The significance of hepatopulmonary syndrome in liver transplantation

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The objective of the study is to determine the diagnostic role of pulmonary functional tests and perfusion pulmonary scintigraphy for quantifying the oxygenation and vascular abnormality in patients with liver cirrhosis. The prospective study included 70 patients with liver cirrhosis. Arterial blood gases analysis were performed in both supine and sitting positions while inhaling room air, and 15 minutes after exposure of hypoxic mixture. Perfusion pulmonary scintigraphy using albumin macroaggregate labelled with radioactive technetium (99mTc-MAA) was performed for the visualisation of intrapulmonary vascular dilatation. The diagnosis of hepatopulmonary syndrome was made in 10 (14.3%) patients. The patients with hepatopulmonary syndrome had severe hypoxemia (P\textsubscript{a,O2} 7.41 ±1.81 kPa), and poor response to 100% oxygen inhalation (P\textsubscript{a,O2} 21.07 ±14.41 kPa) and higher alveolo-arterial gradient (5.73 ± 2.65 kPa). Radioisotope marker 99mTc-MAA skipped intrapulmonary circulation in all patients with HPS and in no one without pulmonary vascular dilatations. The combined approach of 100% inspired oxygen and perfusion pulmonary scintigraphy may identify early oxygenation disorders and alter the priority for liver transplantation, especially in view of potential syndrome resolution.

Key words: hepatopulmonary syndrome, liver transplantation.

INTRODUCTION

Pulmonary abnormalities are common in patients with chronic liver disease. If questioned, up to 70% of candidates for liver transplantation complain of dyspnea. In patients with liver cirrhosis and prominent hypoxemia, the intrapulmonary right-to-left shunts represent the major pathogenetic mechanism in the development of severe respiratory disorders, in spite of accompanied ventilation-perfusion (Va/Q) disorder. Kennedy and Knudson suggested, in 1977, to introduce the term hepatopulmonary syndrome (HPS), which characterises advanced liver disease accompanied with hypoxemia, an increase of alveolo-arterial gradient during inhalation of room air and intrapulmonary vascular dilatation (IPVD). Pathoanatomic substrate of intrapulmonary vascular dilatation consists of: dilated precapillaries, direct arterio-venous communications and dilated pleural blood vessels. Dilated pleural blood vessels resemble the cutaneous (spider-like) nevi, and therefore, they are denoted as pleural spidery. Hypoxemia with partial oxygen pressure (P\textsubscript{a,O2}) less than 8 kPa without any other cardiorespiratory diseases suggests the presence of intrapulmonary vascular dilatation.

Now, it is believed that nitric oxide (NO), prostaglandin's, endothelin-1 (ET-1) and serotonin are of tremendous importance in the develop a groupment of portal hypertension and the other hemodynamic complications of cirrhosis. Recently, nitric oxide the most important vasodilating mediator of pulmonary circulation has been suggested to play a major role in oxygen uptake alterations of patients with cirrhosis, particularly those with HPS.

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METHODS

The prospective study analysed results of 70 patients treated at the Institute of Digestive Diseases and Institute of Pulmonary Diseases, Clinical Centre of Serbia. The initially performed hepatological examinations were based on: medical history, physical examination, laboratory tests and puncture liver biopsy. The degree of liver failure was assessed according to the Child-Pugh classification.
Following the hepatologic examination, the morphological and pulmonary function tests were carried out. Gas analyses were carried out using Blood Gas Manager 1312 equipment, while predicted values for the partial oxygen pressure were calculated using Sornin equation \( P_{a,02} = 103.5 - 0.42 \times \text{years} \). Arterial blood gases analysis were performed in both supine and sitting positions while exposed to the room air and after 15 minutes of breathing of hyperoxic mixture using a direct method, which includes arterial blood sample with a heparinized syringe.

The alveolo-arterial gradient of oxygen pressure \( (P_{A,a}\text{O}_2) = P_{A,02} - P_{a,02} \) was calculated in the way usually used in practice. The oxygen pressure in the alveolar gas is calculated on the basis of the measured atmospheric pressure and carbon-dioxide in the exhaled air, while \( P_{a,02} \) is measured directly in the arterial blood.

Given to the variations of respiration changes in cirrhotics while assuming different body positions, arterial blood changes occurred, the change of \( P_{A,a}\text{O}_2 \) for at least 0.66 kPa is a sign of significant alteration of alveolo-capillary exchange with the assumption of different body positions.

Spirometry was used for the determination of the statical, dynamic pulmonary volumes and capacities: vital capacity (VC), forced vital capacity (FVC) and forced expiratory volume during the first second (FEV1). These tests were performed using Pneumoscreen II spirometer. Body plethysmography was used for measurement of the total lung capacity (TLC), thoracic gas volume (TGV), residual volume (RV), and air flow resistance in the airways (RaW). The measurements were performed using Bodyscreen II.

Morphological studies included plain chest radiography and perfusion pulmonary scintigraphy. With the patient in a supine position, albumin macroaggregate labelled with radioactive technetium \( (^{99m}\text{Tc-MAA}) \) were injected. Following the contrast medium injection, the patient was placed in a sitting position with his back turned toward the gamma camera (Siemens Gammascanics ZLC 3700) connected with the PC (Microdelta computer RT-11, Clinic Menu V 87A). The visualisation was performed in six standard planes - gamma camera positions: anterior, posterior, left lateral, right lateral, left lateral oblique and right lateral oblique until 500,000 impulses per projection was accumulated in the PC matrix 64 x 64. The scanning of extrathoracic organs was applied to the detect the total number of the brain and kidney impulses in order to confirm intrapulmonary arterio-venous shunts.

RESULTS

Hypoxemia was evidenced in 33 (47%) patients. Moreover, based on functional and morphological investigations the diagnosis of hepato-pulmonary syndrome was confirmed in 10 (14.3%) patients with liver cirrhosis. The majority of the HPS patients (7) belonged to the Child C group, while 3 patients were categorized as Child B. The patients with hepato-pulmonary syndrome had severe hypoxemia particular in the upright position \( (P_{a,02} 7.41 \pm 1.81 \text{kPa}) \).

GRAPH 1
ORTHODEOXIA IN PATIENTS WITH HPS

GRAPH 2
ALVEOLO-ARTERIAL GRADIENT IN PATIENTS WITH AND WITHOUT HPS

Hypoxemia caused by ventilation-perfusion mismatching \((V_a/Q)\) was evidenced in 23(32%) patients \( (P_{a,02} 9.68 \pm 1.10 \text{kPa}) \).

When compared to the HPS-free group, the patients with HPS were proved to have severe hypoxemia particularly in a sitting position. When measured in a sitting position, the difference in \( P_{a,02} \) values in patients with and without HPS was highly significant \((p=0.001, t\text{-test})\).

Orthodeoxia was confirmed in all patients with HPS. When room air was breathed, the average \( P_{a,02} \) value in a supine position was \( 9.40 \pm 1.74 \text{kPa} \), while in a sitting position the average \( P_{a,02} \) value was \( 7.41 \pm 1.81 \text{kPa} \). When 100% oxygen was breathed, the average \( P_{a,02} \) value in supine position was \( 35.49 \pm 17.95 \text{kPa} \), while in the sitting position the average \( P_{a,02} \) value was \( 21.07 \pm 14.41 \text{kPa} \) (Fig. I).
In our series, 30 (42.8%) patients had alveolo-arterial gradient over 2 kPa. All patients with HPS had higher alveolo-arterial gradient, whose mean value in the supine position was 4.03 ± 2.36 kPa while it was 5.73 ± 2.65 kPa in the sitting position. Among the patients without HPS, the mean value of alveolo-arterial gradient was 2.77 ± 1.74 kPa in the supine position while it was 1.80 ± 1.74 kPa in the sitting position. Comparing patients with and without HPS, the significant difference in alveolo-arterial gradient (p=0.001, t-test) was found, especially in the sitting position (Fig. 2).

The radioisotope marker 99mTc-MAA skipped intrapulmonary circulation, being accumulated in the brain and kidneys in 10 patients with HPS, what correlated with pulmonary functional findings. No one patient without HPS demonstrated extrapulmonary uptake of radioisotope marker.

**DISCUSSION**

The progression of intrapulmonary vascular dilatation leads to deterioration of arterial oxygenation, indicating fairly poor transplant prognosis. The patients with PaO2 < 9.3 kPa require a special preoperative staging, in order to assess whether adequate oxygenation may be provided during their operative and postoperative periods.

In 1994, Hoboika et al concluded that partial oxygen pressure below 8 kPa makes liver transplantation hazardous. In their series of 9 transplanted patients with HPS, mortality rate was more than 40% (4 deaths). All had PaO2 < 8 kPa, while among 5 cases with PaO2 > 8 kPa, only 1 patient died. As described in recent study of 81 patients with HPS who underwent orthotopic liver transplantation, patients with severe hypoxemia (PaO2 < 6.5 kPa) had the greatest risk for post-orthotopic liver transplantation mortality (30% within 90 days of orthotopic liver transplantation). The main reasons for perioperative mortality associated with HPS include refractory hypoxemia and multiorgan failure, intracerebral haemorrhage, sepsis related to bile leaks, and portal vein thrombosis. A mortality rate of 38% at 1-year post orthotopic liver transplantation in 21 pediatric patients receiving living related transplants for biliary atresia has been reported.

Many centers, especially pediatric, consider HPS an indication for orthotopic liver transplantation. Liver transplant priority considerations in patients with HPS exist in the pediatric population, but has not been applied to adult listing criteria.

HPS resolution after orthotopic liver transplantation reported to be from 62% (Egawa et al 1999) to 82% (Krowka et al 1997).

In pretransplantation assessment, it is important to diagnose and differentiate the vascular pulmonary abnormalities including search for probable intracardiac shunt, pulmonary embolism and pulmonary hypertension.

Dyspnea was present in over 95% of patients with HPS. Dyspnea is sensitive but poorly specific indicator of the presence of HPS.

However, typical manifestation of intrapulmonary vascular dilatation in cirrhosis is platypnea, specifying that dyspnea is more pronounced in the upright and sitting position than in a recumbent one. Orthodeoxia is another clinical sign in HPS, representing the decrease of partial oxygen pressure more then 10% when patient is changing the position from a recumbent to a sitting one. It is presumed that the partial oxygen pressure decrease, occurring during the recumbent-to-sitting position change, is caused by increase of blood flow via dilated basal pulmonary blood vessels due to gravitation.

In the studies with selected patients having hypoxemia characteristic for HPS, the prevalence of platypnea and orthodeoxia was much higher. In 1990, Krowka and Cortese found orthodeoxia in 88% of HPS patients; while Andrivet and associates, in 1993, verified it in all patients with HPS.

In this study we confirmed the sensitivity of orthodeoxia phenomenon, which was diagnosed in all patients with HPS.

The determination of oxygen pressure, PaO2 = PaO2 - PaO2, is the simplest method of assessment the ratio of ventilation and perfusion of the lungs. It is postulated that PaO2 ≥ 2 kPa with or without hypoxemia indicates the intrapulmonary vascular dilatation.

In 1991, Houri and associates reported the increased gradient of oxygen pressure in 45% of patients who were candidates for liver transplantation, and the mean value of gradient was 4.89 kPa. Stressing the significance of this functional disorder, Fahy and associates stated that 69% of patients, being the candidates for liver transplantation, had higher PaO2. In Fallon's cohort of 207 consecutive liver transplant candidates who underwent arterial blood gas screening, 66% had alveolar-arterial oxygen gradient higher than 2 kPa.

In our series, 30(42.8%) patients had alveolo-arterial gradient over 2 kPa. The increased alveolo-arterial gradient (5.73 kPa ± 2.65), particularly in the sitting position, was recorded in all patients with HPS. Significant difference (p=0.001, t-test) was found in relation to patients without HPS.

On the basis of response to exposure to 100% oxygen, two types of vascular abnormalities in patients with hepato cellular insufficiency have been described. HPS type-1 is characterised by diffuse vascular dilatation at precapillary level, while HPS type-2 is defined by true anatomic pulmonary arterio-venous shunting. The application of 100% oxygen leads to significant increase of partial oxygen pressure in the type-1, while the effect is minimal in the type-2. In cirrhosis, the various types of pulmonary vascular abnormalities have been described by angiography: minimal spider-like dilatation, diffuse spongiotic dilations and discrete arterio-venous communications. It has been observed that the patients with significant hypoxemia and excellent response to inhalation of 100% oxygen (PaO2 > 53.3 kPa) usually have normal pulmonary angiogram, due to fact that their vascular abnormalities are at microscopic level. The patients with severe hypoxemia (PaO2 < 8 kPa) and poor response to 100% oxygen.
exposure ($P_aO_2 < 20$ kPa), usually have fixed arterio-venous communications or advanced diffuse spongiotic dilatation.

Liver transplant surgery can improve oxygenation only in a group of patients with subclinical intrapulmonary shunts and mild precapillary dilatation characterised by complete oxygenation response to 100% oxygen. Regression of vascular abnormalities does not occur in patients with true anatomic shunts and marked precapillary dilatation characterised by incomplete oxygenation response to 100% oxygen.

In our series, the patients with HPS had severe hypoxemia ($P_aO_2 7.41 \pm 1.81$ kPa) and poor response to 100% oxygen exposure ($P_aO_2 21.07 \pm 14.41$ kPa), what indicated the advanced pulmonary vascular changes.

In order to confirm the diagnosis of pulmonary vascular changes in liver cirrhosis the visualisation of the intrapulmonary vascular dilatation is necessary.

A significant advantage of the radionuclide lung perfusion scan is specific for the presence of HPS even in the setting of coexistent intrinsic lung disease.

In our study, perfusion pulmonary scintigraphy enabled us to diagnose pulmonary arterio-venous shunts in 10 patients with HPS. This method significantly correlated with pulmonary functional tests, primarily based on the phenomenon of orthodeoxia.

Extrapulmonary uptake of $^{99m}$Tc-MAA has a significant inverse correlation with $P_aO_2$ abnormalities and these 2 studies (lung perfusion scanning and 100% inspired oxygen) may complement the anatomic and physiological characterisations of the syndrome.

**CONCLUSION**

The combined approach of 100% inspired oxygen and perfusion pulmonary scintigraphy may identify early oxygenation disorders and alter the priority for liver transplantation, especially in view of potential syndrome resolution.

**REZIME**

Cilj istraživanja bio je da determinišemo začaj plućnih funkcionalnih testova i perfuzione plućne scintigrafije u određivanju oksigenacijskih i vaskularnih abnormalnosti kod bolesnika sa cirrozom jetre. U prospektivnom radu ispitivali smo 70 bolesnika sa cirrozom jetre. Arterijske gasne analize uzimali smo u ležištu i sredini položaju bolesnika, pri udisanju sobnog vazduha i posle 15 minuta udisanja hiperoksične smese. Perfuzioni scintigrafiji pluća sa radioaktivnim tehneciumom vezanim za makroagregat albumina $^{99m}$Tc-MAA primenjena je za vizualizaciju intrapulmonalne vaskularne dilatacije. Diijagnostika hepatozelenog sindroma postavljena je kod 10 (43%) bolesnika. Bolesnici sa hepatitisnom sindromom imali su teška hipoksemiju ($P_aO_2 7.41 \pm 1.81$ kPa), slab odgovor na inhalaciju 100% kiseonika ($P_aO_2 21.07 \pm 14.41$ kPa) i visok alveolo-arterijski gradijent (5.73 2.65 kPa). Radiozotopski marker $^{99m}$Tc-MAA prošao je kroz plućnu cirkulaciju kod svih bolesnika sa hepatozelenim sindromom. Kombinovanom primenom inhalacije 100% kiseonika i perfuzione plućne scintigrafije, mogu se identifikovati rani oksigenacijski poremećaji i odrediti prioritet za transplantaciju jetre, naročito u slučajevima potencijalne rezolucije sindroma.

**REFERENCES**


