European Review for Medical and Pharmacological Sciences 2024; 28: 2297-2304

Effect of hyperbaric oxygen in hepatopulmonary syndrome: an innovative experimental study

M. ALTINKAYNAK[1], G. SIMSEK[2], Y. UNLU[3], A. ARSLAN[4], S.S. ERDEM[5], A. KARTAL[2], M.A. ERYILMAZ[2]

[1]Department of General Surgery, Istanbul Training and Research Hospital, Istanbul, Turkey
[2]Department of General Surgery, Konya City Hospital, Konya, Turkey
[3]Department of Pathology, Konya City Hospital, Konya, Turkey
[4]Department of Underwater and Hyperbaric Medicine, Konya City Hospital, Konya, Turkey
[5]Department of Biochemistry, Konya City Hospital, Konya, Turkey

Abstract. – OBJECTIVE: This study aimed to analyze the effect of hyperbaric oxygen treatment (HBOT) in hepatopulmonary syndrome (HPS).

MATERIALS AND METHODS: Five-month-old female Wistar-Albino rats were randomly divided into three groups: Group I, the control group; Group II, the cirrhosis group; and Group III, the cirrhosis group + HBOT group. Rats were exposed to HBO sessions (2.4 atm./60 min) for 20 days. Animals were sacrificed 24 hours after the last HBO session. Biochemical analysis, oxygenation parameters, NO and NO synthase (NOS) levels, histopathological changes in the liver and lungs, and pulmonary artery diameter were measured.

RESULTS: A total of 24 rats (10 rats were included in Group I, six rats in Group II, and eight rats in Group III) weighing 220-250 g were included in the study. Significant differences were observed for NO and NOS (9.10±1.05 to 12.17±1.85 µmol/L, $p<0.05$ and 0.46±0.31 to 1.17±0.39 U/ml, $p<0.05$, respectively) at baseline and day 36 only in group II. Inflammatory cell infiltration and bronchial injury were significantly increased in group II compared to group I ($p=0.007$ and $p=0.008$, respectively) but not in group III ($p=0.266$ and $p=0.275$, respectively). Pulmonary artery diameter was significantly lower in group III compared with group II at all sites in both lungs ($p<0.05$).

CONCLUSIONS: HBOT may be a promising treatment for HPS by reducing NO and NOS activity, perialveolar arteriolar dilation, lung inflammation, and injury and guiding future clinical trials.

Key Words:
Hyperbaric oxygen, Hepatopulmonary syndrome, Experimental study, Treatment.

Introduction

Hepatopulmonary syndrome (HPS) is a clinical condition characterized by dyspnea, commonly seen in patients with a history of chronic liver disease and no previous lung disease. Patients with HPS typically develop hypoxia associated with dilation of perialveolar arterioles. HPS is a form of arteriovenous (A-V) shunt arising from perialveolar arteriolar dilation. In HPS, intraparenchymal vascular dilation (IPVD) can be caused by various vasoactive mediators, namely nitric oxide (NO)[1]. Elevated exhaled NO levels have been found[2] in HPS patients, and the administration of NO inhibitors reduces these levels. Complete resolution of HPS following liver transplantation indicates that the main problem is in the liver[3].

Hyperbaric oxygen therapy (HBOT) is typically defined as the continuous or intermittent inhalation of 100% oxygen at greater than 1 atmosphere absolute (ATA) in a pressurized chamber. This oxygen dose potentially increases the tissue oxygen level to 1,500-1,700 mmHg. Moreover, high-dose oxygen is known to have beneficial physiological and biochemical effects on cells. Even in the treatment of COVID-19, hyperbaric oxygen therapy has been observed to increase tissue oxygenation and decrease the inflammatory cytokine storm[4]. On the other hand, HBOT has been shown to reduce hepatocyte damage, bile duct proliferation, and fibrosis in rats induced with experimental liver cirrhosis[5]. A study in Turkey by Tumgor et al[6] suggests that in the A-V shunts resulting from IPVD in HPS, delivering more FiO_2 than required may lead to an increase in intra-alveolar PO_2 compared to other classic A-V shunts, which implicates the beneficial effect of HBOT in HPS. To date, several clinical and experimental trials have been conducted in the literature on HPS treatment. Nevertheless, to our knowledge, hyperbaric oxygen therapy (HBOT) has not been tried in HPS treatment.

Corresponding Author: Murat Altinkaynak, MD; e-mail: murat.altinkaynak@saglik.gov.tr

We investigated the effect of HBOT on the biochemical analysis, oxygenation parameters (PO_2 and O_2 saturation), NO and NO synthase (NOS) levels, and histopathological changes in the liver and lungs of HPS.

Materials and Methods

Ethics Statement

This study was approved by the Konya Meram Faculty of Medicine Experimental Medicine Center Ethics Committee (No.: 2019/010). We adhered to the Helsinki Declaration of the World Medical Association regarding the subjects, materials obtained from the subjects, and material data.

Study Setting

A total of 30 five-month-old female Wistar albino rats weighing 220-250 g were enrolled in the study between November 2019 and May 2020. The rats were randomly divided into three groups:

1. Group I (the control group), laparotomy + common bile duct dissection only.
2. Group II (the cirrhosis group), laparotomy + common bile duct ligation and disconnection.
3. Group III (the cirrhosis group + HBOT group), laparotomy + common bile duct ligation and disconnection + HBOT.

Surgical Technique

All the rats were anaesthetized with intraperitoneal ketamine hydrochloride (2 mg/kg, 10 mg/ml). Two ml of venous blood was collected from the tail vein to determine NO and NO synthase (NOS) levels. After preoperative skin preparation and draping, laparotomy was performed through a 2-cm midline incision, and then the bile duct was accessed and dissected. In group I, no ligation was performed, and the bile duct was simply dissected, and then the abdomen was closed with continuous 3/0 proline suture. In the remaining two groups, the bile duct was ligated with a 5/0 silk suture in two locations and disconnected. Then, the abdomens were closed with a continuous 3/0 proline suture. All rats were returned to their cages and fed standard rat chow from the sixth hour after surgery. During the first week, ibuprofen was added to the drinking water of all rats to achieve analgesia. At the end of week 5 (day 36), all rats were sacrificed after 6-7 ml of intracardiac blood was collected, of which 1 ml was used for arterial blood gas analysis and the remainder for biochemical analysis and assessment of NO, NOS, and estradiol levels. Both lungs and liver were then removed en bloc by thoracotomy and laparotomy. Tissue samples were placed in 10% formaldehyde tubes and sent to the pathology laboratory.

Hyperbaric Oxygen Therapy Procedure

Hyperbaric oxygen therapy (HBOT) was only administered to group III from the eighth day after surgery. In total, HBOT was administered in 20 sessions between the eighth day after surgery and the day before the rats were sacrificed (day 35), with one session per day and five sessions per week. Rats were exposed to HBO sessions (2.4 atm/60 min) for 20 days. Animals were sacrificed 24 hours after the last HBO session.

Biochemical Analysis

Blood gas analysis included an assessment of Ph, PO_2, PCO_2, and oxygen saturation. Blood samples collected on the first and last days of the experiment were analyzed for NO and NOS levels using the ELISA method (Abbott Laboratories, IL, USA). Blood samples collected after the rats were sacrificed were analyzed to assess levels of oestradiol, albumin, total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT).

Pathological Examination

Pathological examination was performed by a pathologist blinded to the study. Five-μm thick paraffin blocks were cut from liver and lung tissues on a microtome, stained with hematoxylin and eosin (H&E), and analyzed by light microscopy. Portal inflammation was determined by cirrhosis, pleomorphism, periductal proliferation, and fibrosis. The presence of portal inflammation was graded as follows: 0: none; 1: mild; 2: moderate; and 3: severe.

To measure pulmonary artery diameter, the diameters of three different arteries were measured to achieve the standard and to minimize the effect of differences in the site of the lungs on the analysis. These arteries were as follows:

1. Site I: The artery with the largest diameter closest to the mainstem pulmonary bronchus in the right or left lung.
2. Site II: The artery with the largest diameter closest to the middle alveolus of the lung in the right or left lung.
3. Site III: The artery with the largest diameter adjacent to the pleura in the right or left lung.

The diameters of the arteries were measured with an oculometer and reported in μm.

Statistical Analysis

Data were analyzed using SPSS for Windows version 21.0 version 21.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed as mean, standard deviation (SD), median, and min-max for continuous variables and as frequencies (n) and percentages (%) for categorical variables. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine the normal distribution of the data. Two independent groups were compared using the Mann-Whitney U test, chi-squared test, slope Chi-squared test, and Fisher's exact test where appropriate. Two dependent groups were compared using the Wilcoxon signed-rank test. Results are presented with a 95% confidence interval (CI), and a *p*-value <0.05 was considered significant.

Results

A total of 30 five-month-old female Wistar Albino rats were included in the study. After randomization, ten rats in group I underwent laparotomy + common bile duct dissection only; ten rats in group II underwent laparotomy + common bile duct ligation and disconnection, and ten rats in group III underwent laparotomy + common bile duct ligation and disconnection + HBOT. Some of the rats used in the experiment died within the first 24 hours after surgery, including four rats in group II and two rats in group III. As a result, ten rats were included in group I, six rats in group II, and eight rats in group III.

Blood gas analysis for pH, partial carbon dioxide pressure (PCO_2), partial oxygen pressure (PO_2), and arterial oxygen saturation ($A.O_2$ Sat.) was performed on day 36. The mean PO_2 was 87.47±4.59 mmHg in group I, 66.92±9.51 mmHg in group II, and 71.56±6.45 mmHg in group III. It was significantly higher in group I compared to group II (87.47±4.59 *vs.* 66.92±9.51, $p<0.05$) and group III (87.47±4.59 *vs.* 71.56±6.45, $p<0.05$). Although mean PO_2 was higher in group III than in group II, no significant difference was found ($p>0.05$). Mean oxygen saturation was 92.9±3.1% in group I, 75.3±9.5% in group II, and 81.1±5.3% in group III. It was significantly higher in group I than in groups II and III ($p<0.05$). Similarly, mean oxygen saturation was higher in group III than in group II, but no significant difference was found ($p>0.05$). When comparing the mean pH and PCO_2 values between the three groups, no significant differences were found ($p>0.05$) (Table I).

The mean NO and NOS levels were analyzed at baseline (day 1) and at the end of the experiment (day 36). Significant differences were observed for NO and NOS (9.10±1.05 to 12.17±1.85 μmol/L, $p<0.05$ and 0.46±0.31 to 1.17±0.39 U/ml, $p<0.05$, respectively) at baseline and day 36 only in group II. No significant differences were observed for NO and NOS in group I (8.22±2.52 to 8.81±2.52 μmol/L, $p>0.05$ and 0.48±0.22 to 0.82±0.61 U/ml, $p>0.05$, respectively) and group III (9.33±1.40 to 10.20±1.78 μmol/L, $p>0.05$ and 0.65±0.55 to 0.76±0.64 U/ml, $p>0.05$, respectively) at baseline and day 36 (Table II).

Biochemical parameters such as aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin (T-bil), direct bilirubin (D-bil), albumin and estradiol were analyzed on day 36. The highest mean AST level was found in group II (835.5±177.1 U/L), followed by group III (590±173.5 U/L) and group I (173.4±170.8 U/L). The highest mean ALT level was found in group II (124±25.5 U/L), followed by group III (101.7±26.3 U/L) and group I

Table I. Blood gas parameters analyzed at the end of the experiment (The mean± SD).

	Group I (n=10)	Group II (n=6)	Group III (n=8)	Group I *vs.* II (*p*)	Group I *vs.* III (*p*)	Group I *vs.* III (*p*)
pH	7.33±0.1	7.35±0.04	7.33±0.05	0.588	0.859	0.606
PCO_2	35.22±4.41	39.20±4.75	37.71±5	0.103	0.306	0.477
PO_2	87.47±4.59	66.92±9.51	71.56±6.45	**0.001**	**0.001**	0.245
$A.O_2$.Sat.	92.90±3.11	75.35±9.57	81.19±5.35	**0.001**	**0.001**	0.196

$A.O_2$ Sat.: arterial oxygen saturation, PCO_2: partial carbon dioxide pressure, PO_2: partial oxygen pressure, SD: standard deviation. $p<0.05$.

Table II. NO and NOS levels measured at the beginning and end of the experiment.

	Day 1	Day 36	*p*
Group I (n=10)			
NO (µmol/L)	8.22±2.52	8.81±2.52	0.646
NOS (U/ml)	0.48±0.22	0.82±0.61	0.092
Group II (n=6)			
NO (µmol/L)	9.10±1.05	12.17±1.85	**0.028**
NOS (U/ml)	0.46±0.31	1.17±0.39	**0.046**
Group III (n=8)			
NO (µmol/L)	9.33±1.40	10.20±1.78	0.327
NOS (U/ml)	0.65±0.55	0.76±0.64	0.575

NO: nitric oxide, NOS: nitric oxide synthase. $p<0.05$.

(57.8±45.3 U/L). There was a significant increase in AST, ALT, GGT, T-bil, and D-bil in groups II and III compared to group I ($p<0.05$). However, when group III was compared with group II, only T-Bil and D-Bil levels were significantly different ($p<0.05$) (Table III).

Histological examination of liver tissue revealed cirrhosis in all rats in groups II and III. In addition, portal inflammation, hepatocellular pleomorphism, periductal proliferation, hepatic fibrosis, and cirrhosis were also detected in all rats in groups II and III. On the other hand, histological examination of lung tissues was performed to evaluate the presence of inflammatory cell infiltration and bronchial injury. The highest incidence of inflammatory cell infiltration was found in group II and was significantly higher compared to groups I and III ($p<0.05$). However, no significant difference in inflammatory cell infiltration was observed between groups I and III ($p>0.05$). The highest incidence of bronchial injury was found in group II and was significantly higher compared to group I ($p<0.05$) (Table IV).

Arteriole diameters were measured at the three sites in the lung tissue. The largest arteriole diameters were found in the arterioles closest to the mainstem pulmonary bronchus, and the greatest dilation of arteriole diameter measured at the first site in both lungs was found in group II, which was significantly higher than in groups I and III ($p<0.05$). At other sites, however, there was no significant difference in mean arteriolar diameter between groups I and III ($p>0.05$). At all three sites, mean arteriole diameters were significantly lower in group III than in group II ($p<0.05$) (Table V).

Analysis of the pulmonary artery measurements showed that the arteries with the largest diameters in all three sites defined in our study were in group II (Figure 1).

Discussion

In our study, we evaluated the efficacy of hyperbaric oxygen therapy in the development and treatment of hepatopulmonary syndrome by biochemical parameters, blood gas evaluation, NO and NOS levels, pathological evaluation of liver and lung, and measurement of pulmonary artery

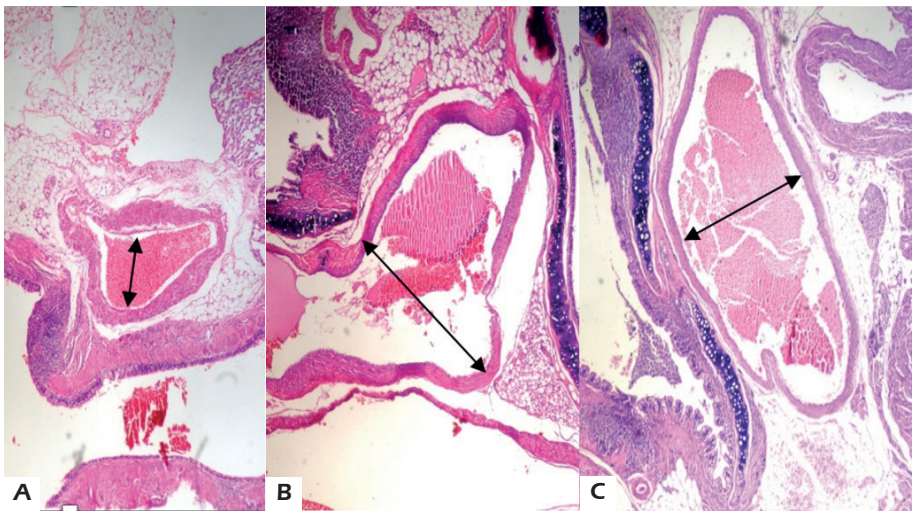

Figure 1. Arterioles adjacent to the mainstem bronchus in rat lung in group I (**A**), II (**B**), and III (**C**) The arteriole in group II is remarkably larger (H&E staining, x40 magnification).

Table III. Biochemical parameters analyzed at the end of the experiment.

	Group I (n=10)	Group II (n=6)	Group III (n=8)	Group I *vs.* II (*p*)	Goup I *vs.* III (*p*)	Group II *vs.* III (*p*)
AST (U/L)	173.4±170.86	835.5±177.10	590±173.54	**0.002**	0.002	0.028
ALT (U/L)	57.8±45.32	124±25.58	101.75±26.32	**0.001**	**0.001**	0.175
ALP (U/L)	114.9±45.32	203.67±61.96	166.25±160.34	**0.007**	0.722	0.071
GGT (U/L)	5±0	57.2±16.44	33.58±12.53	**0.001**	**0.001**	0.014
T-Bil (mg/dL)	0.96±2.83	8.75±0.79	6.76±1.36	**0.004**	**0.004**	**0.039**
D-Bil (mg/dL)	0.69±2.15	6.70±0.58	4.48±1.22	**0.003**	**0.004**	**0.007**
Albumin (g/dL)	29.01±1.85	26.58±2.62	28.36±3.68	0.065	0.894	0.366
Estradiol (pg/ml)	48.48±10.93	54.12±22.14	54.62±11.21	0.515	0.286	0.519

AST: aspartate transaminase, ALT: alanin transaminase, ALP: alkaline phosphatase, GGT: gamma glutamyl transferase, T.Bil: total bilirubin, D. Bil: direct bilirubin. $p<0.05$.

diameter. This is the first study to demonstrate the efficacy of hyperbaric oxygen therapy in hepatopulmonary syndrome.

Hypoxia arises from IPVD due to several factors, including incomplete oxygenation of the blood in dilated arteries, insufficient gas exchange time caused by accelerated blood flow, and insufficient alveolar wall in hepatocellular syndrome[7]. The pathophysiology of HPS implicates that hyperbaric oxygen may have a beneficial effect on hypoxia. In addition, the literature[6] indicates that in HPS, if more than required FiO_2 is given, it may lead to an increase in PO_2 within the alveoli. We found that the mean PO_2 and $A.O_2$ Sat. levels were lower in rats with HPS and in those treated with HBOT, but the mean PO_2 and $A.O_2$ Sat. values were higher in mice with HPS, although not significant in the HBOT group, and this appears to be effective in reducing inflammatory cell infiltration in the lung.

Intraparenchymal vascular dilatation (IPVD) is a fundamental physiopathological change in HPS, and several vasodilators have been implicated in its pathogenesis, including NO, atrial natriuretic peptide, prostacyclin, and platelet-activating factor (PAF)[8,9]. A previous study[10] showed that administration of NO inhibition resulted in several beneficial effects in the prevention of HPS. In our study, no significant increase in levels was observed in the HBOT group. The present study showed that NO activity, which is the main cause of IPVD in HPS, was reduced and inhibited by HBOT, suggesting that HBOT may be a promising approach for the treatment of HPS.

A 2016 study[11] found no difference in ALP and GGT levels in hepatopulmonary syndrome, but bilirubin and bile acids were significantly higher, highlighting the association of bile acid retention with HPS and $PaO_2/AaPO_2$ abnormalities. In our study, cirrhosis developed at the end of week 5 in groups II and III, and no significant difference was found in biochemical analyses of AST, ALT, and GGT levels. However, T-bil, D-bil, and ALP levels were significantly lower in group III than in group II. A previous study by Terzioglu et al[12] reported that HBOT reduced hepatic oxidative stress and bile duct proliferation in rats induced by an experimental bile duct ligation model. Accordingly, we believe that the lower bilirubin and ALP levels in rats receiving HBOT may be related to the effect of HBOT in reducing bile duct proliferation in biliary cirrhosis. The hepatic metabolism of estrogens may be impaired or inadequate in the presence of cirrhosis. As a result, increased estrogen concentration, together with some other factors, may lead to arterial dilation (e.g., spider angioma, cutaneous angioma)[13]. Consistent with the literature, cirrhosis developed in groups II and III in our study, and estradiol levels increased in these groups, although not significantly compared with group I.

Previous studies[5,12] investigated the effect of HBOT on bile duct ligation-induced oxidative damage and fibrosis and reported that HBOT reduced hepatocellular damage, bile duct proliferation, and fibrosis in the liver. Idetsu et al[14] found that HBOT accelerated biliary cell regeneration and improved postoperative cholestasis. In a study[15] investigating lung tissue levels of oxidative and antioxidative stress enzymes with HBOT duration in rats, it was observed that both oxidative and antioxidative enzymes increased with 20 sessions and above. All these studies evaluated enzyme activities but not histological evaluation. Although no signifi-

Table IV. Histological evaluation of liver and lung tissues.

Histopathological finding		Group I (n=10)	Group II (n=6)	Group III (n=8)	Group I *vs.* II (*p*)	Group I *vs.* III (*p*)	Group II *vs.* III (*p*)
Inflammatory cell infiltration in the portal region	**Yes**	0%	100%	100%	**0.002**	**0.004**	0.703
	No	100%	0%	0%			
Hepatocellular pleomorphism	**None**	100%	0%	12.5%	**0.001**	**0.001**	0.4
	Mild	0%	16.7%	25%			
	Moderate	0%	50%	37.5%			
	Severe	0%	33.3%	25%			
Periductal proliferation in liver	**None**	90%	0%	0%	**0.002**	**0.001**	0.863
	Mild	10%	50%	50%			
	Moderate	0%	16.7%	25%			
	Severe	0%	33.3%	25%			
Liver fibrosis	**None**	100%	0%	0%	**0.001**	**0.001**	0.801
	Moderate	0%	66.7%	62.5%			
	Severe	0%	33.3%	37.5%			
Liver Cirrhosis	**None**	100%	0%	0%	**0.001**	**0.001**	0.780
	Mild	0%	33.3%	37.5%			
	Moderate	0%	33.3%	37.5%			
	Severe	0%	33.3%	25%			
Inflammatory cell infiltration in lung	**None**	10%	0%	0%	**0.007**	0.226	**0.017**
	Mild	50%	0%	37.5%			
	Moderate	40%	50%	62.5%			
	Severe	0%	50%	0%			
Bronchial injury in lung	**No**	90%	16.7%	62.5%	**0.008**	0.275	0.138
	Yes	10%	83.3%	37.5%			

Table V. Arteriole diameters measured on the three sites in lung tissues.

	Group I (n=10) (μm)	Group II (n=6) (μm)	Group III (n=8) (μm)	Group I *vs.* II (*p*)	Group I *vs.* III (*p*)	Group II *vs.* III (*p*)
Right lung - Site I	66.9±14.11	128.67±30.59	100.88±15.84	**0.001**	**0.001**	**0.037**
Right lung - Site II	26.5±4.63	47.83±11.80	28.38±7.39	**0.003**	0.655	**0.007**
Right lung - Site III	9.45±2.41	18±3.29	10.5±1.20	**0.001**	0.175	**0.002**
Left lung - Site I	67.2±13.9	130.33±31.69	99.63±16.29	**0.002**	**0.002**	**0.003**
Left lung - Site II	26.8±4.56	49±11.42	27.5±7.25	**0.002**	0.893	**0.004**
Left lung - Site III	9.8±2.78	18.50±3.45	10±1.07	**0.002**	0.277	**0.002**

Site I: The artery with the largest diameter closest to the mainstem pulmonary bronchus. Site II: The artery with the largest diameter closest to the middle alveolus of the lung. Site III: The artery with the largest diameter adjacent to the pleura.

cant difference was found in the liver, significant changes were observed in the lungs, making our study unique. In our study, rats receiving 20 sessions of HBOT prevented inflammatory cell infiltration and lung injury. The lack of a significant difference between group 2 and group 3 in terms of lung injury may be due to the small number of rats included in the study (Table IV).

Vascular dilatation, which is known to be the main pathological feature of HPS, is commonly assessed by measuring the diameter of the perialveolar vein[1,2]. However, to our knowledge, there is

no standard method for this measurement. In our study, unlike other studies, the perialveolar vein diameter was measured from three defined sites on the lung to achieve a reliable measurement. In this study, the significant reduction in perialveolar artery dilatation in the HBOT group was associated with a reduction in lung inflammation and injury in this group.

Limitations

Our study also had some limitations. Firstly, the blood samples taken at the beginning of the experiment were not sufficient to analyze all parameters, so blood gas and biochemical parameters could not be analyzed at baseline. Another limitation was that the already small number of participants was reduced by 6 rats during the study.

Conclusions

This innovative study is the first to histologically evaluate liver and lung tissue in experimental HPS treated with HBOT. The HBOT group showed reduced NO and NOS activity, perialveolar arteriolar dilation, and reduced lung inflammation and injury. These findings suggest the potential of HBOT as a promising treatment for HPS. The results will guide future clinical trials.

Conflict of Interest

The authors declare no competing interests.

Ethics Approval

This study was approved by the Konya Meram Faculty of Medicine Experimental Medicine Center Ethics Committee (No: 2019/010). We adhered to the Helsinki Declaration of the World Medical Association regarding the subjects, materials obtained from the subjects, and material data.

ORCID ID

Murat Altinkaynak: 0000-0002-5173-6056
Gurcan Simsek: 0000-0003-4087-9331
Yasar Unlu: 0000-0002-3951-8881
Abdullah Arslan: 0000-0001-5575-326X
Said Sami Erdem: 0000-0002-1011-7240
Adil Kartal: 0000-0002-5045-3273
Mehmet Ali Eryilmaz: 0000-0002-5280-3943

Authors' Contributions

MA, AK, MAE – designed study protocol, writing the manuscript; MA, GS, YU, AA, SSE, AK, MAE – collecting patients date during study; MA, GS, YU, AA, SSE – searching of world literature and discussion of the obtained results with the results of previous research; YU, AA, SSE – statistical data analysis. All the authors approved the final version of the article to be published.

Funding

None.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

References

1) Rolla G. Is nitric oxide the ultimate mediator in hepatopulmonary syndrome? J Hepatol 2003; 38: 668-670.
2) Cremona G, Higenbottam TW, Mayoral V, Alexander G, Demoncheaux E, Borland C, Roe P, Jones GJ. Elevated exhaled nitric oxide in patients with hepatopulmonary syndrome. Eur Respir J 1995; 8: 1883-1885.
3) Rodríguez-Roisin R, Krowka MJ. Hepatopulmonary syndrome--a liver-induced lung vascular disorder. N Engl J Med 2008; 358: 2378.
4) Allam NM, Eladl HM, Eid MM. Hyperbaric oxygen therapy as a supportive therapy for COVID-19 patients: a narrative review. Eur Rev Med Pharmacol Sci 2022; 26: 5618-5623.
5) Ayvaz S, Kanter M, Aksu B, Sahin SH, Uzun H, Erboga M, Pul M. The effects of hyperbaric oxygen application against cholestatic oxidative stress and hepatic damage after bile duct ligation in rats. J Surg Res 2013; 183: 146-155.
6) Tumgor G. Cirrhosis and hepatopulmonary syndrome. World J Gastroenterol 2014; 20: 2586.
7) Krowka MJ, Cortese DA. Hepatopulmonary syndrome. Current concepts in diagnostic and therapeutic considerations. Chest 1994; 105: 1528-1537.
8) Chang S, Ohara N. Pulmonary circulatory dysfunction in rats with biliary cirrhosis. An animal model of the hepatopulmonary syndrome. Am Rew Respir Dis 1992; 145: 798-805.
9) Lee KN, Yoon SK, Lee JW. Hepatopulmonary syndrome induced by common bile duct ligation in a rabbit model: correlation between pulmonary vascular dilatation on thin-section CT and angiography and serum nitrite concentration or endothelial nitric oxide synthase (eNOS)1 expression. Korean J Radiaol 2004; 5: 149-516.
10) Sztrymf B, Rabiller A, Nunes H. Prevention of hepatopulmonary syndrome by pentoxifylline in cirrhotic rats. Eur Respir J 2004; 23: 752-758.
11) Horvatits T, Drolz A, Rutter K, Roedl K, Fauler G, Müller C, Kluge S, Trauner M, Schenk P, Fuhrmann V. Serum bile acids in patients with hepatopulmonary syndrome. Z Gastroenterol 2017; 55: 361-367.
12) Terzioglu D, Uslu L, Simsek G, Atukeren P, Erman H, Gelisgen R, Ayvaz S, Aksu B, Uzun H. The

Effects of Hyperbaric Oxygen Treatment on Total Antioxidant Capacity and Prolidase Activity after Bile Duct Ligation in Rats. J Invest Surg 2017; 30: 376-382.

13) Yol S, Erikoglu M, Toprak SS, Tavlı S, Tavlı L. The effects of serum estrogen levels on hypoxemia and blood nitric oxide levels in experimental hepatopulmonary syndrome. Hepatol Res 2005; 33: 7-13.

14) Idetsu A, Suehiro T, Okada K, Shimura T, Kuwano H. Hyperbaric oxygenation promotes regeneration of biliary cells and improves cholestasis in rats. World J Gastroenterol 2011; 17: 2229-2235.

15) Simsek K, Ay H, Topal T, Ozler M, Uysal B, Ucar E, Acikel CH, Yesilyurt O, Korkmaz A, Oter S, Yildiz S. Long-term exposure to repetitive hyperbaric oxygen results in cumulative oxidative stress in rat lung tissue. Inhal Toxicol 2011; 23: 166-172.