Hepatopulmonary syndrome (HPS) is a complication of liver cirrhosis and is responsible for chronic hypoxemia and its negative health consequences. The most relevant diagnostic criterion of HPS is evidence of pathological intrapulmonary blood shunting (IPBS). There is still insufficient knowledge about the subclinical forms of HPS. The aim of this study was to determine whether an erect posture in patients with liver cirrhosis had a significant effect on IPBS, the diagnosis of HPS and oxygen saturation. Thirty cirrhotic patients considered for liver transplantation were enrolled in this study. Pulse oximetry and lung perfusion scintigraphy were conducted in patients while they were in supine and upright body positions. Pathological IPBS was observed in 16% and 20% of patients examined in the supine and upright body positions, respectively (mean difference 0.59%; \( P = 0.046 \)). Postural-related IPBS changes were markedly greater in patients with HPS (1.76%; \( P = 0.011 \)). Oxygen saturation was significantly lower in the erect posture compared to the supine posture (mean difference 1.2%; \( P = 0.02 \)); however, there was no relationship between oxygen saturation and IPBS. In conclusion, an erect posture in patients with advanced liver cirrhosis leads to a subtle increase in IPBS, which is more pronounced in patients with HPS, and oxygen saturation measurements are not sensitive enough to detect these changes.

Key words: erect posture, hepatopulmonary syndrome, intrapulmonary blood shunting, liver cirrhosis, orthostasis, gravity, oxygen saturation
influence on the degree of right-to-left blood shunting. This hypothesis is confirmed by the fact that patients with HPS suffer from dyspnea when changing their position from supine to upright. The prerequisite for an HPS diagnosis is low oxygen tension in the arterial blood, but definite cut-off values are still debated and do not depend on body position. Studies of an intrapulmonary blood shunt with echocardiography or scintigraphy with albumin macroaggregates (MAA) are routinely performed while patients are in the supine position despite the fact most people spend their time in an erect position.

All studies investigating postural-related changes in intrapulmonary shunting were performed with contrast echocardiography, a method showing poor specificity for HPS that, in contrast to MAA scintigraphy, does not allow quantitative measurement of intrapulmonary blood shunting. The purpose of this study was to determine whether IPBS in cirrhosis patients is dependent on body position and to measure the magnitude of change in shunting by perfusion lung scintigraphy. We also addressed whether changes in intrapulmonary blood flow are detectable by measuring oxygen saturation in the blood.

**MATERIAL AND METHODS**

**Patients**

This study was conducted in a tertiary referral center that determined the qualification of liver transplantation for patients with liver diseases. The eligibility criteria for the study were as follows: age > 18 years, presence of decompensated cirrhosis (metabolic or hemodynamic) and a model for end-stage liver disease (MELD) score > 14. The exclusion criteria were as follows: any acute or chronic lung disease, intracardiac blood shunting, lack of alcohol abstinence, the inability to maintain an erect posture for at least 5 minutes, apparent hepatic encephalopathy, hepatocellular carcinoma (HCC), diagnosis of other cancers, contraindications to liver transplantation and pregnancy.

We prospectively enrolled 30 adult patients with liver cirrhosis who ranged in age from 19 to 67 years (mean 47.2 ± 12.2 years). There were 23 men (76.7%) in the study. Five patients did not complete the study for the following reasons: one patient withdrew his/her consent during the study, one patient developed hepatic encephalopathy, one qualification for liver transplantation was suspended because of a detected HIV infection, and two patients died.

**Experimental procedures**

Clinical, laboratory, radiological, endoscopic or histopathological criteria were essential for the diagnosis of liver cirrhosis. The MELD score was calculated according to the formula: $\text{MELD} = 9.6 \times \ln \text{creatinine (mg/dl)} + 3.8 \times \ln \text{bilirubin (mg/dl)} + 11.2 \times \ln \text{INR} + 0.643$.

In all patients, the following examinations were performed: chest X-ray, electrocardiography, echocardiography, abdominal ultrasound, panendoscopy, spirometry, measurement of $\text{PaO}_2$ and partial of carbon dioxide pressure ($\text{PaCO}_2$) by arterial blood gasometry (femoral artery) and routine laboratory testing, including measurements of hematological, hepatic and renal parameters.

Pulse oximetry and perfusion lung scintigraphy were performed on the same patient twice, once in the supine position and once in the erect position in a random order (according to generated random code). Pulse oximetry (M3046A/M3000A detector connected to a Philips cardiac monitor) was performed by fixing the detector on the index finger and recording the arterial hemoglobin oxygen saturation (O$_2$ sat.). The measurement time was 2 - 3 minutes, but there was a 10-minute delay prior to starting the measurement after changing the body position (13). A value of 96% was assumed as the lower reference value of a normal arterial O$_2$ sat.

Perfusion lung scintigraphy was performed by injecting the preparation containing $^{99m}$technetium (Tc)-labeled MAA (MAASOL, GE Healthcare, GB) into the vein of the left forearm. The number of albumin particles in a single dose was lower than 300,000, and the exposure to radioactivity of the technetium administered in two examinations did not exceed 200 MBq. The MAA biological half-life is 2 - 8 hours, and the duration of the half disintegration of technetium is approximately 6 hours; therefore, the period of time between the two studies ranged from 2 to 4 days.

Tc-MAA was injected intravenously (via venflon) while the patient was in a supine or an erect body position, which position was maintained for 1 minute. Next, patients laid down for 30 minutes. During this time, the body distribution of the radiotracer was recorded by a gamma camera, DIACAM type (SIEMENS, Erlangen, Germany). The lung-brain ratio reflected the IPBS, which was calculated according to the formula: $\text{LungBrain} = \frac{\text{GMTbrain}}{(\text{GMTbrain} + \text{GMTlung})} \times 100\%$, where GMT is the geometric mean of technetium radioactivity calculated from the front-to-back and back-to-front images targeted at the brain or lungs, and $\kappa$ is a constant coefficient depending on the distribution of peripheral blood to different organs (for the brain = 0.13). An IPBS higher than 6% was the criterion for pathological intrapulmonary shunting (hepatopulmonary syndrome) (20). For five patients in the study, the second examination with MAA scintigraphy was not performed because the patients withdrew their consent (n = 1), the transplantation protocol was suspended (n = 1) or the patients' clinical status deteriorated (n = 3).

We used the following criteria for the diagnosis of HPS: a) evidence of liver cirrhosis, b) alveolar-arterial oxygen gradient ($\text{AaDO}_2$) > 20 mmHg (regardless of the age), c) existence of pathological pulmonary arterio-venous flow (lung perfusion scintigraphy), and d) exclusion of organic diseases of the heart and lungs (chest X-ray, spirometry, electrocardiography, echocardiography). $\text{AaDO}_2$ was calculated using the equation $\text{FiO}_2 \times (\text{PB} - 47) - \text{PaCO}_2 / 0.8 - \text{PaO}_2$, where $\text{FiO}_2$ is the oxygen content in the breathing air (assumed to be 0.21) and $\text{PaO}_2$ is the atmospheric pressure read on the day of investigation from the public weather maps for Katowice downtown of Institute Meteorology and Water Management.

The study protocol was approved by the Ethics Committee of Silesian Medical University and conformed to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008).

**Statistical analysis**

Statistical analysis was conducted using the STATISTICA version 10 software (StatSoft, Kraków, Poland). The distribution of quantitative variables was tested using the Shapiro-Wilk test. For variables having a normal distribution, the means and standard deviations were calculated; for variables deviating from a normal distribution, the median values were chosen. For quantitative variables with a normal distribution, subsequent statistical analysis involved Student's t-test. In the case of variables with a non-normal distribution, the Mann-Whitney test, the Wilcoxon signed-rank test or Student's t-test following logarithmic transformation was applied. To define the relationships between the variables, analyses of correlations and regressions were conducted. For comparisons of categorical variables, such as the prevalence of a disease or condition, the
chi-square test was used. A P level less than 0.05 was considered statistically significant.

RESULTS

Alcoholic cirrhosis was diagnosed in 16 patients, chronic viral hepatitis C in three patients, autoimmune hepatitis or primary sclerosing cholangitis in 10 patients and non-alcoholic steatohepatitis in one patient. Twenty-six (86.7%) patients used non-selective β-blockers during the study. The mean MELD score was 20.2 ± 4.45 points (range of 14.1 to 27.7). From the Child-Pugh classification, 18 patients were categorized as class B and 12 patients as class C; the mean number of points in this classification was 9.5 ± 1.43. Ascites were found in 14 patients, and peripheral edema was present in nine patients. Skin spider naevi were reported in 27 patients. Esophageal varices were endoscopically diagnosed in 26 (86.7%) patients, and severe portal gastropathy occurred in 15 patients. In six patients, there was a history of upper digestive tract bleeding. Dyspnea was reported by eight patients, but no one presented with cyanosis or platypnoe.

Selected laboratory data are presented in Table 1. Pulse oximetry and gasometry data are presented in Table 2.

The mean ejection fraction of the left heart ventricle was 59.8 ± 5.13%. In the supine position, the diagnostic criteria for HPS were met in three (12%) patients and IPBS exceeded 6% in four (16%) patients. In the erect position, the diagnostic criteria for HPS were fulfilled in four (16%) patients and IPBS exceeded 6% in five (20%) patients. The mean difference in IPBS measured in both positions in four patients with HPS was 1.76% (P = 0.011). The remaining mean difference was 0.37% (P = 0.38). The mean IPBS in the erect position was 0.59% higher than that in the supine position (P = 0.046) (Fig. 1, Table 3). In the erect position, the mean O₂ sat. was 1.2% lower than that in the supine position (P = 0.02) (Fig. 2, Table 3). There were no significant correlations between PaO₂ or O₂ sat. and IPBS in either the erect or supine body positions.

DISCUSSION

Patients with liver cirrhosis present the whole spectrum of metabolic and hemodynamic derangements, including

<table>
<thead>
<tr>
<th>Variable, unit</th>
<th>LRN</th>
<th>URN</th>
<th>Mean</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, g/dl</td>
<td>13.5 (11.5 *)</td>
<td>16.5 (15.0 *)</td>
<td>11.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Red blood cell count, ×10⁶/mm³</td>
<td>4.2 (3.7 *)</td>
<td>5.7 (5.0 *)</td>
<td>3.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Red blood cell volume, fl</td>
<td>84</td>
<td>98</td>
<td>97.2</td>
<td>7.4</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>40 (36 )</td>
<td>53 (46 )</td>
<td>33.7</td>
<td>5.2</td>
</tr>
<tr>
<td>White blood cell count, × 10³/mm³</td>
<td>4</td>
<td>10</td>
<td>6.4</td>
<td>3.7</td>
</tr>
<tr>
<td>Platelet blood cell count, × 10³/mm³</td>
<td>130</td>
<td>400</td>
<td>147</td>
<td>145</td>
</tr>
<tr>
<td>Bilirubin, mg/dl</td>
<td>0.3</td>
<td>1.2</td>
<td>9.2</td>
<td>7.4</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>0.66</td>
<td>1.09</td>
<td>1.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Albumin, g/dl</td>
<td>3.5</td>
<td>5.2</td>
<td>2.6</td>
<td>0.4</td>
</tr>
<tr>
<td>C-reactive protein, mg/l</td>
<td>-</td>
<td>5</td>
<td>14.5</td>
<td>14.1</td>
</tr>
<tr>
<td>Alanine aminotransferase, U/l</td>
<td>-</td>
<td>34</td>
<td>78</td>
<td>108</td>
</tr>
<tr>
<td>Aspartate aminotransferase, U/l</td>
<td>-</td>
<td>31</td>
<td>106</td>
<td>76</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/l</td>
<td>30</td>
<td>120</td>
<td>204</td>
<td>183</td>
</tr>
<tr>
<td>γ-Glutamyltransferase, U/l</td>
<td>-</td>
<td>38</td>
<td>208</td>
<td>286</td>
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<tr>
<td>INR</td>
<td>0.8</td>
<td>1.2</td>
<td>1.59</td>
<td>0.36</td>
</tr>
<tr>
<td>α-fetoprotein, ng/ml</td>
<td>0</td>
<td>7</td>
<td>11.5</td>
<td>5.92</td>
</tr>
</tbody>
</table>

Abbreviations: LRN, lower range of norm; URN, upper range of norm; INR, international normalized ratio; SD., standard deviations; * in women.

Conversion factors to SI units are as follows: for bilirubin 17.1, for creatinine 88.4, for albumin 10.0.

<table>
<thead>
<tr>
<th>Parameter, unit</th>
<th>Mean</th>
<th>LRN</th>
<th>URN</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂, mmHg</td>
<td>88.1</td>
<td>83</td>
<td>108</td>
<td>12.6</td>
</tr>
<tr>
<td>PaCO₂, mmHg</td>
<td>31.9</td>
<td>35</td>
<td>48</td>
<td>5.5</td>
</tr>
<tr>
<td>O₂ sat., %</td>
<td>96.7</td>
<td>95</td>
<td>98</td>
<td>2.04</td>
</tr>
<tr>
<td>AaDO₂, mmHg</td>
<td>21.6</td>
<td>-</td>
<td>20</td>
<td>14.4</td>
</tr>
</tbody>
</table>

In 25 patients who completed the supine and upright study, the AaDO₂ (Mean ± S.D.) was 20.5 ± 13.2 mmHg.

Abbreviations: LRN, lower range of normal; URN, upper range of normal; PaO₂, partial oxygen pressure; PaCO₂, partial carbon dioxide pressure; O₂ sat., hemoglobin oxygen saturation; AaDO₂, alveolar-arterial oxygen gradient; n, number of patients; S.D., standard deviations.

Conversion factors to SI units are as follows: for PaO₂, PaCO₂, AaDO₂ 0.133.
Table 3. Intrapulmonary blood shunting (IPBS) and hemoglobin oxygen saturation (O₂ sat.) in relation to body position.

<table>
<thead>
<tr>
<th>Parameter, unit</th>
<th>Body position</th>
<th>n</th>
<th>Mean</th>
<th>Median</th>
<th>S.D.</th>
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</thead>
<tbody>
<tr>
<td>IPBS, %</td>
<td>Erect</td>
<td>25</td>
<td>3.82</td>
<td>2.7</td>
<td>2.76</td>
</tr>
<tr>
<td>O₂ sat., %</td>
<td>Erect</td>
<td>30</td>
<td>95.6</td>
<td>96</td>
<td>3.4</td>
</tr>
<tr>
<td>IPBS, %</td>
<td>Supine</td>
<td>25</td>
<td>3.23</td>
<td>2.5</td>
<td>2.26</td>
</tr>
<tr>
<td>O₂ sat., %</td>
<td>Supine</td>
<td>30</td>
<td>96.8</td>
<td>97</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Abbreviations: n, number of patients; S.D., standard deviations.

Fig. 1. The difference of IPBS (intrapulmonary blood shunting = lung-brain ratio). IPBS values in both the supine and erect positions did not have normal distribution characteristics. This type of distribution was achieved by logarithmic transformation.

Fig. 2. Difference in O₂ sat. (hemoglobin oxygen saturation). O₂ sat. values in both the erect and supine positions did not have normal distribution. This type of distribution was achieved by logarithmic transformation.
The purpose of this study was to investigate the presence of IPBS in cirrhotic patients eligible for liver transplantation while the patients were in two body positions. IPBS is the most relevant diagnostic measure of HPS, which may be an independent criterion for liver transplantation (24, 25). In clinical practice, IPBS is detected with satisfactory sensitivity by either saline contrast echocardiography or perfusion lung scintigraphy (26-30). It should be noted that only the scintigraphy method may provide a quantitative measurement of IPBS. Both examinations are routinely conducted while patients are in a supine body position. This is the first study to use perfusion lung scintigraphy to estimate IPBS with regard to body posture in the same person.

Based on pathophysiological knowledge, it is thought that maintaining an upright posture in patients with liver cirrhosis may enhance blood flow through the basal lung segments, where vascular shunts are more prominent. Therefore, we hypothesized that an erect posture may reveal signs of subclinical, early stages of HPS. In our study IPBS was detected in 16% of patients in the supine position and in 20% of patients in the upright position. Moreover, we found that an erect posture led to an increase in the absolute value of pulmonary blood shunting by 0.59%. This difference was significantly larger in patients with HPS.

Knowledge about IPBS in liver cirrhosis patients in an erect position is still limited. Lenci et al. found a higher frequency of IPBS in liver cirrhosis patients who were in an erect posture during examination with saline contrast echocardiography (27). In another study, IPBS was examined by saline contrast echocardiography, subjectively divided into small, moderate and large, and was significantly increased in terms of both frequency and size after maintaining an erect posture in liver cirrhosis patients awaiting liver transplantation (31). Mild hypoxemia occurs in 50% of cirrhotic patients without acute or chronic cardiopulmonary disease (32-34). In this study, hypoxemia was found in 30% of patients. It is known that more factors than IPBS or O$_2$ saturation, with regard to body position have been investigated in several studies (31, 35). Lenci et al. found that the mean difference in PaO$_2$ in patients with O$_2$ saturation of 90% and 95% was 0.9 kPa in patients with HPS and 0.6 kPa in patients without HPS (31). In another study, the mean O$_2$ saturation was significantly lower in the upright position than in the supine body position in patients with liver cirrhosis (35). These results led to a recommendation to measure O$_2$ saturation while patients are in the upright position as a screening test for IPBS and HPS (13, 35, 36). In our study, O$_2$ saturation in the erect posture was significantly lower than that in the supine position; however, the 1.2% change that was observed could have negligible clinical relevance. In a study by Lenci et al., correspondingly small differences were also observed (31).

Our study showed that the diagnostic criteria of HPS were met in 12% of patients and 16% of patients in the supine position and the standing position, respectively. Therefore, performing perfusion lung scintigraphy in patients with an erect posture may result in more diagnoses of HPS. These figures agree with the general prevalence of HPS in cirrhotic patients waiting for liver transplantation, which ranges from 15% to 20% and is even higher in patients with Budd-Chiari syndrome (37-40).

The diagnostic criteria for HPS are still under debate. The European Respiratory Society recommends that PaO$_2$ should be regarded as an estimate of the severity HPS but not the major determinant of this syndrome. In addition, according to consensus of this society, ruling out acute or chronic cardiopulmonary disease is not a compulsory step in the diagnosis of HPS (30). Moreover, adapting a low cut-off value for AaDO$_2$ might result in the over-diagnosis of HPS, especially in persons aged above 30 years (41), in whom higher values of AaDO$_2$ may be physiologically normal (42, 43). It has been proposed to make 15 mmHg the upper limit of normal values in persons younger than 64 years and 20 mmHg the upper limit in older adults (41). In this study, we cautiously accepted 20 mmHg as a diagnostic cut-off for AaDO$_2$, for all patients, as patients above 30 years old constituted 87% of study population. In our patients, the measurements of PaO$_2$ were performed while the patients were in the supine position, while in other studies, this parameter was examined while the patients were in supine, upright or sitting body positions (44, 45).

Most of our patients (86.7%) used non-selective β-blockers to prevent bleeding from esophageal varices. It has been previously shown that these drugs do not have a beneficial effect on HPS (8, 24) and that they may cause orthostatic hypotension. For this reason, there was a minimum of a 10-minute time interval between the two studies using pulse oximetry. Moreover, the dose of propranolol or carvedilol was stable over the duration of the study.

In summary, this study identified pathological IPBS in an erect body posture in 20% of liver transplant candidates, but not all patients with IPBS suffered the hypoxemia required for diagnosis of HPS. The postural change in IPBS, although statistically significant, was subtle and more apparent only in patients with HPS. Oxygen saturation tended to decrease in an erect body posture but was not correlated with IPBS. It is still unclear if the presence of mild-to-moderate IPBS has any effect on individual outcomes in cirrhotic patients. Moreover, the clinical significance of aggravating IPBS while in the upright position, as is typical for most human activities, remains unknown.

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