Semiquantitative echocardiographic evaluation of intrapulmonary vascular dilatations: correlation with evaluation of shunt levels and pulmonary function parameters*

Avaliação semiquantitativa ecocardiográfica de dilatações vasculares intrapulmonares em candidatos a transplante hepático: correlação com avaliação de shunt e parâmetros funcionais pulmonares

Maria Angélica Pires Ferreira, Sérgio Saldanha Menna Barreto, Marli Maria Knorst, Mario Reis Álvares da Silva, Antonio Furlan Pinotti

Abstract

Objective: To correlate semiquantitative evaluation of intrapulmonary vascular dilatations (IPVD) with quantitative evaluation of shunt levels, as well as to describe clinical and pulmonary function findings in a sample of liver disease patients with IPVD. Methods: Patients presenting transthoracic echocardiography (TTE) positivity for IPVD underwent clinical evaluation, pulmonary function tests and pulmonary shunt quantification (scintigraphy with technetium-99m-labeled macroaggregated albumin and blood gas analysis after pure oxygen breathing). Results: A total of 28 liver cirrhosis patients were studied (mean age, 47.5 years; 60.7% were Child-Pugh class B). A 4-point, ascending scale was used as a measure of IPVD intensity, which was scored as 1, 2, 3 and 4, respectively, in 13 (46.4%), 9 (32.1%), 2 (7.1%) and 4 (14.3%) of the patients. Patients were divided into a low-intensity group (scores 1 and 2) and a high-intensity group (scores 3 and 4). The mean shunt assessed using scintigraphy was 14.9% in the sample as a whole and was lower in the low-intensity group (11.7% vs. 26.3%; p = 0.01). The mean shunt by blood gas analysis was higher in the high-intensity group (8.3% vs. 16.3%; p < 0.001). Mean PaO₂ was lower in the high-intensity group. There was a negative correlation between DLCO and IPVD severity (r = −0.406, p = 0.01). Conclusions: TTE is a safe, useful tool for assessing IPVD severity in liver disease patients. The IPVD intensity assessed using TTE correlated with the intrapulmonary shunt values obtained through the quantitative methods evaluated, as well as with pulmonary gas exchange abnormalities.

Keywords: Anoxia; Liver cirrhosis; Hepatopulmonary syndrome; Echocardiography.

Resumo

Objetivo: Verificar a relação entre a avaliação semiquantitativa de dilatações vasculares intrapulmonares (DVIP) e a avaliação quantitativa de shunt, e descrever achados clínicos e funcionais pulmonares em uma amostra de hepatopatas com DVIP. Métodos: Pacientes com ecocardiografia transtorácica (ETT) positiva para DVIP foram submetidos à avaliação clínica e de função pulmonar assim como à quantificação de shunt intrapulmonar (cintilogia com macroagregados de albumina marcados com tecnécio-99m e por gasometria com oxigênio a 100%). Resultados: Foram estudados 28 pacientes cirróticos (média de idade, 47,5 anos; 60,7% dos casos classificados como Child-Pugh B). Uma escala de 4 pontos, em ordem ascendente, foi utilizada para medir a intensidade das DVIP, classificada de 1 a 4, respectivamente, em 13 (46,4%), 9 (32,1%), 2 (7,1%) e 4 (14,3%) dos pacientes. A amostra foi dividida em grupo baixa intensidade (escores 1 e 2) e grupo alta intensidade (escores 3 e 4). A média de shunt por cintilografia foi 14,9% na amostra total, sendo menor no grupo baixa intensidade (11,7% vs. 26,3%; p = 0,01). O grupo alta intensidade teve maiores valores de shunt através de gasometria (8,3% vs. 16,3%; p < 0,001). A PaO₂ média foi inferior no grupo alta intensidade. A intensidade de DVIP e a DLCO correlacionaram-se de forma inversa (r = −0,406, p = 0,01). Conclusões: A ETT é um método útil e seguro para avaliação da gravidade das DVIP em pacientes com hepatopatia. A classificação ecocardiográfica da intensidade das DVIP se correlacionou com valores de shunt intrapulmonar obtidos pelos métodos quantitativos avaliados, bem como com anormalidades nas trocas gasosas pulmonares.

Descritores: Anoxia; Cirrose hepática; Síndrome hepatopulmonar; Ecocardiografia.

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Introduction

Hepatopulmonary syndrome, which consists of the triad of intrapulmonary vascular dilatations (IPVD), hypoxemia and liver disease, has been described in 5–29% of individuals with liver disease. Occurring in 5–47% of all cases of advanced liver disease, IPVD constitute the leading cause of severe hypoxemia in such cases. However, not all patients with IPVD present hypoxemia; the clinical significance and prognosis of IPVD in the absence of gas exchange abnormalities remain undefined.

The diagnosis of intrapulmonary shunt can be made through functional studies, such as pure oxygen inhalation tests and imaging studies. The latter include contrast-enhanced echocardiography, lung scintigraphy with radioisotope-labeled albumin and pulmonary angiography. Contrast-enhanced transthoracic echocardiography detects right-to-left shunts and is considered the method of choice for IPVD screening, since it presents greater sensitivity than does scintigraphy with macroaggregated albumin. Other advantages of echocardiography include its routine use for the diagnosis of pulmonary hypertension. In addition, it allows the differentiation between intracardiac and intrapulmonary shunts. Furthermore, echocardiography makes it possible to evaluate IPVD intensity semiquantitatively.

The present study aims at comparing levels of venous mixture (intrapulmonary shunt) obtained with two methods (radioisotope scintigraphy and blood gas analysis after pure oxygen breathing) and relating them to the IPVD level determined using contrast-enhanced echocardiography in a group of patients under evaluation for liver transplant. Our secondary objectives were to describe clinical and pulmonary function findings in liver transplant candidates with IPVD and to correlate these findings with IPVD intensity.

Methods

We included consecutive patients over the age of 16 with chronic liver disease or any type of portal hypertension who were under evaluation for liver transplant at the Porto Alegre Hospital de Clínicas, with positive screening for IPVD using transthoracic echocardiography. Since the literature indicates that transthoracic echocardiography is the method of choice for IPVD screening and diagnosis of hepatopulmonary syndrome, patients with negative screening results were not submitted to intrapulmonary shunt quantification using other methods. We excluded patients presenting any of the following characteristics: severe structural chronic pulmonary disease; moderate to severe COPD (stage II to IV according to the Brazilian Thoracic Association); severe cardiopathy; intracardiac shunt; voluminous pleural effusion seen on chest X-ray (more than one third of the hemithorax); diaphragmatic paralysis or other restrictive lung diseases of moderate to severe intensity; and tense refractory ascites.

The patients were evaluated as outpatients, all presenting clinical stability at the time of evaluation. Chest X-ray, arterial blood gas analysis, spirometry (including a pharmacodynamic test) and DLCO (single-breath method) were performed, in accordance with the American Thoracic Society criteria. In addition, pulse oximetry and orthodeoxia investigation were performed. Orthodeoxia was performed using pulse oximetry, \( \text{SpO}_2 \) being determined after 5 min in the horizontal supine position and after 5 min in a sitting position. Positivity was defined as a decrease in \( \text{SpO}_2 \) \geq 4\%. Arterial blood gas analysis was performed through radial artery puncture, with the patient in a sitting position and on room air. Patients with a \( \text{PaO}_2 \) < 80 mmHg on room air and an alveo-
Pulmonary function in 28 liver transplant candidates with intrapulmonary vascular dilatations.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
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<tbody>
<tr>
<td>PaO₂ on room air, mmHg</td>
<td>85.9 ± 12.7</td>
</tr>
<tr>
<td>PaCO₂, mmHg</td>
<td>33.10 ± 4.4</td>
</tr>
<tr>
<td>P(A-a)O₂, mmHg</td>
<td>21.8 ± 15.0</td>
</tr>
<tr>
<td>Prebronchodilator FVC (% of predicted)</td>
<td>87.8 ± 13.1</td>
</tr>
<tr>
<td>Prebronchodilator FEV₁ (% of predicted)</td>
<td>86.6 ± 14.0</td>
</tr>
<tr>
<td>DLCO, mmHg (% of predicted)</td>
<td>62.01 ± 14.4</td>
</tr>
</tbody>
</table>

P(A-a)O₂: alveolar-arterial oxygen gradient.
distribution. Bland & Altman plots were used in order to improve the visualization of the concordance between shunt values measured by scintigraphy with $^{99m}$Tc-MAA and blood gas analysis after pure oxygen breathing. Bilateral tests were employed, and the level of statistical significance was set at 5% ($p < 0.05$). The study was approved by the ethics in research committee of the institution.

**Results**

Of the 51 patients submitted to contrast-enhanced echocardiography, 1 presented early contrast passage and was diagnosed with patent foramen ovale. Another 28 presented echocardiographic positivity for IPVD and were included in the study. Of those 28 patients, 9 were female. The mean age was 47.5 years. The most common etiology of liver disease, seen in 11 patients (39.3%), was viral hepatitis C. In the majority of the patients (60.7%), the severity of the liver disease was classified as Child-Pugh class B (Table 1).

Dyspnea was reported by 2 patients, 1 of which also presented platypnea. Both were diagnosed with hepatopulmonary syndrome and were hypoxemic at rest. Two cases of orthodeoxia were detected: one accompanied by dyspnea and platypnea; and one asymptomatic from a respiratory standpoint. Most of the patients (71.4%) reported current or previous smoking, and 9 (32.1%) were current smokers. The mean tobacco intake was 14.6 pack-years.

Non-voluminous unilateral pleural effusion was present in two cases. Minimal ascites was identified using echocardiography in seven cases.

Arterial blood gas analysis on room air was analyzed in 27 of the 28 patients, and in 1 case the test was excluded due to a collection error. Hypoxemia was identified in 8 patients (29.6%). In the sample as a whole, the mean prebronchodilator FEV$_1$ was 86.6% of predicted. Data related to arterial blood gases and pulmonary function are presented in Table 2.

All echocardiographic tests were considered technically adequate. There were no method-related complications. Among the 28 patients included in this study, echocardiography-determined IPVD intensity was scored as 1, 2, 3 and 4 (ascending intensity) in 13 (46.4%), 9 (32.1%), 2 (7.1%) and 4 (14.3%) of the patients, respectively. None of the patients presented echocardiographic signs of pulmonary arterial hypertension.

Mean PaO$_2$ was higher in the patients with IPVD scores of 1 or 2 (Student's t-test, $p = 0.01$; Table 3). The correlation coefficient between PaO$_2$ on room air and echocardiography-determined IPVD score presented borderline statistical significance ($r = -0.368; p = 0.05$).

Hepatopulmonary syndrome was diagnosed in 16 of the 28 patients studied (57.1% of the patients), taking into consideration the concomitance between IPVD and increased alveolar-arterial oxygen gradient. However, when the 51 patients submitted to echocardiographic screening for IPVD were considered, the prevalence of hepatopulmonary syndrome was 31.4% (16 of the 51 patients).

There was an inverse correlation between DLCO and echocardiography-determined IPVD score ($r = -0.406; p = 0.01$). Mean DLCO was significantly higher among patients with IPVD.

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**Table 3** – Blood gas analysis parameters, pulmonary diffusion and shunt fraction in 28 patients with low and high scores for echocardiography-determined intrapulmonary vascular dilatations.

<table>
<thead>
<tr>
<th>Variable</th>
<th>IPVD scores 1 and 2 (n = 22)</th>
<th>IPVD scores 3 and 4 (n = 6)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO$_2$ on room air, mmHg</td>
<td>89.1 ± 11.0</td>
<td>74.7 ± 13.2</td>
<td>0.01</td>
</tr>
<tr>
<td>P(A-a)O$_2$, mmHg</td>
<td>16.9 ± 9.4</td>
<td>39.1 ± 19.1</td>
<td>0.001</td>
</tr>
<tr>
<td>DLCO* (% of predicted)</td>
<td>65.0 ± 13.4</td>
<td>51.2 ± 13.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Q$<em>{S}$/Q$</em>{T}$, $^{99m}$Tc-MAA (% Q)</td>
<td>11.7 ± 3.8</td>
<td>26.3 ± 9.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Q$<em>{S}$/Q$</em>{T}$ 100% (% Q)</td>
<td>8.3 ± 2.3</td>
<td>16.3 ± 2.6</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*P(A-a): alveolar-arterial oxygen gradient; Q$_{S}$/Q$_{T}$, 100%: shunt fraction using blood gas analysis after pure oxygen breathing; Q$_{S}$/Q$_{T}$, $^{99m}$Tc-MAA: shunt fraction using scintigraphy with technetium-99m-labeled macroaggregated albumin; and Q: cardiac output. *Transference factor. Values expressed as means ± SD.
Of the 28 patients with IPVD identified using contrast-enhanced echocardiography, the degree of shunting was quantified using scintigraphy and blood gas analysis in 21 (75%), only scintigraphy in 6 (21.4%) and only blood gas analysis in 1 (3.6%). Therefore, 27 scintigraphic imaging tests and 22 blood gas analyses after pure oxygen breathing were performed. Shunt quantification could not be performed in 4 patients due to adherence problems (3 patients did not undergo the pure oxygen breathing test, and 1 patient did not undergo scintigraphy). Another 3 patients were not submitted to the pure oxygen breathing test due to clinical complications, established after performance of the first two tests (slowly resolving pneumonia, aggravation of ascites and liver transplant).

For the 27 patients submitted to scintigraphy, the mean scintigraphy-determined shunting of cardiac output was $14.9 \pm 9\%$ (range, 6.9-39%; median, 12%). When scintigraphy was used, none of the patients presented a normal shunt fraction ($< 6\%$). A positive correlation was observed between echocardiography-determined IPVD score and scintigraphy-determined shunt fraction ($r = 0.567$; $p < 0.001$; Figure 1).

The mean shunt value obtained using the pure oxygen breathing test was $9.8 \pm 3.9\%$ (range, 4-19%). Final PaO$_2$ in the test ranged from 317.8 mmHg to 615 mmHg (mean, 513.6 mmHg) and was significantly higher among the patients with IPVD scores of 1 or 2 than among those with IPVD scores of 3 or 4 ($p = 0.03$; Table 3).

There was no significant correlation between severity of the underlying disease, according to the Child-Pugh classification, and echocardiography-determined IPVD score ($r = -0.13$; $p = 0.48$). Similarly, there was no correlation between time since diagnosis of liver disease and echocardiography-determined IPVD score.

![Figure 1](image1.png)

**Figure 1** - Distribution of shunt values, as determined using scintigraphy with technetium-99m-labeled macroaggregated albumin, according to echocardiography-determined intrapulmonary vascular dilatations (IPVD) score ($r = 0.567$; $p < 0.001$).

Scores of 1 or 2 were observed in 13 patients (46.4%) and scores of 3 or 4 in 15 patients (53.6%). The mean shunt values obtained using scintigraphy were significantly higher than those obtained using blood gas analysis after pure oxygen breathing ($p < 0.001$; Figure 1).

![Figure 2](image2.png)

**Figure 2** - Shunt values evaluated using scintigraphy with technetium-99m-labeled macroaggregated albumin and blood gas analysis after pure oxygen (O$_2$) breathing. In A, correlation between shunt values evaluated by the two methods ($r = 0.666$; $p < 0.001$). In B, Bland & Altman plots were used in order to improve the visualization of shunt values evaluated by the two methods; mean of the differences, 4.3%; upper limit, 11.75%; lower limit, −3.15% (1.96 SD).

Scintigraphy-determined shunt correlated significantly with that determined using blood gas analysis after pure oxygen breathing ($r = 0.666$; $p < 0.001$). The correlation between shunt values obtained using the two methods and the comparison of results using Bland & Altman plots are shown in Figure 2. The mean shunt difference determined using the two methods
was 4.3 ± 3.8%. There was greater discrepancy between the results of the two methods in three cases: scintigraphy overestimated shunt in two cases and underestimated shunt in one case.

**Discussion**

Of the pulmonary functional parameters analyzed, the principal abnormality observed was a decrease in DLCO, which correlated inversely with IPVD score. This finding is in accordance with the data in the literature. We observed a high frequency of increased alveolar-arterial oxygen gradient and hypocapnia, both of which correlated significantly with IPVD score. The effects of smoking might have contributed to the gas exchange alterations described here, although vascular abnormalities resulting from liver disease are possibly the predominant factors.

Mean PaO₂ was within the limits of normality. Taking into account the exclusion of patients with respiratory comorbidities, this reflects a low to moderate IPVD score found in most cases, since 78.5% of the cases presented echocardiography-determined scores of 1 or 2, and the majority presented scintigraphy-determined shunt < 20%. According to the literature, echocardiography is frequently positive in patients with normal arterial blood gases, presumably reflecting an IPVD level insufficient to be reflected in gas exchange.

There was a statistically significant correlation between hypoxemia and echocardiography-determined IPVD score, and the patients with higher IPVD score presented significantly lower PaO₂ on room air. Few studies have assessed the relationship between echocardiography-determined IPVD score and arterial oxygenation levels. One group of authors reported that mean PaO₂ on room air is significantly lower among patients with ventricular opacification of at least 2 crosses (IPVD score of 2) than among those who present no echocardiographic evidence of IPVD. Another group of authors reported the evolution of a case after liver transplant, in which PaO₂ was increased, as evidenced by a lower echocardiography-determined IPVD score. In another study, no statistically significant difference in mean PaO₂ was found between patients with an IPVD score of 1 and those with an IPVD score of 2, 3 or 4, possibly due to the small size of the sample. However, in 81% of the patients who presented IPVD without hepatopulmonary syndrome, IPVD was scored as 1+.

In the present study, echocardiography-determined IPVD score was found to correlate significantly with shunt fraction calculated using either of the two quantitative methods employed (blood gas analysis after pure oxygen breathing and scintigraphy).

All of the patients evaluated in the present study presented echocardiographic and scintigraphic positivity. Nevertheless, in functional terms, there were no cases of total lack of response to pure oxygen, and final PaO₂ after pure oxygen inhalation was > 300 mmHg in all cases. This is consistent with the theoretical model employed in order to explain the diffusion-perfusion mismatch related to impaired gas exchange among the hemoglobin molecules in the center of the dilated vessel. In addition to the distance between the alveoli and the hemoglobin molecules in the central stream of the vessel, the shorter transit time of red cells in the pulmonary capillary would contribute to the worsening of the disturbance. This abnormality in oxygenation can be significantly improved with pure oxygen, resulting in lower shunt indices obtained through blood gas analysis after pure oxygen breathing. Together with ventilation-perfusion mismatch and anatomical shunt, diffusion-perfusion mismatch is considered a central mechanism in the genesis of hypoxemia related to liver disease.

Data in the literature show that the isotopic method frequently overestimates the shunt values obtained using blood gas analysis. One group of authors, evaluating 8 patients with hepatopulmonary syndrome, found individual differences between the methods ranging from 2% to 30%. Convergence of shunt values calculated using the two methods was associated with anatomical shunt demonstrated using angiography, whereas the divergence was related to a combination of anatomical shunt and diffusion disturbance.

According to the literature, scintigraphy is less sensitive than is transthoracic echocardiography in the identification of IPVD. The scintigraphic positivity in all 27 of the patients submitted to the test might be due to differences in the reading of the test, since there is an operator-dependent aspect in the demarcation of areas with abnormal uptake of the radioac-
tive drug. However, the significant correlation between the scintigraphy-determined shunt values and those obtained using the other two methods, as well as that between shunt values and abnormalities in arterial oxygenation are aspects to be considered in weighing the results obtained. Regarding the role of radioisotope scintigraphy in the evaluation of patients with liver disease and hypoxemia, in agreement with others authors, we believe that this method can be useful in the evaluation of hypoxemic patients with low echocardiography-determined IPVD score, in the cases in which echocardiography presents technical difficulties, such as obesity or deformities in the rib cage, or in those cases of accompanying pulmonary disease which make the diagnosis of hepato pulmonar y syndrome difficult. The combined analysis of the severity of oxygenation disturbance and the assessment of shunt using the method with \(^{99m}\)Tc-MAA can be useful in the risk stratification of patients with hepato pulmonary syndrome for mortality associated with liver transplants, with worse prognosis associated with \(\text{PaO}_2 \leq 50 \text{ mmHg and scintigraphy-determined shunt fraction} \geq 20\%\). In the present study, patients with higher echocardiography-determined IPVD scores (3 or 4) presented advanced dilatation of the vascular bed, demonstrated by a great passage of particles of the radioactive drug. However, the significant correlation between the scintigraphy-determined shunt values and those obtained using the other two methods, as well as that between shunt values and abnormalities in arterial oxygenation are aspects to be considered in weighing the results obtained. Regarding the role of radioisotope scintigraphy in the evaluation of patients with liver disease and hypoxemia, in agreement with others authors, we believe that this method can be useful in the evaluation of hypoxemic patients with low echocardiography-determined IPVD score, in the cases in which echocardiography presents technical difficulties, such as obesity or deformities in the rib cage, or in those cases of accompanying pulmonary disease which make the diagnosis of hepato pulmonary syndrome difficult. The combined analysis of the severity of oxygenation disturbance and the assessment of shunt using the method with \(^{99m}\)Tc-MAA can be useful in the risk stratification of patients with hepato pulmonary syndrome for mortality associated with liver transplants, with worse prognosis associated with \(\text{PaO}_2 \leq 50 \text{ mmHg and scintigraphy-determined shunt fraction} \geq 20\%\). In the present study, patients with higher echocardiography-determined IPVD scores (3 or 4) presented advanced dilatation of the vascular bed, demonstrated by a great passage of particles of the radioactive drug in scintigraphy, with a mean shunt fraction of 26%. Transthoracic echocardiography is considered less sensitive than transesophageal echocardiography in IPVD detection. Among the advantages of the transthoracic approach are the lower costs, the fact that sedation is unnecessary and, theoretically, the lower risk, especially for individuals with esophageal varices. In conclusion, transthoracic echocardiography is a useful and safe method of assessing IPVD severity in individuals with advanced liver disease. Transthoracic echocardiography-determined IPVD intensity correlated with the intrapulmonary shunt values obtained through the quantitative methods evaluated, as well as with pulmonary gas exchange abnormalities.

References


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