Original Article

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

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Objective

To determine the importance of contrast echocardiography in the diagnosis of intrapulmonary vascular dilations (PVD) in patients with severe hepatic diseases, eligible for transplantation.

Methods

Transthoracic ecocardiography (TTE) with second harmonic imaging 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 opacicification 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% e 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 intrapulmonar 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

contraste chocardiography, intrapulmonary vascular dilations, hepatic transplantation

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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 pulmonary 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 alteration in this group of patients [3,6,12,16-19-26].

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 liver transplantation.

Methods

Seventy-six patients with severe and advanced hepatic diseases enrolled in the liver transplant protocol underwent contrast echocardiography. Patients with a diagnosis of chronic pulmonary diseases, heart failure, and congenital heart disease with intracardiac communication had beer excluded. The study was performed after subjects had been informed individually about the objectives of

the investigation and given written consent. The research protocol was assessed and approved by the Research Ethical Committee of the Institution.

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 hepatocellular 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 (primary biliary obstruction), 1 hemochromatosis, 1 nonalcoholic steatosis-hepatitis, and 1 Wilson disease. Among the patients with intrahepatic and extrahepatic fibrosis, 1 had schistosomiasis, 1 paracoccidioidomycosis, and 2 obstructive vein diseases (1 portal vein thrombosis, 1 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 topic anesthesia of the pharynx. The use of 4-chamber echocardiographic view allowed simultaneous visualization of the atrium and, 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 ventricle 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 (PaO_2) was determined in arterial blood samples, collected from the radial artery, in open air, as close as

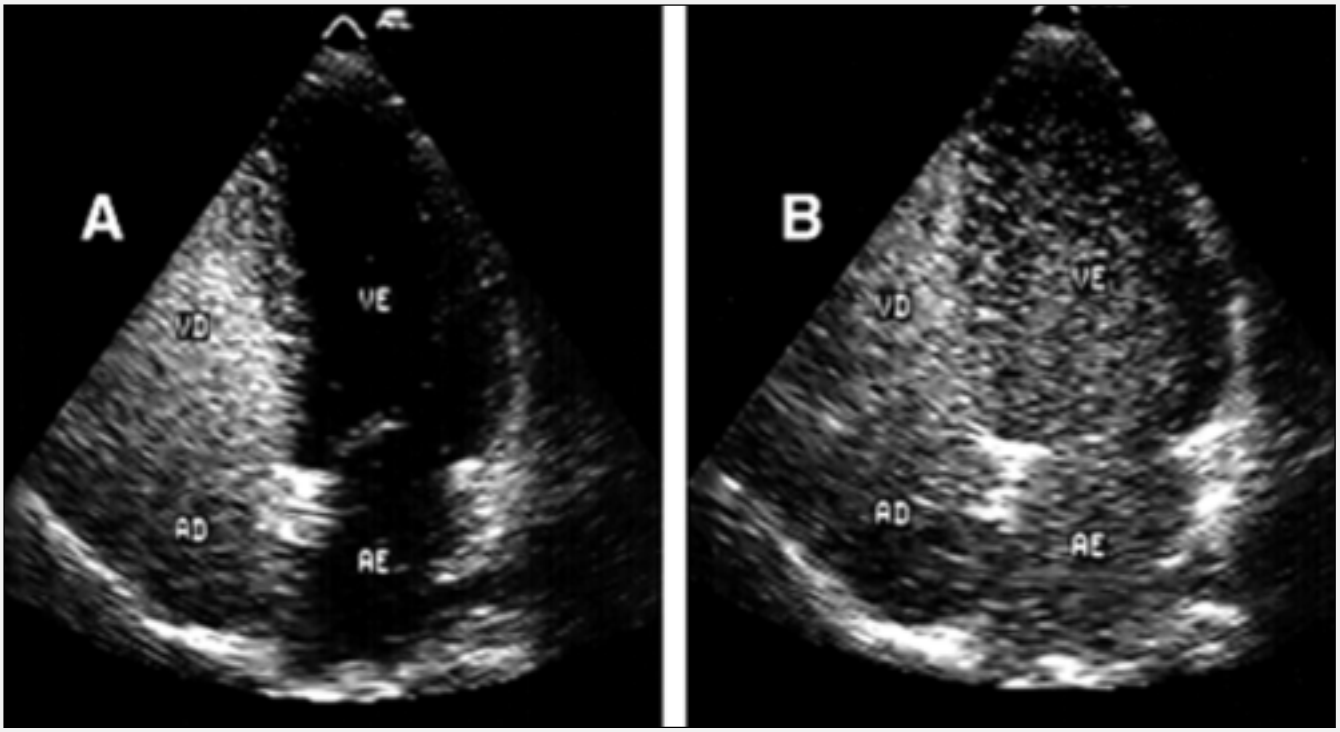

Fig. 1 - Bidimensional transthoracic echocardiogram, 4 chambers apical view: A) presence of contrast in right cambers; B) presence of contrast in left chambers after 6 cardiac cycles, compatible with intrapulmonary vascular dilations.

possible to the days of the echocardiographic study (1-3 days). Values of PaO_2 < 70 mmHg were considered an indication of arterial hypoxemia.

Continuous quantitative variables were assessed with the Student *t* test, using Tukey's correction if necessary. Comparison of the frequencies was performed using the chi-square test or Fisher exact test. Five percent alpha error was accepted, and P values ≤ 0.05 were considered significant.

Results

All diagnostic procedures were well tolerated, and the transesophageal echocardiogram was performed without complications. The use of transesophageal and transthoracic contrast echocardiography demonstrated the presence of pulmonary artery dilation 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 transesophageal 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. [3], 16 (21%) patients had mild pulmonary artery vasodilations; 25 (33%) significant pulmonary artery dilation, 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 dilations, when compared with that in transesophageal echocardiography, considered the gold standard.

Assessing the causes of hepatic disease, 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 diseases had positive echocardiograms. Comparing the results of patients with cryptogenic cirrhosis and pulmonary artery dilation to those of patients with all other etiologies, by χ^2 test, a statistically significant difference was not found between the groups (P=0.059). However, when cryptogenic cirrhosis 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 dilations. Of the 67 patients without arterial hypoxemia, 37 (55.2%) had a positive echocardiogram.

Discussion

Pulmonary vascular alterations found in patients with chronic hepatic disease are wide vasodilations with diameters ranging from 15 to 150 µm, usually found at the capillary level, and close to gas exchange regions. Pulmonary blood flow deviation for the dilated capillary avoids alveolar functioning units, impairing the pulmonary diffusion-perfusion correlation, with a consequent decrease in the arterial oxygen saturation [1,5,7,9-11].

Intrapulmonary vascular abnormalities are not routinely detected because of their uncommon presentation in the general population and because of their unspecified aspects in routine examinations [34]. Studies with contrast echocardiography in patients with hepatic cirrhosis demonstrate the presence of intrapulmonary vascular dilation in 13 to 47% of patients, even in normal angiographic studies [1,3,4,7,11,16,17,35,36]. In our study, the identification of pulmonary vascular dilations 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 Vedrinne et al [24] and Aller et al [3] demonstrated the superiority of contrast transesophageal echocardiography in the diagnosis of intrapulmonary vascular dilation in patients eligible for hepatic transplantation [3,24,25]. Transesophageal echocardiography, considered the gold standard for the diagnosis of intrapulmonary vascular dilation, 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 dilations was only possible after the use of transesophageal echocardiography. The use of second harmonic imaging in transthoracic echocardiography in our study contributed significantly to obtaining satisfactory results, similar to those in the transesophageal study. Comparing the proportion of individuals with pulmonary vascular dilations diagnosed by transthoracic and transesophageal echocardiography, using Fisher's exact test, no significant differences were noted between the data (P=1), demonstrating that both methods are equally efficient. The comparison of the results of transthoracic and transesophageal contrast echocardiography, consecutively performed in 32 patients, demonstrated

Table I - Gasometric and Doppler echocardiographic variables

	Negative echocardiogram (level 1+2)	Positive echocardiogram (level 3+4+5+6)	P value
Mean PaO_2 (mmHg)	93.2 ± 17.8	92.4 ± 20.3	0.859
PaO_2 < 70 mmHg	5/35 patients	4/41 patients	0.724
RVSP > 30 mmHg	12/35 patients	16/41 patients	0.850
Mean LA diameter (mm)	38.9 ± 5.4	37.2 ± 4.4	0.135
Mean LV diameter (mm)	49.8 ± 4.4	49.8 ± 6.0	0.981
LAD > 40 mm	11/35 patients	11/41 patients	0.851
LVDD > 55 mm	5/35 patients	6/41 patients	0.965

PaO_2 - partial arterial oxygen pressure; RVSP - right ventricle systolic pressure; LA - left atrium; LV - left ventricle; LAD - left atrium diameter; LVDD - left ventricle diastolic 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 validates contrast transthoracic 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 to 29% of cases with hepatic failure [1,3,7,16,17], was present in 5.3% of the cases in our 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 [18], who did not find correlations between pulmonary vascular abnormalities and blood gasometry in patients with positive echocardiograms (13.2% of cases) when compared with those with a normal study. Mimidis et al [4] also found normal blood gasometry in 56 individuals with hepatic cirrhosis, and only 8 (14.3%) had positive contrast echocardiograms. Vedrinne et al [24], however, found hypoxemia in 56% and 33% of patients with intrapulmonary shunt diagnosed by transesophageal and transthoracic echocardiography, respectively. Regarding mean PaO_2 values found in these studies, they were similar in the different levels of left cardiac chamber opacification (P=0.859), despite the results of Hopkins et al[36], whose values were significantly lower in individuals 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 pulmonary 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 physiopathologic support that allows stating that pulmonary vascular disturbances 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 and in follow-up of patients with severe hepatic disease, eligible for hepatic transplantation, to identify intrapulmonary vascular dilations or hepatopulmonary syndrome diagnosis. The inconclusive cases, with strong clinical suspicion, must undergo transesophageal study. The clinical meaning of these findings in the prognosis of patients with terminal hepatic disease needs further study.

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