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NEÜ YAYINEVİ

How Can Hyperbaric Oxygen Therapy Affect The Diaphragm and Respiratory Functions of The Patients?

Hiperbarik Oksijen Tedavisi Uygulanan Hastalarda Solunum Fonksiyonları ve Diyafram Üzerine Etkisi Nedir?

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Öz

Amaç: Bu retrospektif çalışmada, hiperbarik oksijen tedavisinin ardışık uygulamalarda hastaların solunum fonksiyonları ve diyafragma hareketleri üzerindeki etkilerini değerlendirmeyi amaçladık.
Hastalar ve Yöntem: Çalışma grubu, Haziran 2019-Aralık 20219 tarihleri arasında hiperbarik oksijen tedavisi uygulanan çeşitli hastalık tanısı alan 22 hastadan oluşuyordu. Dinamik ve statik akciğer hacimleri, difüzyon kapasitesi, maksimum inspiratuar ve ekspiratuar basınçlar gibi solunum fonksiyonları tedavi seanslarının başlamasından ve bitiminden önce değerlendirildi. Ayrıca torasik ultrasonografi ile diyafram kalınlığı, gelgit volümü ve derin inspirasyon sırasındaki diyafram hareketleri ölçüldü.
Bulgular: Çalışmaya yaş ortalaması 53.3±10.0 yıl olan yirmi iki hasta (16 erkek;6 kadın) dahil edildi. Hastaların hiperbarik oksijen tedavilerinin sonunda yapılan ölçümlerde total akciğer kapasitesi, vital kapasite ve rezidüel volüm de artış görüldü (p<0.05). Diğer statik akciğer hacimleri, maksimum inspiratuar ve ekspiratuar basınçlar, akciğer karbon monoksit difüzyon kapasitesinde değişiklik gözlenmedi. Tidal volümü hareketi ve vital kapasite sırasında diyafram kalınlığı ve diyafram hareketi artmıştır (p<0.05).
Sonuç: Çalışmamızda hiperbarik oksijen tedavisinin diyafram ve solunum fonksiyonları üzerindeki etkisini, spirometri, diyafram görüntüleme teknikleri ve difüzyon kapasitesi yöntemleri ile değerlendirdik. Sonuç olarak, hiperbarik oksijen tedavisi pulmoner ve diyafram kası fonksiyonlarında anlamlı bir değişikliğe yol açmıştır.

Anahtar Kelimeler: Akciğer, difüzyon kapasitesi, diyafram, hiperbarik oksijen, toksisite

Abstract

Aim: In this retrospective study, we aimed to evaluate the repetitive effects of hyperbaric oxygen treatment on patients' pulmonary functions and diaphragmatic movement.
Patients and Methods: The study group consisted of 22 patients diagnosed with various diseases who were administered hyperbaric oxygen treatment between June 2019 and December 2019. Respiratory functions such as dynamic and static lung volumes, diffusion capacity, and maximum inspiratory and expiratory pressures were evaluated before the start and end of the treatment sessions. Besides, the diaphragm thickness and the diaphragm movements during tidal volume and deep inspiration were measured with thoracic ultrasonography.
Results: Twenty-two patients (16 male;6 female) with a mean age of 53.3±10.0 years were included. At the end of hyperbaric oxygen therapy total lung capacity, vital capacity, and residual volume were significantly increased (p<0.05). The other static lung volumes, maximum inspiratory and expiratory pressures, and diffusing capacity of the lungs for carbon monoxide did not change. The thickness of the diaphragm and diaphragmatic movement during tidal volume and vital capacity were also increased (p<0.05).
Conclusion: In our study, we evaluated the effect of hyperbaric oxygen therapy on diaphragmatic and respiratory functions by using, diffusing capacity, as well as spirometry and diaphragmatic imaging techniques. As a result, hyperbaric oxygen treatment led to a significant change in pulmonary and diaphragmatic functions.

Keywords: Lung, diffusing capacity, diaphragm, hyperbaric oxygen, toxicity

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INTRODUCTION

Hyperbaric oxygen treatment (HBOT) has been widely preferred as an adjunctive treatment to improve the healing process of many ailments, and therapeutic indications are determined by international medical societies. Hyperbaric oxygen increases tissue oxygenation, improves wound healing, may exert bactreiostatic effect, regulates immune system which is compromised due to the local tissue hypoxia. Treatment is usually applied systemically with the patient inside a pressurized chamber (1-3). Although the clinical practice of hyperbaric oxygen and its scientific basis has proceeded significantly, the clinical use of HBOT is limited due to the low availability of pressurised chambers, problems concerning patient compliance, and belief of high oxidative potential.

HBOT has been accepted as a successful treatment modality with better outcomes in various diseases. Although it has been suggested as a successful tool for the treatment of many ailments, it is also stated that functional changes of some organs may also occur in the long term. The main organs on which temporary or permanent effects have been observed in scientific studies are eye, central nervous system and respiratory system (4).

It is commonly known that oxygen toxicity of the lungs may appear after exposure to oxygen at more than 0.5 ATA (1 ATA: one atmosphere absolute). Toxic effects in the pulmonary system are encountered mostly after long-term or prolonged treatments rather than acute exposures (4,5). Diaphragm muscle is one of the vital anatomical structures that plays significant role in the function of the respiratory system with its neighbor of the tissue. Naturally, it supports breathing function with its mobility in inspiration and expiration. The effect of HBOT on the function of the diaphragm muscle was shown in a few experimental studies (6,7).

Several laboratory tests are commonly used to evaluate the anatomical and functional changes of the tissues in order to determine and follow the possible toxic effects. Pulmonary function tests and ultrasound guided evaluation of diaphragmatic movements related to this issue are considered to be valuable tests with their easy applicability. Additionaly, pulmonary function tests are performed and changes are monitored in order to detect the toxic effects of oxygen early in some studies related to the administration of HBOT (8,9).

After searching in the scientific literature, we have noticed that there is not much published clinical research regarding effects of the HBOT on respiratory and diaphragm functions. Therefore, we aimed to evaluate the cumulative effects of the daily HBOT on pulmonary functions and diaphragmatic movement in this study.

PATIENTS AND METHODS

The study group consisted of 22 patients who are above 17 years and underwent HBOT for various diseases between June 2019 and December 2019. None of these patients had risk enhancers for oxygen toxicity and history of previous lung disease. Exclusion criteria included pregnancy, previous HBOT within one year prior to inclusion, ear disease, claustrophobia, pulmonary disease, active smoking and contraindication for HBOT.

The patients were mostly diagnosed with the delayed wound healing problems from different causes. Patients who had radiological image of chest and lung function at the start of the study participated to the study. The study was approved by the medical ethics committee of the hospital (06.12.2019-2019/514/167/14). Informed consent was obtained from the participants after comprehensive explanation of the study. They all agreed to participate the study and signed the written informed consent. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2000.

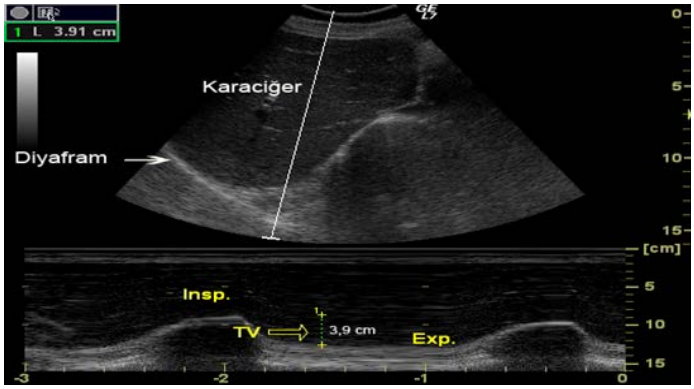
Patients underwent hyperbaric oxygen treatment at 2.4 ATA for routine sessions in the multiplace chamber for twelve patients (Zyron 12 multiplace MLT 09, Hipertech). The treatment protocol consisted of 90 minutes of oxygen in three 30-minute periods with a 5-minute air breaks, 5 times a week. Patients breathed 100 % of oxygen via a mask during the therapy. All measurements were repeated by the same physician at the start and end of series of therapy administered for each medical indication (over more than 10 consecutive sessions). A number of total sessions per patient ranged from 10 to 60 consecutive treatments depending on the diagnosis of disease.

The dynamic and static lung volumes, diffusion capacity as well as the maximum inspiratory and expiratory pressures (MIP and MEP) were evaluated. Besides, the diaphragm thickness, as well as the diaphragm movements during tidal volume and deep inspiration, were measured with thoracic ultrasonography by a pulmonary medicine specialist

well trained in thoracic ultrasonography, before and after the HBOT consecutive sessions. The average of the three acceptable measurements was used.

The chest physician who had been trained by a radiologist and had taken the course regarding thoracic ultrasonography performed the thoracic ultrasonography. GE Logic 7 ultrasound device with 3.5 MHz convex probe was used for sonographic examination. In the clinical practice, thoracic Ultrasound can be used to investigate the chest wall structures, position, morphology and the position of diaphragm thickness and the lung parenchyma. M-mode US may be used to measure the direction of diaphragmatic motion and the amplitude of excursion. The diaphragm is a good reflector for the sound waves. It is seen as Ultrasonographic bright white and thin echogenic band. Vertical movement of the diaphragm during respiration can be measured by M-mode ultrasonography. By using the subcostal approach in the supine position, both diaphragms can easily be seen from the acoustic diaphragm window created by the spleen, liver on the right and left. On the right side of the patient, by using the subcostal approach, the probe is placed between the midclavicular line and the front axillary line by directing it into medial, posterior and cranial. After seeing the diaphragm on top of the liver dome, it is possible to see the movement of the diaphragm during the tidal volume or deep inspiration from M-mod sections that they have been taken previously (Figure 1).

Data were statistically analyzed using SPSS software version (17.0). Continuous data were expressed as means±standard deviations. The normal distribution for all variables was tested using the Kolmogorov-Smirnov test. Categorical data were expressed in numbers and percentages and compared by chi square tests. Univariate analysis was performed using Mann-Witney U test to identify significant variables ($p<0.05$).



Karaciğer: Liver, Diyafram: Diaphragm

Figure 1. Measurement of diaphragm movement in M-mode during tidal volume

RESULTS

This study consisted of 22 cases, including 16 males and 6 females with the mean age of 53.3 ± 10.0 years. Patients were treated for different indications as follows; 11 patients (50%) wound healing problem, 3 patients (14%) avascular necrosis, 2 patients (9%) osteomyelitis, 6 patients (27%) acute idiopatic hearing loss. As a result, we have found out that the lung volumes such as total lung capacity, residual volume and vital capacity increased significantly ($p<0.05$). We have also noticed that other static lung volumes, MIP, MEP, and DLCO remained the same ($p>0.05$) as an outcome of the study. Interestingly, there was a significant increase in the thickness of the diaphragm, and diaphragmatic mobility during tidal volume and deep inspiration in the median for the post-treatment ($p<0.05$). Measurement results were significantly greater than pretreatment values.

Of all the indices of pulmonary mechanical and gas exchange function that were measured before and after HBOT, treatment periods are presented in Table 1. And values which were measured statistically significant is also presented in Table 2.

DISCUSSION

There may be different causes of tissue hypoxia such as vascular compromise, heavy infection burden, deep anemia resulted from chronic disease and acute or chronic toxic inhaled gases. Despite surgical and traditional medical treatment approaches, adequate tissue healing may not be achieved. The presence of facilitating factors such as infection, necrosis, foreign material and ischemia in the tissue can delay wound healing. As these factors limit oxygen delivery to the wound bed, the most striking way to reverse the limitations goes through correcting deficiency in the tissue. Therefore, it may be necessary to improve tissue oxygenation, and interdisciplinary approach is a must to cure the ailments. (1,2)

Tissue oxygenation is crucial for sustaining life and the management of wide range of medical conditions. Therefore systemic oxygen administration is widely used as a drug to increase the partial pressure of oxygen in the tissue in order to repair the tissue damage in many diseases due to the lack of efficient

Table 1. The results of measurements of pulmonary function before and after HBOT period.

	Before HBOT		After HBOT		P value
	Mean	Std. Deviation	Mean	Std. Deviation	
FVC (ml)	3767	1041	3805	1069	>0.05
FVC %	101,2	16,96	102,2	18,79	>0.05
FEV1(ml)	2955	878	2939	776	>0.05
FEV1%	98,1	23,0	96,7	19,4	>0.05
FEV1/FVC	78,5	6,53	77,8	6,55	>0.05
FEF 25-75% (L/seconds)	2,87	1,6	2,74	1,2	>0.05
%FEF25-75%	85,4	49,22	78,8	33,83	>0.05
DLCO (mlCO/min/mm)	24,18	5,94	24,90	8,77	>0.05
DLCO%	91,2	24,1	94,0	35,4	>0.05
MIP (cmH_2O)	113,4	43,0	87,5	6,36	>0.05
MIP%	101,1	30,0	95,4	36,6	>0.05
MEP (cmH_2O)	108,7	31,5	105,5	10,6	>0.05
MEP%	112,5	43,4	108,3	34,7	>0.05
TLC (ml)	7492	3677	7906	4131	<0.05
TLC%	127,0	59,4	133,6	75,3	<0.05
VC (ml)	3767	1041	4858	1006	<0.05
VC%	98,3	15,6	108,0	16,5	<0.05
RV (ml)	4140	3459	4452	3693	<0.05
RV%	211,2	181,7	224,9	201,5	<0.05
FRC (ml)	5322	3546	5685	4014	>0.05
FRC %	169,9	110,9	172,7	137,0	>0.05

DLCO: Diffusing capacity of the lungs for carbon monoxide, FEF25-75%: Forced expiratory flow over the middle one-half of the forced vital capacity, FEV1: Forced expiratory volume exhaled in the first second, FVC: Forced vital capacity, FEV1/FVC: FEV1/FVC ratio, FRC: Functional residual capacity, HBOT: Hyperbaric oxygen treatment, MEP: Maximal expiratory pressure, MIP: Maximal inspiratory pressure, RV: Residual volume, TLC: Total lung capacity, VC: Vital capacity

oxygenation. As a result, adequate oxygenation acting as a nutrient, antibiotic and therapeutic agent enables difficult untreatable health problems to be effectively and safely solved (10). Therefore, HBOT the reference treatment modality in order to repair the damage caused by hypoxia accelerates the healing process in the tissue.

Hyperbaric oxygen therapy is defined as the treatment modality and a curative tool by the application of 100 % oxygen at pressures above one atmosphere absolute (1 ATA = 101.3 kPa). HBOT is delivered using either monoplace or multiplace hyperbaric chamber which is filled with air and systemic oxygen is delivered by mask, hood or anesthetic circuit as needed (11,12). It has been mostly applied in the treatment of both acute and chronic ischemia/hypoxia-related diseases including decompression sickness, carbon monoxide poisoning, compromised flaps and grafts, sudden sensorineural hearing loss, radiation tissue damage, crush injury, diabetic foot ulcer, thermal burns, necrotising soft tissue infections and others in compliance with the indication's guideline for HBOT in worldwide (13-18). As it is stated in the literature we applied hyperbaric oxygen treatment for the various indications in accordance with the scientific background.

It has been reported that partial oxygen level in difficult to healing wounds has been in the range of 5 to 20 mm Hg, compared with 35 to 50 mm Hg measured in normal tissue (19). The increased partial pressure

Table 2. Results of the thickness of the diaphragm, and diaphragmatic mobility during tidal volume and deep inspiration in the median for the post-treatment

	Before HBOT	After HBOT	P value
Diaphragmatic thickness	0.77±0.26	1.08±0.24	0.026
Diaphragmatic mobility during tidal volume	1.49±0.54	1.97±0.54	<0.01
Diaphragmatic mobility during deep inspiration	5.29±1.50	8.14±1.59	<0.01

The value of $p < 0.05$ shows statistically significant increase in measurements

of oxygen in the tissue plays a critical role in terms of healing power because it helps to accomplish needs for the energy of all cell types including epithelial, cells, myocytes, neurons, endothelial cells, immune cells involved in the treatment period. It is commonly believed that the success of treatment regarding HBOT in chronic wounds is partially relevant to increase in fibroblastic activity, collagen production, angiogenesis, and epithelialization (20-22). HBOT improves neovascularization inducing bone marrow stem/progenitor cells migration, circulation, and settling in the peripheral wound, developing vascular buds (23,24). It is emphasized that HBOT is an effective and safe modality in the management of nonhealing hypoxic wounds and an integral part of the interdisciplinary medical-surgical approach to the patients (25). Larsson and colleagues (26) evaluated potential benefits of hyperbaric oxygen in the treatment of deep postoperative infections in a case series of pediatric patients with neuromuscular spine deformity. They reported that HBOT is a safe and beneficial adjunctive treatment in such complex deep tissue infections with spinal implants in high-risk pediatric patients.

Apart from the therapeutical effects of the oxygen, there may have been some side effects affecting mostly ears, eyes, lungs and brain in terms of pressure and oxygen reactive substances (27,28). It's also being argued that toxic damage to the pulmonary tissue mostly depends on the dose, application time and individual predisposing risk factors. Toxic effects in the lungs are encountered after long-term treatments rather than acute exposures. The information about the mechanism of how this therapy supports the healing process and side effects are still very limited.

The side effects of hyperbaric oxygen treatment is a striking issue to explore. Discussions of the influence on lung function are so limited that it may cause difficulty to the medical practitioners in terms of the decision to terminate or resume of the treatment. After searching in the literature, we have found only a few articles that may be partially relevant to our study. In 1998, researchers studied pulmonary functions and dynamic lung volumes, forced expiratory flows and the transfer factor of the lung for carbon monoxide (TLCO). The researchers evaluated the results before the hyperbaric oxygen treatment, on first, second, third weeks of the treatment and then 3-4 weeks after treatment. At the end of the therapy series given over 21 consecutive days, there were statistically significant but quantitatively small changes in lung expiratory function. Although the observed changes were clinically insignificant, they were still present 4 weeks later. There was a progressive reduction in forced expiratory volume in one second (FEV1) ($p<0.001$), mean forced mid-expiratory flow rate (FEF25-75%) ($p<0.001$) and forced expiratory flows at 50 and 75% of forced vital capacity (FVC) expired during hyperberic oxygen treatment. Four weeks after treatment there was a partial normalization. TLCO was slightly reduced on day 21 of treatment only ($p<0.01$) and fully normalized one month later. In this study with intermittent exposure to hyperoxia, some pattern of changes in pulmonary function took place without any changes in vital capacity. The reduction in pulmonary function after three weeks of HBOT is not considered (29). In another study conducted by Pott and colleagues (30) in 1999, they have investigated the effects of HBOT on pulmonary functions of 14 patients treated in a monoplace chamber. Patients underwent 30 daily sessions at 2,4 ATA and oxygen was breathed freely and continuously inside the chamber. Although the patients were smokers and had an average carbon monoxide diffusing capacity that was 81% of a normal reference population, it was reported that pulmonary function parameters remained unchanged and stated that the HBOT protocol is safe even in lungs with a reduced diffusing capacity as a result.

Apart from the above-mentioned studies, another group of researchers, Plafki and colleagues (31) investigated the complications and side effects of Hyperbaric oxygen in a research of 782 treated patients. 10 of 172 patients in this group were screened out due to pulmonary irregularities. As a conclusion, the researchers reported that after prolonged HBOT sessions none of the group means revealed a significant reduction in pulmonary function values.

In recent years, Hadanny and et al (9) conducted a prospective cohort study and evaluated the effect of hyperbaric oxygen therapy on pulmonary functions. Reseachers showed that there were no significant changes in FEV1, FEV1/FVC ratio and FEF25-75%. According to the researchers the increase in FVC and PEF was statistically significant with a 0.014 and 0.001 respectively. They concluded that HBOT protocol which was scheduled for 60 daily sessions at 2 ATA is safe.

In our study, findings show that some lung volumes may slightly change and increase may be significant. But it is not clear to explain how it happens and what

may cause such changes. Apart from that, static lung volumes and other test results remained same and results showed in accordance with the previous studies.

Related to the proper function of the respiratory system, diaphragm muscle with its mobility plays a significant role in the phases of respiration such as inspiration and expiration. In previous studies, there is a lack of sufficent information regarding the effect of HBOT in the function of diaphragm. Only limited experimental studies evaluated a few functions of the diaphragm. In an experimental study, researchers evaluated the effects of HBOT on the function of the diaphragm muscle of animals following medulla spinalis injury. According to the authors HBOT showed protective effect after the injury (6). Another study showed that it did not increase metabolic enzyme activity of the diaphragm muscle in healthy rabbits (7). Although the changes in the thickness of the diaphragm, and diaphragmatic mobility can be result from various causes, there is a slight probability of explanation with the increase dynamic lung volumes.

CONCLUSION

In our study, we evaluated the effect of daily hyperbaric oxygen therapy on diaphragmatic and respiratory functions by using, diffusing capacity, as well as spirometric and diaphragmatic imaging techniques. As a result, HBOT did not impair the pulmonary and diaphragmatic functions. On the contrary, it may cause an increase in pulmonary and diaphragmatic functions. It is not well known whether this increase is long-lasting with the available data.

The significant increase in the test results of lung capacity, residual volume and vital capacity in our study may of course be due to the positive effect of HBOT on the diaphragm muscle and other auxillary respiratory muscles. This claim should be studied by the enrolment of high numbers of patients and multicenter studies.

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