Original Article

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

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Objective

To determine the importance of contrast echocardiography in the diagnosis of intrapulmonary vascular dilations in patients with severe liver disease, who are candidates for liver transplantation.

Methods

The study comprised 76 patients with chronic liver disease and no evidence of intrinsic pulmonary disease, heart failure, or congenital heart disease with intracardiac communications, who underwent transthoracic echocardiography with second harmonic imaging. Thirty-two of them underwent consecutive transesophageal study. The result of contrast echocardiography was considered positive when the presence of contrast was detected in the left cardiac chambers with a delay of 4 to 6 cardiac cycles after initial opacification of the right cardiac chambers.

Results

The prevalence of intrapulmonary vascular dilations was 53.9% (41/76 patients). The sensitivity, specificity, positive and negative predictive values, and accuracy of transthoracic echocardiography as compared with those of transesophageal echocardiography for confirming pulmonary vascular abnormalities in patients with liver disease were, respectively, 75%, 100%, 100%, 80%, and 87.5%. The degree of arterial oxygenation showed no correlation with the occurrence of a positive echocardiographic study. Arterial hypoxemia (PaO_2 < 70 mm Hg) was observed in 9 (15.9%) of the 76 patients. The echocardiographic study was positive in 37 (55.2%) of the 67 nonhypoxemic patients and in 4 (44.4%) of the 9 hypoxemic ones.

Conclusion

Contrast echocardiography proved to be effective, easy, and safe to use in candidates for liver transplantation. Transthoracic echocardiography may be used in the diagnostic routine of intrapulmonary vascular dilations, the transesophageal study being reserved for inconclusive cases with clinical suspicion.

Key words

contrast echocardiography, intrapulmonary vascular dilations, liver transplantation

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The association of liver disease and pulmonary vascular dilations has been emphasized by several authors for years, allowing for greater knowledge of the pathophysiological aspects of the arterial hypoxemia found in some patients with the chronic liver disease called hepatopulmonary syndrome. This clinical condition is characterized by the triad of liver dysfunction, intrapulmonary vascular dilation, and hypoxemia[1-11]. Pulmonary capillary vasodilation is an extrahepatic complication of severe liver disease, probably due to the vasoactive mediation of nitric oxide[2,7,11-13], causing the occurrence of an intrapulmonary right-to-left shunt with a consequent alteration in alveolar-capillary diffusion and pulmonary ventilation/perfusion imbalance[1,9,11,14,15]. In advanced stages of liver disease, both arterial vasodilation and true pulmonary arteriovenous communications may be present[1,15]. The patients may have normal arterial blood gas analysis or arterial hypoxemia in 9-29% of the cases, which may be severe and associated with cyanosis and dyspnea[1,3,7,16,17]. Hemodynamic conditions with elevated cardiac output, low systemic and pulmonary vascular resistances, and a reduction in the mixed arterial and venous oxygen content may also be present[1,5-7,10-12,18].

Contrast echocardiography, lung perfusion scan with technetium99-labeled macroaggregated albumin, and pulmonary angiography are some of the diagnostic methods used for identifying intrapulmonary vascular alterations in patients with chronic liver disease. Contrast echocardiography is considered the gold standard for the diagnosis of this condition with numerous advantages as compared with other methods, allowing the detection of intrapulmonary shunts in patients with normal angiographic study or arterial blood gas analysis, or both. Recent studies have emphasized the diagnostic superiority of contrast transesophageal echocardiography in the research for pulmonary vascular alterations in this group of patients[3,6,12,16-19-26].

The objective of this study was to compare the results of contrast echocardiography in the transthoracic and transesophageal modalities, in addition to determining its importance in the diagnosis of intrapulmonary vascular dilations in candidates for liver transplantation.

Methods

Contrast echocardiography was consecutively performed in 76 patients with severe and advanced liver diseases, who had been included in the protocol for liver transplantation. Patients diagnosed

with chronic pulmonary diseases, heart failure, and congenital heart diseases with intracardiac communications were excluded from the study. The study was conducted after an individual explanation about the objectives of the investigation was provided and informed written consent was obtained. The research protocol was evaluated and approved by the Committee on Ethics in Research of the institution.

The patients' mean age was 44 ± 14.6 years, 59 (77.6%) were males and 18 (22.4%) were females. Of the 76 patients with advanced liver disease, 72 had been diagnosed with liver cirrhosis and 4 with liver fibrosis. Of the patients with hepatic cell damage, 12 had alcoholic cirrhosis, 9 had hepatitis B, 16 had hepatitis C, 3 had hepatitis B and C, 15 had mixed cirrhosis (hepatitis B or C, or both, associated with alcohol), 9 had cryptogenic cirrhosis, 2 had autoimmune cirrhosis, 3 had biliary cirrhosis (primary biliary obstruction), 1 had hemochromatosis, 1 had nonalcoholic steatohepatitis, and 1 had Wilson's disease. Of the patients with intrahepatic or extrahepatic fibrosis, 1 had schistosomiasis, 1 had paracoccidiodomycosis, and 2 had veno-occlusive diseases (1 thrombosis of the portal vein and 1 Budd-Chiari syndrome).

For obtaining 2-dimensional images, an ATL device (Advanced Technology Laboratories Inc., Bothel, WA, USA) was used according to previously established techniques and sections, with the patient in the left lateral decubitus position [27]. Contrast transthoracic echocardiography was performed in an HDI 5000 device with an electronic broadband phased-array transducer with a frequency of 2 to 4 MHz. Second harmonic imaging was used in all examinations to reduce imaging artifacts and to increase contrast resolution. Contrast transesophageal echocardiography was performed in a CX 200 Apogee device with the introduction of a multiplanar esophageal probe of 5.0 MHz at a depth of approximately 30 cm from the superior dental arch after local anesthesia of the pharynx. The use of 4-chamber echocardiographic view allowed for the simultaneous visualization of the atria and, when possible, of the left and right superior pulmonary veins[28,29].

The following measurements were taken: diameter of the left atrium, diastolic and systolic dimensions of the left ventricle, the left ventricular ejection fraction using cubed diameters, and systolic pressure of the right ventricle estimated based on tricuspid regurgitation using the modified equation of Bernoulli[28,30-33].

The echocardiographic study was developed following the methods reported by Krowka et al[11] and Aller et al[3]. The microbubbles were manually produced by transferring 10 to 15 times 10 mL of saline solution from 1 syringe to another connected in a 3-way device, and, then, rapidly administered in a peripheral venous route. The study was considered positive when the abnormal presence of contrast was detected in left cardiac chambers with a delay of 4 to 6 cardiac cycles, after initial opacification of the right cardiac chambers (fig. 1). Three injections were usually performed to determine the reproducibility. The results were recorded in videocassette tapes and analyzed by 2 observers. The subsequent injections were initiated only after complete removal of the microbubbles from the right and left cavities. According to the opacification of the left atrium, a semiquantitative analysis of the microbubbles was performed according to the criteria established by Aller et al[3]. The simultaneous comparison of the maximum intensity of the echocardiographic images produced by the microbubbles between the right and left cardiac cavities provided

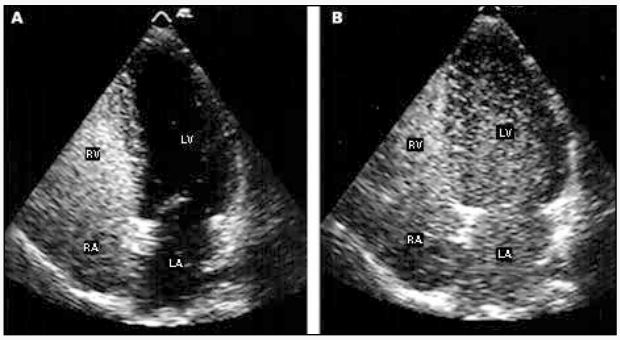

Fig. 1 - Transthoracic 2-dimensional echocardiogram, apical 4-chamber view: A) presence of contrast in the right chambers; B) presence of contrast in the left chambers after 6 cardiac cycles, compatible with intrapulmonary vascular dilations.

the following classification: degree 1 - absence of microbubbles; degree 2 - passage of a few isolated microbubbles; degree 3 - passage of numerous isolated microbubbles; degree 4 - passage of numerous microbubbles resulting in an increase in echogenicity; degree 5 - opacification of the left atrium, but to a lesser extent as compared with that of the right atrium; degree 6 - complete opacification of the left atrium similar to that of the right atrium. Degrees 1 and 2 were considered normal or the absence of pulmonary vasodilations; degree 3 was considered to represent mild pulmonary vasodilations; and finally, degrees 4 to 6 were considered significant or important pulmonary vasodilations.

The arterial oxygen partial pressure (PaO_2) was determined in samples of arterial blood collected from the radial artery under normal conditions, as close as possible to the day of echocardiographic study (1-3 days). A PaO_2 value lower than 70 mm Hg was considered an indication of arterial hypoxemia.

The continuous quantitative variables were analyzed with the aid of the Student *t* test, and Tukey correction was used when necessary. The frequencies were compared using the chi-square test or Fisher exact test. An alpha level of 5% was admitted, and P values ≤ 0.05 were considered significant.

Results

All diagnostic procedures were well tolerated, and transesophageal echocardiography was performed with no complications. The use of transthoracic and transesophageal contrast echocardiography showed the presence of pulmonary vascular dilations in 53.9% (41/76) of the patients. In the transthoracic study in isolation, prevalence of intrapulmonary vascular dilations was observed in 48.7% (37/76) of the cases. Of the 32 patients consecutively undergoing transesophageal study, 16 (50%) had a positive contrast echocardiography (P = 1.0; Fisher exact test). Four patients with an initially inconclusive transthoracic study underwent transesophageal echocardiography and were considered positive. Hepatopulmonary syndrome was observed in only 4 (5.3%) patients. According to the criteria established by Aller et al[3], 16 (21%) patients had mild pulmonary vasodilations, 25 (33%) patients had significant pulmonary vasodilations, and 35 (46%) had normal echocardiograms. Transthoracic echocardiography had a sensitivity of 75%, specificity of 100%, positive predictive value of 100%, negative predictive value of 80%, and accuracy of 87.5% for the

diagnosis of intrapulmonary vascular dilations as compared with transesophageal echocardiography, which is considered the gold standard.

Analyzing the etiology of liver disease, 28 (46.7%) of the 60 patients with cirrhosis due to hepatic cell destruction, 8 (88.9%) of the 9 patients with cryptogenic cirrhosis, 3 with biliary cirrhosis, and 2 with cirrhosis due to veno-occlusive diseases had a positive echocardiogram. Comparing the results of the patients with cryptogenic cirrhosis and pulmonary vascular dilations with those of patients with cirrhosis due to all the other etiologies, by using the chi-square test, no significant statistical difference was found between the groups (P = 0.059). However, comparing cryptogenic cirrhosis in isolation with those with hepatic cell destruction, the difference was statistically significant (P = 0.044).

The variables of blood gas analysis and of Doppler echocardiography are shown in table I. Arterial hypoxemia was present in 9 (15.9%) of 76 patients, but only 4 (44.4%) had evidence of pulmonary vascular dilations. Of the 67 patients with no arterial hypoxemia, 37 (55.2%) had a positive echocardiogram.

Discussion

The pulmonary vascular changes found in patients with chronic liver disease are disseminated vasodilations with diameters ranging from 15 to 150 µm, which are more prominent at the capillary level and close to gas exchange areas. The deviation of pulmonary blood flow to the dilated capillaries avoids the functioning alveolar units, impairing the pulmonary diffusion-perfusion relation with a consequent decrease in arterial oxygen saturation[1,5,7,9-11].

The intrapulmonary vascular abnormalities are not routinely detected because of their uncommon presentation in the general population and because of their unespecific appearance on routine examinations[34]. Studies[1,3,4,7,11,16,17,35,36] with contrast echocardiography in patients with severe liver cirrhosis have revealed the existence of intrapulmonary vascular dilations in 13 to 47% of the patients, even in normal angiographic studies. In our study, the identification of pulmonary vascular dilations using contrast echocardiography was possible in 41 of 76 patients studied, ie, 53.9% of the cases, a result similar to those in the literature.

Studies by Vedrinne et al[24] and Aller et al[3] showed the superiority of contrast transesophageal echocardiography for diagnosing intrapulmonary vascular dilations in candidates for liver transplantation[3,24,25]. Transesophageal echocardiography, considered the gold standard for diagnosing intrapulmonary vascular dilations, allowed demonstration of the presence of that condition in 50% (16/32) of our cases. In 4 patients with previously inconclusive transthoracic study, due to an inadequate acoustic window, intrapulmonary vascular dilations could only be demonstrated after using transesophageal echocardiography. In our study, the use of second harmonic imaging in transthoracic echocardiography significantly contributed to the obtainment of satisfactory results similar to those in the transesophageal study. Comparing the proportion of individuals with pulmonary vascular dilations diagnosed on transthoracic and transesophageal echocardiography using the Fisher test, no statistical difference was found (P=1), showing that the efficacy of the 2 diagnostic methods is equivalent. The comparison of the results of contrast transthoracic and transesophageal echocardiography consecutively performed in 32 patients showed the following results: sensitivity, 75%; specificity, 100%; positive predictive value, 100%; negative predictive value, 80%; and accuracy, 87.5%. This validates contrast transthoracic echocardiography with second harmonic imaging as a rapid, safe, noninvasive, reliable, and inexpensive diagnostic test for studying these patients.

Hepatopulmonary syndrome, usually reported in 9 to 29% of liver failure cases[1,3,7,16,17], was found in 4 (5.3%) of our patients. In the present study, the degree of arterial oxygenation had no statistical correlation with the occurrence of a positive echocardiography. These findings are similar to those of Krowka et al[18], who also did not report a correlation between pulmonary vascular abnormalities and blood gases in patients with a positive echocardiogram (13.2% of the cases) as compared with those with a normal echocardiogram. Mimidis et al[4] also found normal arterial blood gas analysis in 56 cirrhotic individuals, 8 (14.3%) of whom had a positive contrast echocardiogram. Vedrinne et al[24], however, found hypoxemia in 56% and 33% of the patients with intrapulmonary shunts diagnosed on transesophageal and transthoracic echocardiography, respectively. In regard to the mean PaO_2 values found in this study, they were similar in the different degrees of opacification of the left cardiac cavities (P= 0.859), despite the results by Hopkins et al[36], which were significantly lower in individuals with greater opacification of the left cavities (P < 0.01). Based on our results, one may state that occasional abnormalities in arterial oxygenation of patients with chronic liver disease should not be considered indicators of intrapulmonary shunts, and, in isolation, they do not indicate that condition.

In the face of a probable hyperdynamic circulatory condition existing in individuals with intrapulmonary vascular shunts, which could cause alterations in the diameter and volume of the left

Table I - Variables of blood gas analysis and Doppler echocardiography

	Negative echocardiogram (degree 1+2)	Positive echocardiogram (degree 3+4+5+6)	P Value
Mean PaO_2 (mm Hg)	93.2 ± 17.8	92.4 ± 20.3	0.859
PaO_2 < 70 mm Hg	5/35 patients	4/41 patients	0.724
RVSP > 30 mm Hg	12/35 patients	16/41 patients	0.850
Mean diameter of the LA (mm)	38.9 ± 5.4	37.2 ± 4.4	0.135
Mean diameter of the LV (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 - arterial oxygen partial pressure; RVSP - right ventricular systolic pressure; LA - left atrium; LV - left ventricle; LAD - left atrial diameter; LVDD - left ventricular diastolic diameter; mm - millimeters; mm Hg - millimeters of mercury; P - statistical significance level

cavities or in pulmonary vascular bed pressure, the present study did not find any correlation between these variables and the diagnosis of intrapulmonary vascular dilations on contrast echocardiography. In regard to the findings of the etiology of liver disease, although interesting, there is no pathophysiological support for the statement that pulmonary vascular disorders are more frequent in certain groups of patients with chronic liver disease.

Briefly, contrast transthoracic echocardiography with microbubbles using second harmonic imaging should be recommended for routine assessment and follow-up of patients with severe liver disease, candidates for liver transplantation, for identifying intrapulmonary vascular dilations or diagnosing hepatopulmonary syndrome. The inconclusive cases with a strong clinical suspicion should undergo transesophageal study. The clinical significance of these findings in the prognosis of patients with terminal liver disease awaits further studies.

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