Association between hepatic disease and pulmonary vascular dilations has been emphasized by several authors for many years, providing knowledge of the physiopathologic aspects of arterial hypoxemia found in some patients with chronic hepatic disease: the hepatopulmonary syndrome. This clinical condition is characterized by the triad hepatic dysfunction, intrapulmonary vascular dilation, and hypoxemia 1-11. Pulmonary capillary vasodilation is an extrahepatic complication of severe hepatic disease, probably due to vasoactive mediation of nitric oxide 2,7,11-13, leading to the occurrence of right-left intrapulmonary shunt, with consequent alteration of alveolar-capillary diffusion and ventilation/perfusion pulmonar imbalance 1,9,11,14,15. In advanced stages of severe hepatic disease, both arterial vasodilation and true pulmonary arterial venous communications may be present 1,15. The patients may have normal arterial gasometry or severe arterial hypoxemia associated with cyanosis and dyspnea in 9-29% of cases 1,3,7,16,17. Hemodynamic condition with increased cardiac output, low systemic and pulmonary vascular resistance, and a decrease in the content of arterial and mixed venous oxygen may be present 1,5-7,10-12,18.

Contrast echocardiography, pulmonary perfusion scintigraphy with Tc 99m macro aggregated albumin and pulmonary angiography are among the diagnostic methods used to identify pulmonary vascular alterations in patients with chronic hepatic diseases. Contrast echocardiography is considered the gold standard for diagnosing this condition, having several advantages over other methods. It also enables pulmonary shunt detection in patients with normal angiographies or arterial gasometry, or both. Recent studies have stressed the superiority of contrast transesophageal echocardiography in the diagnosis of pulmonary vascular alterations in this group of patients 3,6,12,16-19.

The objective of this study was to compare the results of transthoracic and transesophageal contrast echocardiography, in addition to determining its importance in the diagnosis of pulmonary arterial vascular dilation in patients eligible for hepatic transplantation.

**Methods**

Transthoracic echocardiography (TTE) was performed in 76 patients, among them 32 patients were consecutively undergone to a transesophageal study (ETE). Echocardiographic contrast was obtained from microbubbles derived from the injection of agitated saline solution, in venous peripheral access. Abnormal presence of contrast in the left cardiac chambers was considered positive, with a delay of 4 to 6 cardiac cycles, after initial opacification of the right cardiac chambers.

**Results**

PVD diagnosis was performed in 53.9% of the patients (41/76). Sensibility, specificity, positive predictive value, negative predictive value, and accuracy of the TTE in relation to the ETE was 75%, 100%, 100%, 80% and 87.5%, respectively. Echocardiography was positive in 37 (55.2%) of 67 nonhypoxemic patients, and in 4 (44.4%) hypoxemic ones. No cardiologic hemodynamic repercussions from intrapulmonary shunt were observed.

**Conclusion**

The contrast echocardiography is efficient, easy to be used, and safe in the search for and identification of intrapulmonary vascular alterations in patients eligible for hepatic transplantation.

**Key words**

contrast echocardiography, intrapulmonary vascular dilations, hepatic transplantation
Contrast echocardiography in the diagnosis of intrapulmonary vascular dilations in patients eligible for liver transplantation

Mean age of patients was 44 ± 14.6 years; 59 (77.6%) were men and 18 (22.4%) were women. Of the 76 patients with advanced hepatic disease, 72 had a diagnosis of hepatic cirrhosis and 4 of hepatic fibrosis. Among the patients with hepatic cellular alterations, 12 had alcoholic cirrhosis, 9 had hepatitis B, 16 hepatitis C, 3 hepatitis B and C, 15 mixed cirrhosis (hepatitis B and/or C associated with alcohol), 9 cryptogenic cirrhosis, 2 autoimmune cirrhosis, 3 biliary cirrhosis, 1 had schistosomiasis, 1 paracoccidioidomycosis, and 2 obstructive vein diseases (portal vein thrombosis, Budd-Chiari syndrome).

ATL brand equipment (Advanced Technology Laboratories Inc., Bothel, WA, USA) was used to obtain bi-dimensional images with the patient in left lateral decubitus 27, according to techniques and cuts previously established. Contrast transthoracic echocardiography was performed using HDI 5000 with an electronic phased-array transducer with a 2 to 4 MHz frequency, using second harmonic imaging in all examinations, to reduce image artifacts and to increase the contrast resolution. Contrast transesophageal echocardiography was performed with Apogee CX200, with the introduction of a 5.0 MHz multiplane esophageal probe approximately 30 cm deep of the dental arcade, after topical anesthesia of the pharynx. The use of 4-chamber echocardiographic views allowed simultaneous visualization of the atrium, when possible, left and right superior pulmonary veins 28,29.

Measurements of left atrium diameter and diastolic and systolic left ventricle dimension were obtained; left ventricle ejection fraction was calculated based on cube method for ventricular volume determination and estimation of right ventricular systolic pressure through tricuspid regurgitation, using a modified Bernoulli’s equation 28,30-33.

Echocardiographic study was developed according to methods published by Krowka et al 11 and Aller et al 3. Microbubbles were manually produced, promoting the transference of 10 mL of saline solution between 2 syringes connected to 3-vial equipment, 10 to 15 times, and then, quickly administered through the peripheral venous access. The study was considered positive when the abnormal presence of contrast in left cardiac chambers was detected, with a 4 to 6 cardiac cycle delay, after initial opacification of the right cardiac chamber (fig. 1). Three injections were given in general, to determine the reproducibility; the results were recorded on VCR and assessed by 2 observers. The following injections were started only after complete removal of microbubbles from the left and right cavities. According to left atrium opacification, semi-quantitative analysis of the microbubbles was performed following the criteria established by Aller et al 3. Simultaneous comparison of the maximum echocardiographic images produced by microbubbles between the right and left cardiac cavities established the absence of microbubbles as level 1; the passage of a few isolated microbubbles as level 2; several isolated microbubbles as level 3; passage of several microbubbles resulting in an increase in echogenicity as level 4; left atrium opacification in the lower level compared with that in the right atrium was considered as level 5; and the complete left atrium opacification similar to that in the right atrium was considered level 6. Levels 1 and 2 were considered normal or absence of pulmonary vasodilations; level 3 as the presence of mild pulmonary vasodilations; and finally, levels 4 to 6 as significant or important pulmonary vasodilations.

Partial oxygen pressure (PaO2) was determined in arterial blood samples, collected from the radial artery, in open air, as close as
Results

All diagnostic procedures were well tolerated, and the transeosophageal echocardiograms were performed without complications. The use of transeosophageal and transthoracic contrast echocardiography demonstrated the presence of pulmonary arterial dilatations in 53.9% (41/76) of patients. In the transthoracic study, alone, a prevalence of intrapulmonary arterial vasodilations was observed in 48.7% (37/76) of cases. Of the 32 patients undergoing transseosphageal study, 16 (50%) had a positive contrast echocardiogram (P = 1.0; Fisher’s exact test). Four patients with an initially inconclusive transthoracic study underwent transesophageal echocardiography and were considered positive. Hepatopulmonary syndrome was present in only 4 (5.3%) patients. According to the criteria established by Aller et al., 16 (21%) patients had mild pulmonary artery vasodilatations; 25 (33%) significant pulmonary artery dilatations, and the 35 remaining (46%) patients had normal echocardiograms. Transthoracic echocardiography demonstrated 75% sensitivity, 100% specificity, 100% positive predictive value, 80% negative predictive value, and 87.5% accuracy in the diagnosis of intrapulmonary arterial dilatations, when compared with that in transeosophageal echocardiography, considered the gold standard.

Assessing the causes of hepatic deasease, 28 (46.7%) of the 60 patients with cirrhosis due to hepatic cell destruction, 8 (88.9%) of 9 patients with cryptogenic cirrhosis, 3 with biliary cirrhosis, and 2 with cirrhosis due to venous-occlusive disease had positive echocardiograms. Comparing the results of patients with cryptogenic cirrhosis and pulmonary artery dilatation to those of patients with all other etiologies, by $\chi^2$ test, a statistically significant difference was not found between the groups (P = 0.059). However, when cryptogenic cirrhosis and alone was compared with hepatic cellular destruction, the difference was statistically significant (P = 0.044).

Gasometric and Doppler echocardiographic variables are presented in Table I. Arterial hypoxemia was present in 9 (15.9%) of the 76 patients, and only 4 (44.4%) had evidence of pulmonary arterial dilatations. Of the 67 patients without arterial hypoxemia, 37 (55.2%) had a positive echocardiogram.

Discussion

Pulmonary vascular abnormalities in patients with chronic hepatic disease are wide vasodilatations with diameters ranging from 15 to 150 mmHg usually found at the capillary level, and close to gas exchange regions. Pulmonary blood flow deviation for the dilated capillary areas is due to dilatation of the pulmonary capillaries caused by interstitial edema and dilatation of the small arterioles with secondary dilatation of the capillaries. Pulmonary capillary blood flow is increased, and because of their unspecified aspects in routine examinations, 35, 36. Studies with contrast echocardiography in patients with hepatic cirrhosis demonstrate the presence of intrapulmonary vascular dilatations in 13 to 47% of patients, even in normal angiographic studies. 3, 4, 7, 11, 16, 17, 35, 36. In our study, the identification of pulmonary vascular dilatations using contrast echocardiography was possible in 41 to 76 of the patients, 53.9% of cases, and these results are similar to those in the literature.

A study by Vedrine et al. 24 and Aller et al. 3 demonstrated the superiority of contrast transeosophageal echocardiography in the diagnosis of intrapulmonary vascular dilatations in patients eligible for hepatic transplantation. 3, 24, 25. Transeosophageal echocardiography, consi dered the gold standard for the diagnosis of intrapulmonary vascular dilatation, allowed demonstration in our study of the presence of this condition in 50% (16/32) of cases. In 4 patients, with a previously inconclusive transthoracic study, due to an inadequate acoustic window, demonstration of intrapulmonary vascular dilatations was only possible after the use of transeosophageal echocardiography. The use of second harmonic imaging in transthoracic echocardiography in our study contributed significantly to obtaining satisfactory results, similar to those in the transeosophageal study. Comparing the proportion of individuals with pulmonary vascular dilatations diagnosed by transthoracic and transeosophageal echocardiography, using Fisher’s exact test, no statistically significant differences were noted between the data (P = 0.851), demonstrating that both methods are equally efficient. The comparison of the results of transeosophageal and transeosophageal contrast echocardiography, successively performed in 32 patients, demonstrated

<table>
<thead>
<tr>
<th>Table I - Gasometric and Doppler echocardiographic variables</th>
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<tbody>
<tr>
<td>Negative echocardiogram (level 1-6)</td>
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<tr>
<td>Mean PaO₂ (mmHg)</td>
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<tr>
<td>PaO₂ &lt; 70 mmHg</td>
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<tr>
<td>RVSP &gt; 30 mmHg</td>
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<tr>
<td>Mean LA diameter (mm)</td>
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<td>Mean LV diameter (mm)</td>
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<td>LVDD &gt; 55 mm</td>
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PaO₂ - partial arterial oxygen pressure; RVSP - right ventricular systolic pressure; LA - left atrium; LV - left ventricle; LAD - left atrial diameter; LVDD - left ventricular diameter; mm - millimeters; mmHg - mercury millimeters; P - statistical significance level.
75% sensitivity and 100% specificity, 100% positive predictive value, 80% negative predictive value, and 87.5% accuracy, which validated contrast transtracheal echocardiography and second harmonic imaging as a safe, fast, and noninvasive diagnostic test, reliable and inexpensive, in the study of these patients.

Hepatopulmonary syndrome, usually reported in 9-29% of cases with hepatic failure,1-3, 7-16, was present in 5.3% of the cases in this study (only 4 patients). The level of arterial oxygen was not statistically correlated to the occurrence of a positive echocardiogram in the present study. These findings are similar to those of Krowka et al.16, who did not find correlations between the pulmonary vascular abnormalities and blood gasometry in patients with positive echocardiograms (13.2% of cases) when compared with those with a normal study. Misdraji et al.4 also found normal blood gasometry in 56% of patients with hepatic cirrhosis, and only 8 (14.3%) had positive contrast echocardiograms. Veldhuisen et al.24, however, found hypoxemia in 56% and 33% of patients with intrapulmonary shunt diagnosed by transesophageal and transthoracic echocardiography, respectively.

Regarding mean PaO2 values found in these studies, they were similar in the different levels of left cardiac chambers opacification (P = 0.859), despite the results of Hopkins et al., whose values were significantly lower in patients with greater opacification of the left chambers (P = 0.01). With our results, it is possible to state that eventual abnormalities in arterial oxygen in patients with chronic hepatic disease should not be considered as indicators of intrapulmonary shunt and, alone, do not confirm this condition.

With a probable hyperdynamic circulatory condition, present in individuals with intrapulmonary vascular shunts that could lead to left cavity diameter and volume alterations, or pressure alteration in the pulmonal vascular bed, the present study did not find any correlation between these variables and the diagnosis of intrapulmonary vascular dilations with the use of contrast echocardiography. Regarding the findings of hepatic disease causes, although they were interesting, they did not have physical or histologic support that allows stating that pulmonary vascular abnormalities are more frequent in certain groups of patients with chronic hepatic disease.

In summary, contrast transthoracic echocardiography with microbubbles using second harmonic imaging must be recommended in the routine evaluation of patients with severe hepatic disease, eligible for hepatic transplantation, to identify intrapulmonary vascular dilations or hepatopulmonary syndrome diagnosis. The clinical use of these findings in the prognosis of patients with hepatic disease needs further study.

References


Contrast Echocardiography in the Diagnosis of Intrapulmonary Vascular Dilations in Patients Eligible for Liver Transplantation


