Cancer

Hyperbaric oxygen inhibits benign and malignant human mammary epithelial cell proliferation.

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BACKGROUND: Hyperbaric oxygenation (HBO) therapy is the administration of 100%-inhaled oxygen to patients at increased atmospheric pressure. MATERIALS AND METHODS: We used an in vitro model to examine the effects of HBO on mammary cell proliferation. Normal mammary epithelia, primary tumor and metastatic tumor cells derived from the same patient and immortalized by transfection with the human papilloma virus E6 oncogene, as well as the MCF7 human mammary adenocarcinoma cell line, were studied. RESULTS: HBO (97.9% O2, 2.1% CO2, 2.4 atmospheres absolute) inhibited the proliferation of all 4 cell types as measured by light microscopy, [3H]thymidine uptake, a tetrazolium-based colorimetric assay and a clonogenicity assay. The anti-proliferative effect of HBO was time-dependent ($p < 0.01$ for all 4 cell types). Hyperoxia alone (95% O2, 5% CO2, 1 atmosphere absolute) and increased atmospheric pressure alone (8.75% O2, 2.1% CO2, 2.4 atmospheres absolute) also inhibited proliferation, but their effects were not as profound as HBO ($p < 0.01$ when either hyperoxia or increased pressure was compared to HBO for all 4 cell types). HBO enhanced the anti-proliferative effects of melphalan ($p < 0.05$), gemcitabine ($p < 0.001$) and paclitaxel ($p < 0.001$). The clonogenicity assay demonstrated that the effects of HBO were still evident 2 weeks after the exposure ($p < 0.01$ for all 4 cell types). Experiments using Hoechst-propidium iodide or annexin V-propidium iodide staining showed no HBO-induced increases in necrosis or apoptosis. CONCLUSION: HBO inhibits benign and malignant mammary epithelial cell proliferation, but does not enhance cell death.

Hyperbaric oxygen therapy and cancer--a review.

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Hypoxia is a critical hallmark of solid tumors and involves enhanced cell survival, angiogenesis, glycolytic metabolism, and metastasis. Hyperbaric oxygen (HBO) treatment has for centuries been used to improve or cure disorders involving hypoxia and ischemia, by enhancing the amount of dissolved oxygen in the plasma and thereby increasing O(2) delivery to the tissue. Studies on HBO and cancer have up to recently focused on whether enhanced oxygen acts as a cancer promoter or not. As oxygen is believed to be required for all the major processes of wound healing, one feared that the effects of HBO would be applicable to cancer tissue as well and promote cancer growth. Furthermore, one also feared that exposing patients who had been treated for cancer, to HBO, would lead to recurrence. Nevertheless, two systematic reviews on HBO and cancer have concluded that the use of HBO in patients with malignancies is considered safe. To supplement the previous reviews, we have summarized the work performed on HBO and cancer in the period 2004-2012. Based on the present as well as previous reviews, there is no evidence indicating that HBO neither acts as a stimulator of tumor growth nor as an enhancer of recurrence. On the other hand, there is evidence that implies that HBO might have tumor-inhibitory effects in certain cancer subtypes, and we thus strongly believe that we need to expand our knowledge on the effect and the mechanisms behind tumor oxygenation.

The ketogenic diet and hyperbaric oxygen therapy prolong survival in mice with systemic metastatic cancer.

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Abnormal cancer metabolism creates a glycolytic-dependency which can be exploited by lowering glucose availability to the tumor. The ketogenic diet (KD) is a low carbohydrate, high fat diet which decreases blood glucose and elevates blood ketones and has been shown to slow cancer progression in animals and humans. Abnormal tumor vasculature creates hypoxic pockets which promote cancer progression and further increase the glycolytic-dependency of cancers. Hyperbaric oxygen therapy (HBO2T) saturates tumors with oxygen, reversing the cancer promoting effects of tumor hypoxia. Since these non-toxic therapies exploit overlapping metabolic deficiencies of cancer, we tested their combined effects on cancer progression in a natural model of metastatic disease.

We used the firefly luciferase-tagged VM-M3 mouse model of metastatic cancer to compare tumor progression and survival in mice fed standard or KD ad libitum with or without HBO2T (2.5 ATM absolute, 90 min, 3x/week). Tumor growth was monitored by in vivo bioluminescent imaging.

KD alone significantly decreased blood glucose, slowed tumor growth, and increased mean survival time by 56.7% in mice with systemic metastatic cancer. While HBO2T alone did not influence cancer progression, combining the KD with HBO2T elicited a significant decrease in blood glucose, tumor growth rate, and 77.9% increase in mean survival time compared to controls.

KD and HBO2T produce significant anti-cancer effects when combined in a natural model of systemic metastatic cancer. Our evidence suggests that these therapies should be further investigated as potential non-toxic treatments or adjuvant therapies to standard care for patients with systemic metastatic disease.

Treatment of brain tumor patients: hyperthermia, hyperbaric oxygenation, electric fields or nanoparticles

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Despite considerable advancements in the therapy of malignant glioma in recent years with modern radiation and surgical techniques, alkylating and antiangiogenic chemotherapy, as well as molecular-based treatment decisions, treatment outcomes are mostly unsatisfactory. Understandably, patients often ask for experimental, sometimes unusual therapeutic modalities and this should be integrated into the clinical practice. In addition to experimental therapeutic approaches based on novel drugs, viral agents, immunotherapy and radiation approaches, experimental procedures of interest for patients particularly encompass mechanical approaches with the aim at physically altering the tumor tissue by temperature, oxygenation or magnetization. These mechanical procedures are based on intuitive concepts and promise fewer side effects than other experimental approaches. In addition, the requirements for approval by medical device regulations in terms of proof of efficacy are generally less stringent. As a consequence approaches, such as hyperbaric oxygenation, hyperthermia and electric fields, which are often heavily advertised and in part reimbursed by health insurances, have been used for many years, often by centers not specialized in the treatment of brain tumor patients, although sound data from prospective controlled clinical trials that determine which patients in which situation may benefit, are generally lacking. In this review we review these clinical therapeutic approaches.

The effect of hyperbaric oxygenation on the indices of lipid peroxidation in the blood of patients with lung cancer

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The effect of hyperbaric oxygenation (HBO) used in the pre- and postoperative periods on the content of lipid peroxidation (LPO) products in the plasma and erythrocyte membranes and on the physiological antioxidant activity has been assessed in patients with lung cancer. It has been shown that hypoxia in patients with lung cancer is accompanied by LPO activation and decreased antioxidant protection. Surgery increases hypoxia and further activates LPO. HBO has a positive effect on LPO processes manifested in a decrease of secondary LPO products content and mobilization of antioxidant activity, i.e. protects the cellular membrane from hypoxia-induced damages, promotes a 1.5-fold reduction in the incidence of postoperative complications, and enhances the efficacy of surgical treatment of patients with lung cancer.

Clinical importance of changes in thrombocytic hemostasis in lung cancer

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Clinico-laboratory examinations of 86 patients have shown that lung cancer develops against the background of activation of the thrombocytic link of hemostasis which manifested itself in thrombocytosis, greater degree of destruction of the lysosomal membranes, lower energy resources of the cells, their tendency to slow and little reversible aggregation. The authors consider that the indicators of the ADP-induced aggregation of thrombocytes may be used for prognosis of postoperative pyo-inflammatory and thromboembolic complications. HBO is good for correction of alterations in the thrombocytic link of hemostasis in lung cancer and its suppurative complications.

The effect of hyperbaric oxygen on growth of human squamous cell carcinoma xenografts.

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Hyperbaric oxygen is an important adjunct to the treatment of patients with head and neck cancer with existing or recurrent wound healing problems. Anecdotal clinical observations and a recent study of chemically induced oral cancer in hamsters have raised concern that hyperbaric oxygen therapy may accelerate tumor growth in such patients. This study evaluated the effect of hyperbaric oxygen therapy on the growth of human squamous cell carcinoma xenografts in a proved animal model. Fresh tumor specimens from three patients with head and neck squamous cell carcinoma of varying degrees of differentiation were first subcutaneously transplanted into a nude mouse host. Growing xenografts were then transplanted into one of three mouse groups. Half of the mice in each group were given hyperbaric oxygen therapy. The transplant volume as an index of tumor growth was measured in controls and mice given hyperbaric oxygen therapy six times during the 3-week course. Xenograft growth was almost linear in all mice. No statistical difference in overall group mean growth rates was observed in mice given hyperbaric oxygen or control mice regardless of the degree of tumor differentiation. Xenograft tissue from all mice was microscopically examined for tumor mitotic indices and degree of differentiation. This study suggests that hyperbaric oxygen therapy has no effect on established tumor xenograft growth.

Evaluation of mutagenic effects of hyperbaric oxygen (HBO) in vitro. II. Induction of oxidative DNA damage and mutations in the mouse lymphoma assay.

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We recently showed that treatment of V79 cells with hyperbaric oxygen (HBO) efficiently induced DNA effects in the comet assay and chromosomal damage in the micronucleus test (MNT), but did not lead to gene mutations at the hprt locus. Using the comet assay in conjunction with bacterial formamidopyrimidine DNA glycosylase (FPG protein), we now provide indirect evidence that the same treatment leads to the induction of 8-oxoguanine, a premutagenic oxidative DNA base modification in V79 and mouse lymphoma (L5178Y) cells. We also demonstrate that HBO efficiently induces mutations in the mouse lymphoma assay (MLA). Exposure

of L5178Y cells to HBO (98% O(2); 3bar) for 2h caused a clear mutagenic effect in the MLA, which was further enhanced after a 3h exposure. As this mutagenic effect was solely due to the strong increase of small colony (SC) mutants, we suggest that HBO causes mutations by induction of chromosomal alterations. Molecular characterization of induced SC mutants by loss of heterozygosity (LOH) analysis showed an extensive loss of functional tk sequences similar to the pattern found in spontaneous SC mutants. This finding confirmed that the majority of HBO-induced mutants is actually produced by a clastogenic mechanism. The induction of point mutations as a consequence of induced oxidative DNA base damage seems to be of minor importance.

Evaluation of hyperbaric oxygen as a chemosensitizer in the treatment of epithelial ovarian cancer in xenografts in mice.

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BACKGROUND. Resistance to chemotherapy is common in bulky hypoxic tumors such as epithelial ovarian cancer. Hyperbaric oxygen (HBO) oxygenates hypoxic tissues and promotes neovascularization. These unique properties of HBO may help overcome chemotherapy resistance by increasing both tumor perfusion and cellular sensitivity. This study was undertaken to determine if HBO increases the response of epithelial ovarian cancer to cisplatin chemotherapy. METHODS. In Phase I, 64 nu/nu mice were divided into four groups and subcutaneously inoculated with cells from the A2780 human epithelial ovarian cancer cell line. Group 1 served as controls. Group 2 received weekly intraperitoneal cisplatin (3.15 mg/kg). Group 3 was exposed to HBO (dives) at 2.4 atmospheres absolute pressure for 90 minutes, 7 days a week. Group 4 received both cisplatin and HBO. In Phase II, 72 mice were divided into two groups and similarly inoculated. Both groups received weekly intraperitoneal cisplatin (2.5 mg/kg). Group 1 was not exposed to HBO. Group 2 was exposed to HBO for 5 days a week. RESULTS. Dramatic tumor neovascularization was found in tumors of mice exposed to HBO ($P = 0.0001$). There was significant ($P = 0.014$) tumor growth retardation in Phase I for mice receiving both cisplatin and HBO compared with those treated with cisplatin alone. This significance was noted after just two doses of cisplatin but subsequently lost due to reduced numbers of mice. In Phase II, neovascularization was detectable after 10 HBO treatments (2 weeks) and was maximal after 15 treatments (3 weeks). CONCLUSIONS. Hyperbaric oxygen increases vascularity in bulky tumors such as epithelial ovarian cancer. There appears to be a relationship between increased vascularity and enhanced response to chemotherapy that merits further investigation.

The effect of hyperbaric oxygen on growth and chemosensitivity of metastatic prostate cancer.

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BACKGROUND: Currently, advanced prostate cancer (CaP) is not curable. In this report hyperbaric oxygen (HBO) is examined as an adjuvant to chemotherapy and as a stand-alone treatment. MATERIALS AND METHODS: CaP cell monolayers grown under normoxic conditions were exposed to cisplatin, taxol or doxorubicin for 90 minutes under HBO (3.0 atmospheres, 100% O2) or normal pressure air. RESULTS: HBO reduced by 47% the concentration of doxorubicin required to produce a 20% reduction in cell numbers, but did not change the concentration required to produce a > 50% reduction. HBO increased the sensitivity of PC-3 cells to taxol at all concentrations, (mean 1.8%). Cisplatin chemosensitivity was not affected by HBO. HBO reduced the growth rate of DU-145 8.1% relative to control ($p = 0.01$), and PC-3 2.7% ($p = 0.12$). CONCLUSIONS: This study shows that HBO can decrease the rate of growth, and increase sensitivity to anticancer agents, however, the effects are cell line dependent.

Acute effects of combined photodynamic therapy and hyperbaric oxygenation in lung cancer--a clinical pilot study.

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BACKGROUND AND OBJECTIVE: Photodynamic tumor therapy (PDT) is based upon a photochemical reaction that is limited by the availability of molecular oxygen in the target tissue. The use of hyperbaric oxygenation (HBO) increases the amount of oxygen available for the process may thereby enhance the efficacy of PDT. We investigated the acute effects on tumor stenosis after combined PDT/HBO. PATIENTS AND METHODS: Thirty patients (22 males, 8 females, mean age: 68.8 years; range: 44-78 years) with inoperable non-small cell bronchogenic carcinoma and endobronchial stenosis were studied prospectively. Photosensitization was carried out using a hematoporphyrin-derivative 2 mg/kg BW 48 hours prior to PDT. The light dose was calculated as 300 J/cm fiber tip. The assessment of outcome 1 and 4 weeks after PDT/HBO was performed by endoscopy, chest X-ray, spirometry, laboratory parameters, subjective report of dyspnea, and Karnofsky performance status. RESULTS: At one and four weeks after the treatment, the patients felt a significant improvement of dyspnea and hemoptysis along with an objective subsiding of poststenotic pneumonia, though spirometric parameters revealed no significant difference. A significant reduction of tumor stenosis ($P < 0.05$) and an improvement of the Karnofsky performance status ($P < 0.05$) were documented 1 and 4 weeks after PDT/HBO. No therapy related complications were observed. CONCLUSIONS: Although the small number of patients does not allow to draw definitive conclusions to be drawn, the results suggests that combined PDT/HBO represents a new, safe, and technically feasible approach. It enables efficient and rapid reduction of the endoluminal tumor load and helps conditioning the patient for further treatment procedures.

Photodynamic therapy enhanced by hyperbaric oxygen in acute endoluminal palliation of malignant bronchial stenosis (clinical pilot study in 40 patients).

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OBJECTIVES: Photodynamic tumor therapy (PDT) is based upon a photochemical reaction that is limited by the availability of molecular oxygen in the target tissue. The use of hyperbaric oxygenation (HBO) increases the amount of oxygen available for the process may thereby enhance the efficacy of PDT. We proved in a prospective, non-randomized clinical pilot study the acute effects on malignant bronchial stenosis and the technical feasibility of combined PDT/HBO. METHODS: Forty patients (29 males, 11 females, mean age: 64.3 years; range 39-82 years) with inoperable, advanced malignant bronchial tumor stenosis were studied prospectively. Photosensitization was carried out using a hematoporphyrin-derivative 2 mg/kg bw 48 h prior to PDT. The light dose was calculated as 300 J/cm fiber tip. The assessment of outcome 1 and 4 weeks after PDT/HBO was done by endoscopy, chest X-ray, spirometry, laboratory parameters, subjective report of dyspnea and Karnofsky performance status. RESULTS: At 1 and 4 weeks after the treatment the patients felt a significant improvement of dyspnea and hemoptysis alongside with an objective subsiding of poststenotic pneumonia, though spirometric parameters revealed no significant difference. A significant reduction of tumor stenosis ($P<0.05$) and an improvement of the Karnofsky performance status ($P<0.05$) were documented 1 and 4 weeks after PDT/HBO. No therapy related complications were observed. CONCLUSION: Although the small number of patients does not allow to draw definitive conclusions, the results suggest that combined PDT/HBO represents a new, safe and technically feasible approach. It enables efficient and rapid reduction of the endoluminal tumor load and helps conditioning the patient for further treatment procedures.

Hyperbaric oxygen and photodynamic therapy in the treatment of advanced carcinoma of the cardia and the esophagus.

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BACKGROUND AND OBJECTIVE: The photochemical reaction of photodynamic therapy (PDT) depends on the presence of molecular oxygen. Because of anoxic regions in tumor tissue and vascular shutdown during PDT, the efficiency is limited. Therefore, the use of hyperbaric oxygen, which increases the oxygen in tumor tissue, as well as the amount of singlet oxygen, may enhance the efficiency of PDT. STUDY DESIGN/MATERIALS AND METHODS: After diagnostic work-up, photosensitization was carried out with a hematoporphyrin-derivate 2 mg/kg body weight 48 hours before PDT. The light dose was calculated as 300 J/cm of fiber tip. Twenty-three patients were treated by PDT alone and 29 patients received PDT under hyperbaric oxygen at a level of two absolute atmospheric pressures. RESULTS: Improvement regarding dysphagia and stenosis-diameter could be obtained in both treatment arms with no significant difference (P = 0.43 and P = 0. 065, respectively). The tumor length also decreased in both groups and showed a significant difference in favour of the PDT/HBO group (P = 0.002). The mean overall survival was 11.3 months. The mean survival time for the PDT group was 8.7 months and for the PDT/HBO group 13.8 months (P = 0.021). CONCLUSION: According to this pilot study, combined PDT/HBO represents a new approach in the treatment of esophageal and cardia cancer, which appears to have enhanced the efficiency of PDT. Copyright 2000 Wiley-Liss, Inc.

Hyperbaric oxygen therapy and squamous cell carcinoma cell line growth.

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Hyperbaric oxygen (HBO) promotes tissue healing by increasing oxygenation. Therefore, HBO therapy is clinically useful for some patients who have undergone major cancer resection and/or radiotherapy to the head and neck. For individual patients, however, there might be undetected viable tumor present at the time of therapy. This study was performed to determine if increased tissue oxygen had a measurable effect on the growth of squamous carcinoma xenotransplants which had been derived from head and neck cancers. After the successful growth of two well-established human squamous cell carcinoma cell lines (183 and 1483), each tumor was transplanted into 20 mice. Every mouse received four transplants of 10(6) cells. Ten mice with 40 xenotransplants in each group were treated with HBO daily for 90 minutes at a pressure of 2 atm, whereas the other 10 formed the control group. The mice transplanted with cell line 1483 were treated for 21 days; mice transplanted with cell line 183 were treated for 28 days. The tumor weight, volume, and histology were evaluated. No significant difference was found between experimental groups. This study suggests that increased tissue oxygen neither significantly increases nor decreases the growth of squamous cell carcinoma.

Oxygenation measurements in head and neck cancers during hyperbaric oxygenation.

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BACKGROUND: Tumor hypoxia has proven prognostic impact in head and neck cancers and is associated with poor response to radiotherapy. Hyperbaric oxygenation (HBO) offers an approach to overcome hypoxia. We have performed pO2 measurements in selected patients with head and neck cancers under HBO to determine in how far changes in the oxygenation occur and whether a possible improvement of oxygenation parameters is maintained after HBO. PATIENTS AND METHODS: Seven patients (five male, two female, age 51-63 years) with squamous cell cancers of the head and neck were investigated (six primaries, one local recurrence). The median pO2 prior to HBO was determined with the Eppendorf histograph. Sites of measurement were enlarged cervical lymph nodes (n = 5), the primary tumor (n = 1) and local recurrence (n = 1). Patients then underwent HBO (100% O2 at 240 kPa for 30 minutes) and the continuous changes in the oxygenation during HBO were determined with a Licox probe. Patients had HBO for 30 minutes (n = 6) to 40 minutes (n = 1). HBO was continued because the pO2 had not reached a steady state after 30 minutes. After decompression, patients ventilated pure oxygen under normobaric conditions and the course of the pO2 was further

measured over about 15 minutes. RESULTS: Prior to HBO, the median tumor pO2 in the Eppendorf histography was 8.6 +/- 5.4 mm Hg (range 3-19 mm Hg) and the pO2 measured with the Licox probe was 17.3 +/- 25.5 mm Hg (range 0-73 mm Hg). The pO2 increased significantly during HBO to 550 +/- 333 mm Hg (range 85-984 mm Hg, p = 0.018). All patients showed a marked increase irrespective of the oxygenation prior to HBO. The maximum pO2 in the tumor was reached after 10-33 minutes (mean 17 minutes). After leaving the hyperbaric chamber, the pO2 was 282 +/- 196 mm Hg. All patients maintained an elevated pO2 for further 5-25 minutes (138 +/- 128 mm Hg, range 42-334 mm Hg, p = 0.028 vs the pO2 prior to HBO). CONCLUSIONS: Hyperbaric oxygenation resulted in a significant increase in the tumor oxygenation in all seven investigated patients. A significant increase at the point of measurement could be maintained for several minutes after decompression and after leaving the hyperbaric chamber.