



Comparison of Doppler Echocardiographic Findings in Patients with Chronic Liver Disease with and without Intrapulmonary Shunt

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Authors' contributions

All authors contributed to the study design and drafting of the article and approved the final version.

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ABSTRACT

Aims: Doppler echocardiography is the gold standard for the diagnosis of intrapulmonary shunt (IPS) and screening for portopulmonary hypertension in chronic liver disease (CLD). Echocardiography has become fundamental to the diagnosis of cirrhotic cardiomyopathy in the last decade. The purpose of this article was to compare echocardiographic changes in patients with CLD, with and without IPS.

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Methodology: A total of 168 patients with CLD and portal hypertension underwent transthoracic contrast echocardiography and were allocated to two groups: Group 1 – 72 (42.9%) patients with IPS; and Group 2 – 96 (57.1 %) patients without IPS (control group). Echocardiographic variables and the presence/absence of IPS were evaluated in bilateral tests, with the level of statistical significance established at 5% ($p < 0.05$).

Results: A higher prevalence of moderate diastolic dysfunction was found in patients with IPS (24 vs. 16 patients; $p = 0.034$). Patients with grade II IPS had a greater frequency of moderate diastolic dysfunction than those with grade I (16 vs. 8 patients; $p = 0.028$). No statistically significant differences between groups were found in left atrial volume (58 vs. 55 ml; $p = 0.181$) or the occurrence of pulmonary arterial hypertension (25 vs. 33 patients; $p = 0.963$).

Conclusion: In the present study, IPS and grade II IPS were associated with moderate diastolic dysfunction determined by contrast-enhanced transthoracic Doppler echocardiography. Moderate diastolic dysfunction appeared to be a predictive factor for the onset of intrapulmonary shunt.

Keywords: Doppler echocardiography; cirrhotic cardiomyopathy; hepatopulmonary syndrome; portal hypertension; schistosomiasis.

1. INTRODUCTION

The incidence and prevalence of chronic liver disease (CLD) are high throughout the world [1]. The main causes of CLD are chronic excessive alcohol intake and viral hepatitis [1]. Additionally, in Brazil, schistosomiasis is also an important etiology of CLD [2]. Doppler echocardiographic findings in patients with CLD have been studied since 1977 [3]. However, the association between liver disease and the cardiovascular system has been described for more than 50 years [4]. The relationship between CLD and the cardiovascular system is defined as cirrhotic cardiomyopathy [4,5]. The impairment of the respiratory system by CLD is defined as hepatopulmonary syndrome, the reports of which through angiographic and histopathologic studies date back to 1884 [6]. However, contrast-enhanced echocardiographic findings suggesting the occurrence of intrapulmonary shunt (IPS) in patients with CLD were first described by Hind and Wong in 1981 [7].

The deterioration of liver function is marked by an increase in nitric oxide and other inflammatory mediators, which have been implicated in splanchnic vasodilation and the reduction in arterial compliance, thereby contributing to the physiopathology of cirrhotic cardiomyopathy and hepatopulmonary syndrome [4,5]. Zardi et al. [4] and Moller et al. [5] define cirrhotic cardiomyopathy as a chronic heart disorder in patients with hepatic cirrhosis and/or portal hypertension characterized by an abrupt reduction in the cardiac contractile response to physical, pathological or pharmacological stress, but with normal cardiac output at rest. In turn, hepatopulmonary syndrome is characterized by

CLD, alveolar-arterial oxygen tension difference ≥ 15 mm Hg or partial oxygen pressure ≤ 80 mmHg and the occurrence of IPS [8–11]. Indeed, the prevalence of IPS among patients with CLD ranges from 15 to 82% [6,12,13].

Most papers evaluating hepatopulmonary syndrome, cirrhotic cardiomyopathy and portopulmonary hypertension using Doppler echocardiography have involved candidates for liver transplants [6,13–15], whereas few investigations have reported echocardiographic findings in patients with portal hypertension secondary to schistosomiasis either alone or associated with viral hepatitis or excessive alcohol intake [12,14,16]. Thus, a more accurate echocardiographic evaluation of such patients is needed.

The aim of the present study was to compare echocardiographic findings in patients with CLD with and without IPS.

2. MATERIALS AND METHODS

2.1 Study Population

A transversal study was carried out involving 168 patients from the Hepatology outpatient clinic of the Federal University of Pernambuco hospital. Patients with CLD and portal hypertension (hepatitis B virus, hepatitis C virus, alcoholic cirrhosis and/or schistosomiasis) were selected consecutively according to demand between June 2010 and December 2012. The patients underwent contrast-enhanced transthoracic echocardiography and were allocated to two groups: Group 1 – 72 patients with IPS; and Group 2 – 96 patients without IPS (control

group). Both groups were from the same geographic region and had similar clinical and socioeconomic characteristics. Individuals with severe cardiopulmonary disease were excluded. This study received approval from the human research ethics committee of the university and each patient signed a statement of informed consent agreeing to participate.

2.2 Doppler Echocardiographic Measures and Contrast-enhanced Echocardiography

The patients were initially submitted to conventional Doppler echocardiography following the guidelines of the American Society of Echocardiography [17], complemented with a contrast study. These procedures were carried out at the Echocardiography Laboratory at the university hospital using an echocardiograph (Philips Medical Systems®, HDI 1500, Eindhoven, Netherlands). The contrast was sterile saline solution 0.9%. The peripheral vein of the right upper limb was assessed with a 20-gauge needle connected to a set of three-way device adapted to two syringes, each one containing 10 mL of saline solution. Microbubbles were produced manually through the agitation of the solution between the two syringes 10 times, immediately followed by injection. The apical four chamber view was obtained with the patient in left lateral decubitus. The images configured in the second harmonic were obtained simultaneously with the introduction of the saline solution after the filling of the right atrium with contrast. The exam was considered indicative of IPS when the left atrium was contrasted between the 4th and 6th cycles following the filling of the right atrium with contrast in the absence of intracardiac shunt [9]. This procedure was repeated twice for each patient, with care taken to await the clearance of the contrast from the heart chambers before the second injection.

The exams were stored on an optical disc and saved in JPEG format. IPS grading was performed using a semi-quantitative method [9]. Two specialists performed independent analyses of the images. In cases of divergence, the images were evaluated by a third examiner.

2.3 Statistical Analysis

Qualitative variables were expressed as absolute (n) and relative (%) frequencies. Quantitative variables were expressed as mean, median, standard deviation, minimum and maximum values. When appropriate, either Pearson's chi-

square test or Fisher's exact test was used for the comparison of the groups with and without IPS with regard to the qualitative variables. For quantitative variables with normal distribution, the Student's t-test was used to compare means between groups. For quantitative variables with non-normal distribution, the non-parametric Mann-Whitney test was used to compare groups. The level of statistical significance was set to 5% ($p < 0.05$). All statistical calculations were performed with the aid of the Statistical Package for the Social Sciences (SPSS for Windows version 18.0).

3. RESULTS

3.1 General Characteristics of Patients (Table 1)

A total of 168 patients were analyzed – 96 (57.1%) without IPS and 72 (42.9%) with IPS. Mean age was 56 ± 11.7 years (range: 19 to 89 years). The male gender accounted for 57.7% of the sample. The most common etiology of CLD was schistosomiasis ($n = 88$; 52%), schistosomiasis with cirrhosis ($n = 61$; 36%) and hepatic cirrhosis ($n = 19$; 12%). The frequency of arterial hypertension was greater among the patients without IPS.

3.2 Doppler Echocardiographic Findings in Patients with and without IPS (Table 2)

All patients exhibited normal segmental contractility and normal systolic function of the left ventricle (LV). A high frequency of increased left atrial volume (LAV) was found in the majority of patients in both groups, in absolute values and when corrected for body surface, with no statistically significant difference between groups. The systolic arterial pulmonary pressure ≥ 35 mmHg estimated by Doppler Echocardiography was found in 25 patients (35%) with IPS and 33 patients (34%) without IPS, with no statistically significant difference between groups. A greater prevalence of moderate diastolic dysfunction was found in the patients with IPS in comparison to those without IPS.

3.3 Doppler Echocardiographic Findings in Patients with IPS (Table 3)

Thirty-three patients (46%) exhibited grade I IPS and 39 (54%) exhibited grade II. There were no

cases of grades III or IV. The patients with grade I had greater LV mass than those with grade II. A significantly smaller E' wave was found among the patients with grade II IPS in comparison to those with grade I. Patients with grade II IPS had a greater frequency of moderate diastolic dysfunction than those with grade I.

No complications related to the procedures occurred in the sample.

4. DISCUSSION

4.1 General Characteristics of Patients

In the present study, the frequency of arterial hypertension was greater among patients without IPS, which is in agreement with data described in the literature [10]. The male gender predominated among the cases of IPS, which is

Table 1. Clinical characteristics of patients with and without IPS

Variables	IPS (n=72)	Non-IPS (n=96)	p*
Age (years)	53.9±13.4	57.5±9.9	0.067
Minimum-maximum	19-89	29-75	
Male gender (%)	42 (58.3%)	55 (57.3%)	0.892
Arterial hypertension (%)	18 (25.0%)	38 (39.6%)	0.047*
Diabetes (%)	11 (15.3%)	20 (20.8%)	0.358
Smoking			
Actual (%)	4 (5.6%)	11 (11.5%)	0.184
Former (%)	25 (34.7%)	31 (32.3%)	0.741
Systolic blood pressure (mmHg)	120.4±15.9	125.3±18.1	0.069
Diastolic blood pressure (mmHg)	73.2±9.0	77.4±9.6	0.004*
Heart rate (bpm)	68.4±12.6	67.5±10.9	0.609
Body surface (m ²)	1.7±0.2	1.7±0.2	0.925
Oxygen saturation [‡] (%)	93.9±1.4	95.4±2.7	0.212

Data expressed as mean ± standard deviation, except when indicated; * statistically significant difference ($p < 0.05$); [‡] measured by digital oximeter with the patient in the sitting at rest

Table 2. Echocardiographic findings and diastolic function in patients with and without IPS

Variables	IPS (n = 72)	Non-IPS (n = 96)	p*
DDLV (mm)	47.28±4.36	47.48±6.19	0.805
SDLV (mm)	27.75±3.85	27.17±4.64	0.375
LVEF (%)	71.44±7.20	73.20±7.17	0.121
LV mass (indexed by BS)	101.42±20.78	102.16±29.21	0.847
LAd (mm)	37.17±4.80	37.33±4.43	0.818
LAV (ml)	58.56±13.86	55.66±13.83	0.181
LAV (ml/m ²)	34.36±6.53	32.92±7.63	0.201
MV E/A ratio	1.19±0.36	1.13±0.38	0.324
E/Em (lateral)	6.07±2.01	6.06±2.01	0.974
SPAP (mmHg)	25.39±10.85	25.34±9.28	0.977
SPAP (35-50) mmHg	25 (34.4%)	33 (34.7%)	0.963
Diastolic function			
Normal	27 (37.5%)	40 (41.7%)	0.699
Mild dysfunction	21 (29.2%)	40 (41.7%)	0.132
Moderate dysfunction	24 (33.3%)	16 (16.7%)	0.020*

A, filling velocity after atrial contraction; LA, left atrium; LAd, diameter of LA; DDLV, diastolic diameter of LV; DSLV, systolic diameter of LV; E, velocity of initial atrial filling; Em, tissue Doppler velocity of lateral mitral annulus; LVEF, LV ejection fraction; SPAP: systolic pulmonary artery pressure; BS: body surface; LAV, left atrial volume; LV, left ventricle; MV, mitral valve.

Data expressed as mean ± standard deviation, except when indicated; * statistically significant difference ($p < 0.05$)

Table 3. Echocardiographic variables and diastolic function in patients with grade I and grade II IPS

Variables	Grade I IPS (n = 33)	Grade II IPS (n = 39)	p*
LV mass (g)	180.97±47.88	159.18±39.75	0.040*
Em lateral (cm/s)	0.17±0.07	0.14±0.06	0.009*
Diastolic function	19 (48.7%)	8 (24.2%)	
Normal	12 (30.8%)	9 (27.3%)	0.058
Mild dysfunction	8 (20.5%)	16 (48.5%)	0.948
Moderate dysfunction			0.024*
Body surface (m ²)	1.75 (0.19)	1.62 (0.11)	0.001*

Data expressed as mean ± standard deviation, except when indicated; * statistically significant difference (p < 0.05)

in agreement with the majority of studies [8,10]. Schistosomiasis was the most common etiology of CLD, which was likely due to the fact that the study was carried out in an endemic region for this disease [2,12].



Fig. 1. Contrast-enhanced transthoracic echocardiogram of 56-year-old male patient with schistosomiasis revealing grade 0 IPS

4.2 Doppler Echocardiographic Findings in Patients with and without IPS

No reduction in systolic function of the LV was found in the overall sample, which is in

agreement with data described in a study by Nazar et al. [18]. However, divergences are found in the literature regarding this aspect [10]. In the present study, a high frequency of increased LAV (both absolute and corrected for body surface) was found in both groups with and without IPS. Indeed, this is a common finding among patients with CLD [4,5,8]. Therefore, one cannot affirm that an increase in LAV in patients with CLD should be considered an isolated indicator of IPS, as suggested in a previous study [8].



Fig. 2. Contrast-enhanced transthoracic echocardiogram of 55-year-old male patient with mixed CLD revealing grade I IPS



Fig. 3. Contrast-enhanced transthoracic echocardiogram of 57-year-old male patient with schistosomiasis associated with alcoholic cirrhosis revealing grade II IPS

No statistically significant difference was found between groups regarding systolic pulmonary artery pressure calculated through tricuspid regurgitation. A number of authors describe Doppler echocardiography as an accurate screening method for the detection of severe pulmonary arterial hypertension, which is one of the contraindications for liver transplant [19]. Other authors state that the evaluation of tricuspid regurgitation can be hindered by portopulmonary hypertension [16]. Poliwczak et al. [15] found higher pulmonary arterial hypertension in patients with cirrhosis in comparison to a control group.

Moderate diastolic dysfunction was the main abnormality with a significant association to the presence of IPS, which has rarely been suggested in the literature [20]. It is believed that a greater prevalence rate of diastolic dysfunction is due to hypertrophy, subendocardial edema and changes in the collagen structure stemming from myocardial fibrosis [4,5,15,21]. Diastolic dysfunction seems to be more prevalent among patients with greater liver impairment [4,22].

4.3 Doppler Echocardiographic Findings in Patients with IPS

In the literature, the prevalence of IPS among individuals with CLD, as diagnosed through contrast-enhanced transthoracic echocardiogram, ranges from 15 to 82% [6,12,23] and was within this range in the present sample. The lack of patients with grade III and IV IPS, together with pulse oximetry readings within normal limits, characterized the present sample as having lesser liver disease severity [10,24-26].

The patients with grade II IPS had a lower mean LV mass (LVM) than those with grade I IPS. This finding could be assigned by chance, since, in contrast to that demonstrated in this study, it was already reported correlation between greater liver impairment and greater LVM as well as its association with the most advanced degree of IPS [23]. On the other hand, the use of beta-blockers, which is common in patients with portal hypertension may reduce LVM, although to a lesser degree than other classes of antihypertensive drugs [27]. This might help to explain the lower mean LVM in grade II IPS.

Diastolic dysfunction evaluated through echocardiography is part of the diagnostic criteria of cirrhotic cardiomyopathy [4,5]. In the present sample, the greater frequency of moderate diastolic dysfunction in patients with more severe IPS suggests greater myocardial damage and/or a worsening of the hepatic disease. However, this finding has not been duly clarified in the literature.

4.5 Limitations

The present study has limitations that should be addressed. It was a cross sectional study. It did not include the role of anti-hypertensive and hypoglycemic medications in the cardiovascular findings. Due to the miscegenation of the Brazilian population, the ethnicity of the patients was not analyzed. As most patients had a low income status, the findings may not be valid for other socioeconomic classes. The grading of the IPS was performed by a semi-quantitative method through a visual quantification.

5. CONCLUSIONS

Contrast transthoracic echocardiogram is a safe, noninvasive, effective method that should be recommended in the routine evaluation and

follow up of patients with CLD and portal hypertension for the screening of IPS, cirrhotic cardiomyopathy and portopulmonary hypertension, as the diagnosis of these complications generally only occurs in patients on the waiting list for a liver transplant.

IPS and grade II IPS were associated with moderate diastolic dysfunction, as determined by the quantitative methods employed herein. Further studies are needed to determine the clinical significance of these findings in the prognosis of patients in the early stages of CLD.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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