HYPERBARIC OXYGEN THERAPY IN THE TREATMENT OF BREAST CARCINOMA: POSSIBILITIES, QUESTIONS, CHALLENGES, RESPONSIVENESS

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Abstract
In the case of the cancer diseases, the hyperbaric oxygen therapy (HBOT) is auxiliary and not primarily life-saving treatment. Thanks to its multiple and general effect on the all tissue and organ systems it seems however to be an important tool of adjuvant therapy in the treatment of late effects of radiotherapy. HBOT is applied during and after breast-conserving therapy, and it is used in the treatment of breast-cancer co-morbidities, e.g. arm/shoulder pain, arm/hand swollen, pain in the affected area, and oversensitivity and skin problems in the area of affected breast. Further research in this area has to be carried out due to the multiple complexity of HBOT effects.

Keywords: Hyperbaric Oxygen Therapy. Breast cancer. Radiotherapy

1 Introduction

Hyperbaric Oxygen Therapy (HBOT) is the therapeutic method in which the patient inhales 100% oxygen at a pressure of more than 1 atmosphere (1 ATA; 101.325 kPa) in a specially treated hyperbaric chamber. During HBOT, oxygen dissolves in all body fluids (e.g. blood plasma, lymph, cerebrospinal fluid) and, moreover, penetrates into ischemic areas deeper than at normobaric pressure [1]. Increased O_2 concentrations in the body, together with higher pressures, are complex, giving HBOT unique therapeutic options. HBOT stimulates aerobic metabolism, reduces lactate production, eliminates local acidosis, allows for greater diffusion of oxygen into tissues, bactericidal effects on anaerobic bacteria, regenerates nerve cells, reduces edema, and many others [1-4]. Overpressure itself also contributes to the treatment of disease processes in the closed bone and tooth tissues as well as to the influence of tissue swelling [5, 6].

For some diseases, HBOT is a life-saving treatment. For many other diseases, HBOT is an important supplement to other treatment methods. The curative effect is not immediate, but begins to manifest in patients after a certain time. The number of exposures ranges from 10 to 30 and the duration of one exposure is usually indicated in the range of 60 to 90 minutes. Generally, the therapy is carried out within the range of an applied working pressure of 1.4-3 ATA, depending on various factors; for children, the applied pressure range is approximately 1.4-1.6 ATA. The effect of HBOT on the organisms of the individual varies widely depending on many factors, including the pressure, exposure duration and health of the individual, as well as the biological variability of the organism [1, 3, 7-9].

In the hyperbaric chamber, the patient is monitored by healthcare professionals. The safety of the equipment is ensured by a technician trained in HBOT. The standard HBOT procedure runs through three phases - compression, isocompression and decompression. During the compression phase, the pressure in the hyperbaric chamber increases. This is a slow compression that takes about 10 minutes. During this time the pressure is increased to the target value of the applied working pressure. The duration of this phase depends on how the patient is able to balance the pressure in the middle ear with the pressure in the chamber. It usually does not last longer than 15 minutes. Isocompression is to achieve the desired therapeutic pressure, with the maximum allowable pressure being 3 ATAs. The length of isocompression varies. At 2 ATA pressure, it may not exceed 180 minutes and may be repeated three times in 24 hours. At 3 ATA pressures, the isocompression phase should not exceed 120 minutes and may be repeated twice every 24 hours. The progress of the decompression phase is precisely determined by the table values. At the time between the individual exposures in the chamber, the patient can inhale 100% oxygen under normobaric conditions [1, 10-13].

2 Indications for treatment with hyperbaric oxygen

The list of indications for HBOT develops in line with the development of scientific evidence in this area. However, it is necessary to consider the extension of this treatment method, which is very different on individual continents. In economically advanced countries (USA, Canada, Australia, or Western Europe countries), where emphasis is placed on adhering to the Evidence-Based Medicine (EBM) and Health Technology Assessment (HTA), the number of indications is in the range of 15 - 20. HBOT is a causal treatment method in some pathological conditions with a significant effect on the therapeutic outcome, mortality and quality of life. For other conditions, it is an adjuvant treatment method that complements the conservative or surgically treated procedure

and affects the course of the disease and subsequent complications. At present, HBOT concerns a wide range of medical disciplines including diabetes, angiology, surgery, traumatology, orthopedics, pediatrics, oncology, neurology, otorhinolaryngology, urology, as well as urgent or intensive medicine [14].

The world's leading professional hyperbaric medicine company is the Undersea and Hyperbaric Medical Society (UHMS). It is a highly respected organization whose list of indications is recognized by the American health insurance system [14, 15]. The European alternative to this company is the European Committee for Hyperbaric Medicine (ECHM) [16]. Its activities are aimed at supporting the continuous improvement of the quality of care and safety in hyperbaric medicine. One instrument for achieving this goal is the organization of consensual conferences, the conclusions of which are generally recognized rules [17]. The conferences are organized at 2-3 year intervals and reflect on various aspects of hyperbaric and diving medicine, including the definition of a recommended list of indications [14].

Indications valid in the Slovak Republic are drawn up by individual health insurance companies in accordance with the criteria of the European Society of Hyperbaric Medicine [18], but they are not uniform. HBOT is a standard therapy e.g. for the treatment of decompression sickness, gas embolism and carbon monoxide poisoning. HBOT is also effective in the treatment of gas gangrene, anaerobic infections, diabetic foot, Burger's disease [19], atherosclerosis, Crohn's disease, ulcerative colitis, atopic dermatitis [8], some hearing and balance disorders, chronic bone inflammation, stroke [5], burns, frostbite [10], as well as in conditions with insufficient oxygenation. Another indication is the number of inflammatory and immune-mediated diseases that have been successfully treated with HBOT [19].

Diagnosis and conditions to which HBOT may be indicated may generally be divided into four groups. The first group is where HBOT provides oxygen substitution. It may be total hypoxia and hypoxemia (e.g. carbon monoxide poisoning) or ischemia (ischemic stroke, ischemic disease of the lower limbs, etc.). The second group of cases uses the physical effect of HBOT to eliminate air bubbles (e.g. air embolism or decompression sickness). The third group of diseases use the immunosuppressive effect of HBOT (e.g. multiple sclerosis) and the fourth group are conditions utilizing a combination of all the above mentioned effects of HBOT (eg wound healing, burns, frostbites) [1, 10, 13, 20-22].

3 Possibilities of HBOT application in oncology

Hypoxia is known to be a critical property of solid tumors that promotes tumor survival, angiogenesis, growth factor production, glycolysis metabolism, and/or production of metastasis. From this aspect, HBOT appears to be a logical alternative to affect these properties in patients with oncological disease. At present, clinical and experimental research is being conducted on the influence of both normobaric and hyperbaric hyperoxia on influencing the process of angiogenesis, cell proliferation, metastasis, cell survival, apoptosis, tumor-cell resistance. However, in clinical practice, the use of HBOT in oncology focuses primarily on the treatment of late effects of radiotherapy (radiation necrosis), either bone (osteoradionectosis) or soft tissues. Another option is to use the so-called radiosensitization - simultaneous application of HBOT and radiotherapy in selected aggressive and radiosensitive tumors. In the past, HBOT has also been shown to reduce unpleasant symptoms after irradiation and after radical breast cancer surgery [14].

4 HBOT and breast cancer

Granowitz et al. [23] used an experimental *in vitro* model to investigate the effects of HBOT 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. HBOT (97.9% O_2, 2.1% CO_2, 2.4 ATA) 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% O_2, 5% CO_2, 1 atmosphere absolute) and increased atmospheric pressure alone (8.75% O_2, 2.1% CO_2, 2.4 atmospheres absolute) also inhibited proliferation, but their effects were not as profound as HBOT ($p<0.01$ when either hyperoxia or increased pressure was compared to HBOT for all 4 cell types). HBOT 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 HBOT 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 HBOT-induced increases in necrosis or apoptosis. Based on the results obtained, the authors noted that HBOT inhibits *in vitro* the benign and malignant mammary epithelial cell proliferation, but does not enhance cell death.

Japanese authors Enomoto et al. [24] presented a case study on the use of HBOT in the treatment of late effects of radiotherapy - radiation necrosis of bones and soft tissues. Radiation therapy is performed as an adjuvant therapy when indicated following surgical resection of malignant tumors. However, radiation exposure induces acute or chronic dermatitis, depending on the radiation dose, interval, tissue volume, or irradiated area of the body. Radiation-induced skin ulcers and osteomyelitis of the underlying bone are intractable late-stage complications of

radiation therapy, and often require reconstructive surgery to cover exposed tissue. HBOT has been suggested as a treatment for delayed radiation injury with soft tissue and bone necrosis. A 74-year-old Japanese female underwent left radical mastectomy for breast cancer (T3N3M0, stage IIIB) in 1987. Radiation therapy was initiated 6 weeks after the surgery. She received telecobalt-60 in a total dose of 50 Gy with 25 fractions to the left supraclavicular, parasternal and left axillary regions, and electron treatment (9 MeV) in a total dose of 50 Gy in 25 fractions to the left chest wall. After irradiation, her skin became thinner and more fragile on the left chest wall, but no severe infections were observed. She noticed a small ulcer that repeatedly healed and recurred in 2000. She visited the hospital where she received radiation therapy and was treated for a skin ulcer on the left chest wall in December 2012. A fistula developed and then pus was discharged in January 2013. She was referred to the hyperbaric medical center in February 2013, and the fistula (1.5 × 3 cm) with pus discharge was observed. She was diagnosed with a late-onset radiation-induced skin ulcer that developed 25 years after radical mastectomy. HBOT (2.5 ATA with 100% oxygen for 60 minutes) was indicated for the refractory ulcer and osteomyelitis of the ribs. The patient was treated with HBOT a total of 101 times over the course of 1 year and completely recovered. The authors concluded the possibility of safe HBOT performance for even more than 100 sessions in patients with radiation-induced skin ulcers and osteomyelitis. HBOT can be considered as an alternative, conservative treatment when surgical resection for late-onset, radiation-induced skin ulcers is not indicated because of fragile skin in the irradiated areas.

In another clinical study from the Netherlands, Teguh et al. [25] examined patient reported outcome measures of women undergoing HBOT after breast-conserving therapy. Included were 57 women treated with HBOT for late radiation-induced tissue toxicity (LRITT). HBOT consisted of (on average) 47 sessions. In total, 80 min of 100% O_2 was administered under increased pressure of 2.4 ATA. Quality of life was assessed before and after treatment using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-BR23, and a NRS pain score. Fifty-seven women were available for evaluation before and after treatment. Before HBOT, patients had severe complaints of pain in the arm/shoulder (46%), swollen arm/hand (14%), difficulty to raise arm or move it sideways (45%), pain in the area of the affected breast (67%), swollen area of the affected breast (45%), oversensitivity of the affected breast (54%), and skin problems on/in the area of the affected breast (32%); post HBOT, severe complaints were still experienced in 17, 7, 22, 15, 13, 15, and 11% of the women, respectively. Differences were all significant. The NRS pain score improved at least 1 point (range 0-10) in 81% of the patients ($p < 0.05$). In these breast cancer patients treated with HBOT for LRITT, the patient-reported outcomes were positive and improvements were observed. HBOT was a well-tolerated treatment for LRITT and its side-effects were both minimal and reversible.

5 Conclusion

HBOT has many physiological and pharmacological effects. These effects provide a relatively broad indication spectrum for HBOT. Some indications are relatively well documented in clinical trials, but many of them are only supported studies that are not in line with modern criteria and evidence is of high scientific value. Despite its effects, HBOT should not be substituted for other, commonly used and successful treatment options and should be used as adjunctive therapy. Since the mechanism of HBOT's action itself is not precisely defined at present, further research in this area is of great importance.

Acknowledgements

This publication was created in the frame of the project "Completion of the technical infrastructure for the development of science and research at Alexander Dubček University of Trenčín through Hyperbaric Oxygen Therapy", ITMS code 26210120019, based on the Operational Programme Research and Development and funded from the European Social Fund.

References

[1] Jain, K.K. Textbook of Hyperbaric Medicine. Hogrefe and Huber Publishers, Göttingen, 2009, 578 s., ISBN: 978-0-88937-361-7.

[2] Beynon, C., Kiening, K. L., Orakciog-Lu, B. et al. Brain tissue oxygen monitoring and hyperoxic treatment in patients with traumatic brain injury. J. Neurotrauma. 2012; 29 (12): 2109-2123.

[3] Krajčovičová, Z., Malay, M., Hollá, M. et al. Hyperbarická oxygenoterapia a možnosti jej využitia v súvislosti s aktivitami vo vodnom prostredí. Zdravotnícke listy. 2015; 3 (3): 23-27.

[4] Krajčovičová, Z., Zigo, R., Mišinová, M. et al. Posúdenie vplyvu hyperbarickej oxygenoterapie na subjektívne vnímanie kvality života pacientov s tinnitom. Zdravotnícke listy. 2016; 4 (1): 7-12.

[5] Informácie pre pacienta. Fakultná nemocnica Trenčín.

[6] Mayo Clinic Staff. Hyperbaric oxygen therapy: Definition. 2014. On-line dostupné na: http://www.mayoclinic.org/tests-procedures/hyperbaric-oxygen-therapy/basics/definition/prc-20019167 [cit. 25.01.2017].

[7] Krajčovičová, Z., Zigo, R., Meluš, V. Possibilities of hyperbaric oxygen therapy usage in comprehensive treatment of selected hearing diseases and disorders. University review. 2015; 9 (2-3): 45-53.
[8] Krajčovičová, Z., Meluš, V. Proposed mechanisms of action of selected antioxidant defences induced by hyperbaric oxygen therapy. University review. 2014; 8 (1-2): 2-8.
[9] Sahni, T., Singh, P., John, M.J. Hyperbaric oxygen therapy: current trends and applications. J. Assoc. Physicians India. 2003; 51: 280-284.
[10] Baňárová, P., Malay, M., Kotyra, J. et al. Potenciál využitia hyperbarickej oxygenoterapie pri funkčných poruchách pohybového systému. Zdravotnícke listy. 2014; 2 (3): 23-27.
[11] Kapturová, H., Ačaiová, G., Chudá, A. et al. Hyperbarická oxygenoterapia. Sestra. 2005; 9 (1): 38-39, ISSN 1210-0404.
[12] Mrásková, E., Kafiová, H., Neuwirtová, J. Hyperbarická oxygenoterapia u kriticky nemocných a možné problémy při ošetřovatelské péči a léčbě. Sestra. 1997; 41 (6): 15, ISSN 1210-0404.
[13] Kmecová, A., Šanta, M., Arvay, Ľ. Úlohy sestry pri hyperbarickej oxygenoterapii. On-line dostupné na: http://www.unipo.sk/public/media/files/docs/fz_veda/svk/ dokument_81_29.pdf [cit. 27.02.2017].
[14] Hájek, M. et al. Hyperbarická medicína. Mladá Fronta, Praha, 2017, 453 s., ISBN: 978-80-204-4235-2.
[15] Undersea and Hyperbaric Medical Society. On-line dostupné na: https://www.uhms.org/
[16] European Commitee for Hyperbaric Medicine. On-line dostupné na: http://www.echm.org/
[17] Mathieu, D., Marroni, A., Kot, J. Tenth European Consensus Conference on Hyperbaric Medicine: recommendations for accepted and non-accepted clinical indications and practice of hyperbaric oxygen treatment. Diving Hyperb Med. 2017; 47 (1): 24-32.
[18] Mathieu, D., Marroni, A., Kot, J. Tenth European Consensus Conference on Hyperbaric Medicine: preliminary report. Diving Hyperb Med. 2016; 46 (2): 122-123.
[19] Kim, H. R., Kim, J. H., Choi, E. J. et al. Hyperoxygenation Attenuated a Murine Model of Atopic Dermatitis through Raising Skin Level of ROS. PLoS One. 2014; 10: 25275529.
[20] Barcal, R., Emmerová, M., Hadravský, M. Hyperbarie a hyperbarická oxygenoterapie. 1.vyd., Plzeň, V. Kuma, 2000, ISBN 80-902017-7-6.
[21] Beznoska, R. Hyperbarické komory – naděje pro pacienty. Sestra. 1994; 41 (2): 22-28, ISSN 1210-0404.
[22] Königová, R. et al. Komplexní léčba popálenín. 1.vyd., Praha: Grada Publishing, 1999, ISBN 8071694169.
[23] Granowitz, E. V., Tonomura, N., Benson, R. M. et al. Hyperbaric oxygen inhibits benign and malignant human mammary epithelial cell proliferation. Anticancer Res. 2005; 25 (6B): 3833-3842.
[24] Enomoto, M., Yagishita, K., Okuma, K. et al. Hyperbaric oxygen therapy for a refractory skin ulcer after radical mastectomy and radiation therapy: a case report. J Med Case Rep. 2017; 11 (1): 5.
[25] Teguh, D. N., Bol Raap, R., Struikmans, H. et al. Hyperbaric oxygen therapy for late radiation-induced tissue toxicity: prospectively patient-reported outcome measures in breast cancer patients. Radiat Oncol. 2016; 11 (1): 130.