenesis. He summarized the literature demonstrating that tumors, which are hypoxic, are less responsive to treatment, less subject to cellular death by apoptosis and more prone to aggressive growth and lethal metastases. Fears that hyperbaric oxygen may promote malignant growth are not supported by scientific evidence, and clinicians should not refuse to consider a patient for hyperbaric oxygen who has had a history of malignancy.

Additional Avenues for Research

As discussed in the Introduction, the identification of certain biochemical markers (mostly cytokines), which have been related to radiation injury, and their serial assay over time may allow for the identification of individuals at risk for radiation injury before the clinical expression of this injury. In this case therapeutic strategies could be investigated to determine whether the injury could be prevented. Hyperbaric oxygen would appear to have potentially broad application in this case.

Additional studies exploring methods by which hyperbaric oxygen can be utilized as a radiosensitizer are also justified by previous publications. The use of oxygen as a safe and effective radiosensitizer is based on sound radiobiologic principles. Some innovative methods to administer radiation during or just after a session of hyperbaric oxygen have been discussed by several authors. At the Children's Cancer Center at the University of Amsterdam researchers have pioneered a technique whereby children with advanced neuroblastoma are infused with a radioactive isotope (MIBG) and then treated with hyperbaric oxygen.[86] Response rates have been far superior to experience with the isotope treatment without HBO_2. Two different groups of investigators from Japan have published their experience in treating patients with high-grade primary brain tumors with radiation immediately after a hyperbaric oxygen exposure.[87-89] These results are also much more successful than historical experience without hyperbaric oxygen. One of these two groups has shown the importance of delivering the radiation within 15 minutes of the hyperbaric exposure.

SUMMARY

Hyperbaric oxygen has shown consistent benefit in treating patients with delayed radiation injury. It has also had success in preventing radiation injury in some instances. Additional study in identifying patients at risk for injury and delivering hyperbaric oxygen with prophylactic intent to prevent these injuries appears to be promising. Additional approaches to applying hyperbaric oxygen as a radiosensitizer also deserve further study. No convincing

evidence exists to support concerns that hyperbaric oxygen enhances or stimulates malignant growth.

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