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Original Article

Contrast Enhanced Echocardiography for Detection of Intrapulmonary Shunts in Liver Transplant Candidates

M. Zamirian, A. Aslani

Abstract

Background: Intrapulmonary vascular abnormalities associated with liver cirrhosis may result in intrapulmonary right-to-left shunt and hypoxemia. The aim of this study was to use contrast enhanced echocardiography to detect intrapulmonary vascular abnormalities in patients with liver cirrhosis candidates for liver transplantation.

Methods: One hundred and two adult patients underwent contrast enhanced echocardiography to determine the prevalence of intrapulmonary right-to-left shunt and its relationship to the severity of hepatic disease, arterial oxygenation, and spider angioma.

Results: The rate of patients with positive and negative contrast enhanced echocardiography was 44% and 56%, respectively. There was no significant difference in age, sex, or etiology of liver cirrhosis in patients with and without intrapulmonary shunt. Patients with intrapulmonary right-to-left shunt had more severe hepatic disease compared with those without shunt (Child-Pugh score 12±2 vs 8±2). There was significant difference in the partial arterial oxygen pressure (PaO_2) values in patients with grade 3^+ to 4^+ left ventricular opacification by microbubbles compared with those without evidence of intrapulmonary right-to-left shunt (64±6 vs 82±10 mmHg). Twenty eight of the patients with intrapulmonary right-to-left shunt had cutaneous spider angioma.

Conclusion: The findings suggest that there was a significant relation between severity of liver cirrhosis and presence of intrapulmonary right-to-left shunt or severity of hypoxemia. The data also indicate that cirrhotic patients with cutaneous spider angioma most likely have the shunt.
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Keywords ● Cirrhosis ● liver transplantation ● echocardiography

Department of Internal Medicine,
Division of Cardiology,
Medical School,
Shiraz University of Medical Sciences,
Shiraz, Iran.

Correspondence:
Mahmood Zamirian MD,
Department of Cardiology,
Medical School,
Shiraz University of Medical Sciences,
Shiraz, Iran.
Tel/Fax: +98 711 6261089
Email: drzamirian@yahoo.com

Introduction

Intrapulmonary vascular abnormalities resulting in right-to-left shunt have been described in patients with liver cirrhosis. Such abnormalities are considered to be extrahepatic complications of advanced hepatic diseases.[1] The abnormalities include precapillary as well as capillary dilatations, which result in arterio-venous communications. Bypassing gas exchange unit can lead to hypoxemia and hepatopulmonary syndrome.[1,2] The prevalence of such intrapulmonary

right-to-left shunt and its relation to the severity of hepatic diseases, arterial oxygenation, and spider angioma has not been studied among Iranian patients. Therefore, this study was aimed at examining such relationships by enrolling 102 patients with liver cirrhosis who were candidates for liver transplantation.

Patients and Methods

The study was approved by local institutional ethics committee. The objectives and protocol of the study were explained to the participants and informed consents were obtained. From June 2005 to January 2006, 102 adult (>18 years old) patients (59 women and 43 men, mean age 49±10 years) with liver cirrhosis who were candidates for liver transplantation were included. Patients were excluded if they did not consent to participate in the study or did have intracardiac shunt.

A complete history including clinical information about the causes of liver cirrhosis was obtained. Physical examination was done and special attention was paid to detect spider angioma. Child-Pugh classification was used to grade the severity of liver cirrhosis. Moreover, laboratory tests including blood gases were reviewed. Then, the patients underwent transthoracic contrast enhanced echocardiography (General Electric, Vingmed, Vivd 3, Norway) using a peripheral intravenous line and two 10-ml syringes connected to 3-way stopcocks for the injection of agitated saline. A positive contrast echocardiogram indicative of intrapulmonary right-to-left shunt was defined as the delayed appearance of microbubbles in the left side of the heart at 3 to 6 beats after the initial appearance of contrast in the right atrium. The appearance of such microbubbles in the left side of the heart during the first or second cardiac cycle or after provocative maneuvers, such as cough or Valsalva, indicates intracardiac shunt.[3] The relative opacification of the left ventricle in patients with positive contrast enhanced echocardiography was assessed semiquantitively on a scale of 1^+ to 4^+. Evidence of minimal left ventricular microbubbles, moderate microbubbles, extensive microbubbles without outlining the endocardium, and extensive microbubbles with clear endocardial definition were scored as1^+, 2^+, 3^+, and 4^+, respectively.[3] The patients were then divided into two groups of negative and positive for contrast echocardiography, and statistical comparisons were made.

Statistical Analysis

Data were compared using the Student's *t*, Chi-square, or Fisher exact tests. A P-value ≤0.05 was considered statistically significant.

Results

Two patients with positive contrast echocardiography who showed an immediate appearance of microbubbles in the left side of the heart, which was indicative of intracardiac shunt because of patent foramen ovale, were excluded from the study. Forty four of the remaining patients (44%) had positive contrast echocardiography with delayed appearance of microbubbles in the left side of the heart.

There was no difference in the age or sex of participants in the two groups (table 1). Moreover, there was no significant difference in the etiology of liver cirrhosis in the two groups (table 2). Also, there was no significant difference in partial arterial oxygen pressure (PaO_2) values in those with 1^+ to 2^+ opacification of left ventricle by microbubbles compared with those without evidence of intrapulmonary right-to-left shunt (figure 1). However, the mean PaO_2 values in patients with 3^+ to 4^+ opacification were significantly lower than those in patients without the shunt (figure 1).

Table 1: Clinical data of patients with positive (n=44) and negative (n=56) contrast echocardiography.

	Negative contrast echocardiography	Positive contrast echocardiography
Age (years)	48 ± 11	50 ± 10
Male-female	27-29	20-24
Spider angioma	1	28
Hypoxemia*	8	14
Child–Pugh score	8 ± 2	12 ± 2

PaO_2< 70 mmHg in room air

Table 2: The frequencies of etiologies of liver cirrhosis in patients with positive (n=44) and negative (n=56) contrast echocardiography.

	Negative contrast echocardiography	Positive contrast echocardiography
Hepatitis B	15	10
Hepatitis C	13	7
Autoimmune	9	7
Primary biliary cirrhosis	6	5
Primary sclerosing cholangitis	3	4
Wilson disease	2	3
Cryptogenic and Alcoholic	7	7
Budd Chiari syndrome	1	1

The Child–Pugh score was significantly higher in patients with positive contrast echocardiography compared with those with negative test (table 1). There was a significant relation

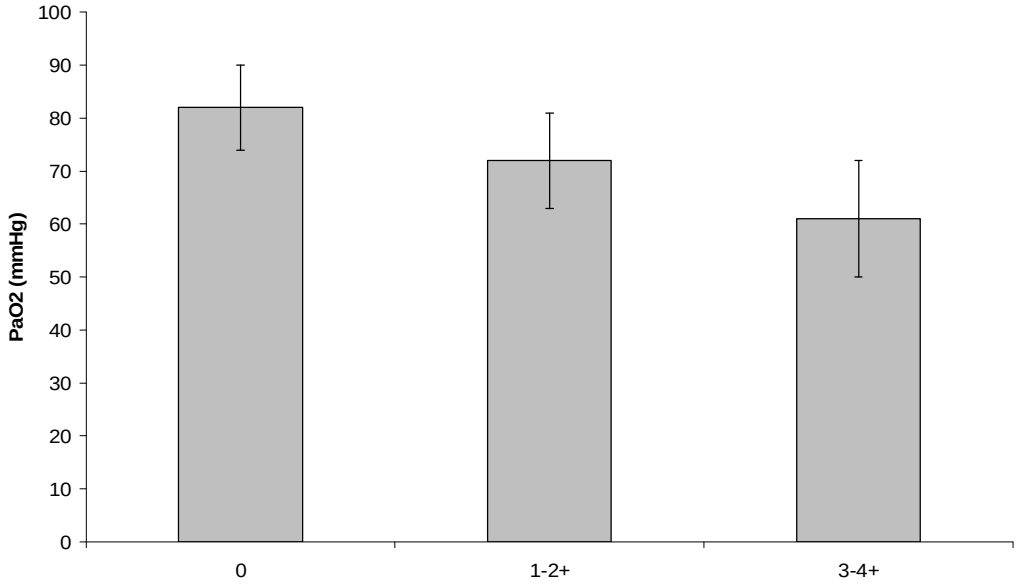

Figure 1: The mean±SD partial arterial oxygen pressure (PaO_2) values in patients with negative contrast echocardiography (n=56; PaO_2 = 82 ± 8 mmHg) and patients with positive contrast echocardiography with grade of opacification of left ventricle by microbubbles of 1^+ to 2^+ (n=30; PaO_2 = 71 ± 9 mmHg) and 3^+ to 4^+ (n=14; PaO_2 = 60.7 ± 11 mmHg).

between the presence of spider angioma and intrapulmonary right-to-left shunt. Of the 29 patients with spider angioma, 28 had a positive contrast echocardiography. Also 30 out of the 44 (68%) patients with positive contrast echocardiography had a PaO2 ≤ 70 mmHg.

Discussion

Intravenous injection of agitated saline results in the appearance of microbubbles in the right heart during echocardiography. Under normal circumstances these microbubbles are filtered in the pulmonary capillary bed and do not appear in the left heart.[4] The presence of either intracardiac or intrapulmonary right-to-left shunt results in the appearance of microbubbles in the left heart.[5]

The findings of the present study suggest that the prevalence of positive contrast echocardiography was 44%. This value is in the range of values (13 to 47%) reported in previous studies.[2,3,6] In one patient with severe (grade 4^+) intrapulmonary right-to-left shunt, pulmonary angiography revealed no evidence of large arterio-venous fistula demonstrating that intrapulmonary shunting in advanced hepatic disease might be due to microscopic arteriovenous connections.

The findings that positive contrast enhanced echocardiography could occur in normo-oxemic cirrhotic patients might suggest that subclincial pulmonary shunt can be present without development of overt hypoxemia. Similar to the findings of Hopkins and colleagues,[3] we found a significant relationship between the extent of intrapulmonary right-to-left shunt and arterial oxygenation. However, in contrast to their findings, we found a relation between the extent of intrapulmonary right-to-left shunt and the severity of liver cirrhosis. The more advanced the liver cirrhosis, the more severe the intrapulmonary right-to-left shunt.

This study also showed a significant relation between the presence of spider angioma and intrapulmonary right-to-left shunt. This suggests that the presence of spider angioma might be indicative of the existence of intrapulmonary right-to-left shunt. Right-to-left shunt due to intrapulmonary vascular abnormality was also described in patients with hereditary hemorrhagic telangiectasia.[7,8]

Of the 44 patients with positive contrast echocardiography 16 had no spider angioma. This might be taken as evidence that the development of intrapulmonary right-to-left shunt in the course of liver cirrhosis precedes the development of cutaneous spider angioma.

Pulmonary angiography, which is an invasive method, is usually used for the detection of intrapulmonary right-to-left shunt. However, contrast enhanced echocardiography seems to be a valuable tool for detection of such a shunt and estimation of its severity in patients with liver cirrhosis.

The existence of hepatopulmonary syndrome has evolved from an absolute or relative contraindication to an indication for liver transplantation.[1,9-11] The exact mechanism of pulmonary vascular changes in patients with advanced liver cirrhosis is not known. However, it has been proposed that intrapulmonary vascular dilatation induced by circulating vasodilators released by the damaged liver,[12,13] or the failure of the damaged liver to clear circulating vasodilators, or inhibition of circulating vasoconstrictors might play a role.

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