Prediction of intrapulmonary right to left shunt with left atrial size in patients with liver cirrhosis

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Background We screened a large number of liver transplant candidates with contrast echocardiography to detect intrapulmonary right to left shunt (IPS). We found that IPS is frequently present in patients with left atrial enlargement. This finding raises a question concerning the correlation between IPS and left atrial size in patients with liver cirrhosis.

Objectives The aim of this prospective study was to evaluate the possible correlation between left atrial size and IPS in patients with liver cirrhosis.

Methods Adult patients (>18 years old) with documented liver cirrhosis underwent trans-thoracic contrast echocardiography with agitated saline. Left atrial dimension was measured by M-mode echocardiography. Stroke volume was calculated using left ventricular M-mode echocardiography. Patients with atrial fibrillation, intracardiac shunt, congenital heart defects, valvular heart disease and diastolic dysfunction were excluded.

Results A total of 92 patients met all study criteria. Of these, 39 (42.3%) had IPS. Cardiac output was significantly greater in patients with IPS compared with those without IPS (5.68 ± 0.83 L/min vs 4.75 ± 0.76 L/min, P < 0.01). In a multi-variable model, after adjustment for body surface area and body mass index, left atrial enlargement was the strong predictor of IPS (area under the curve = 0.66) but when controlling for cardiac output, left atrial size was not an independent predictor of IPS.

Conclusion In the context of liver cirrhosis, patients with IPS have greater cardiac output compared with those without shunt. Left atrial enlargement, which reflects one aspect of increased cardiac output, is an indirect marker of IPS and greater left atrial dimension is associated with the presence of intrapulmonary right-to-left shunt.

KEYWORDS Cirrhosis; Echocardiography; Left atrium; Shunt

Introduction Intrapulmonary arterio-venous malformation is known to occur in patients with chronic liver disease.1-3 These vascular abnormalities are pre-capillary and capillary dilatations that result in arterio-venous communications, bypassing gas exchange unit, and can lead to hypoxemia and hepatopulmonary syndrome.4,5 Hepato-pulmonary syndrome is a rare complication of chronic liver disease characterized by arterial hypoxemia due to intrapulmonary right to left shunting (IPS).4 Previous studies have found that trans-thoracic contrast echocardiography with agitated saline is useful to detect such IPS.6-12

In our liver transplant center, we screened a large number of liver transplant candidates with contrast echocardiography to detect IPS. During the screening period, we found that IPS is frequently present in patients with left atrial enlargement. This finding raises a question concerning the correlation between IPS and left atrial size in patients with liver cirrhosis. The aim of this prospective study was to evaluate the possible correlation between left atrial size and IPS in patients with liver cirrhosis.

Materials and methods

Study population

From June 2005 to February 2006, all adult patients (>18 years old) with documented liver cirrhosis who were referred for liver transplantation were invited to participate in this study and were asked to provide informed written consent. Clinical data including age, gender, height, weight, heart rate and cardiac rhythm were recorded.

Echocardiographic study

Participating patients underwent trans-thoracic contrast enhanced echocardiography by the use of a peripheral intravenous line and...
two 10 ml syringes connected by a 3-way for injection of intravenous agitated saline. IPS was defined as the delayed appearance of micro-bubbles in the left atrium (3 or more beats after the initial appearance of contrast in the right atrium) (Figure 1). Appearance of micro-bubbles in the left atrium during the first or second beat or only after provocative maneuvers (cough or valsalva) is indicative of intracardiac shunt.

Echocardiographic measurement

Left atrial dimension (LAD) was measured by 2D-guided M-mode echocardiography obtained in the parasternal view according to American Society of Echocardiography recommendations. Body size variables used for indexing of LAD included body surface area (BSA) (m²) and body mass index (BMI) (kg/m²). Other echocardiographic variables included M-mode left ventricular dimensions at end-systole and end-diastole. Diastolic function, one of the major determinants of left atrial size, was evaluated by pulsed-wave Doppler examination of mitral and pulmonary venous inflow in each subject. Diastolic dysfunction was categorized as: impaired relaxation (grade I), pseudonormalized filling (grade II), and restrictive filling (grade III–IV), as previously described and validated. Cardiac output, another important determinant of left atrial size, was calculated by the accepted formula (C.O.слив = stroke volume x heart rate). Assessment of stroke volume was done by M-mode left ventricular dimensions at end-systole and end-diastole as previously described.

Exclusion criteria

Patients for any of the following reasons were excluded from the study: (1) refusal or inability to provide informed consent; (2) atrial fibrillation; (3) intracardiac shunt; (4) congenital heart defects; (5) valvular heart disease; and (6) diastolic dysfunction.

Statistical analysis

Continuous variables are presented as means ± 1 standard deviation. Categorical variables are displayed as percentages (%). Differences between groups were evaluated with t tests for continuous variables or chi-square analyses for categorical variables, as appropriate. Ranges of cardiac output, LAD, LAD/BSA and LAD/BMI were calculated in two subgroups of patients (those with IPS and those without IPS) using 5th, 50th and 95th percentile. Left atrial enlargement was summarized by using the odds ratio with corresponding 95% confidence intervals (CIs). To assess the strength of left atrial size for the prediction of IPS, receiver-operator curve was generated. The area under the curve was adjusted for BSA, BMI and cardiac output. A value of P < 0.01 was defined as statistically significant.

Results

Baseline characteristics

A total of 92 patients (mean age 58 ± 6.1 years, 51% women) met all study criteria and consented to participate. Of these, 39 (42.3%) had IPS. Characteristics of the study population are outlined in Table 1. Patients were divided into two groups: those with IPS and those without IPS. Some parameters were significantly different between two groups but not the other. Left atrial dimension was significantly greater in patients with IPS compared with those without IPS (4.58 ± 0.54 cm vs 3.87 ± 0.63 cm, P < 0.01). Patients with IPS had significantly greater cardiac output compared with those without IPS (5.62 ± 0.83 L/min vs 4.75 ± 0.76 L/min, P < 0.01) (Table 1).

Ranges of LA dimension in liver transplant candidates

Body size variables used for indexing of LAD included BSA and BMI. By application of 5th, 50th and 95th percentile, ranges of LAD, LAD/BSA and LAD/BMI were calculated. In each percentile, LAD, with and without indexing, is greater in patients with IPS compared with those without IPS (Table 2). Left atrial enlargement was defined as LAD, LAD/BSA or LAD/BMI > 95th percentile of the negative IPS subgroup. Therefore, according to Table 2, left atrial enlargement is defined as LAD > 4.2 cm, LAD/BSA > 2.3 cm/m² or LAD/BMI > 0.172 cm/kg/m². If left atrial enlargement is defined as LAD > 4.2 cm, the prevalence of left atrial enlargement was greater in patients with IPS (23 vs 5%; Odds ratio = 4.6; 95% CI: 3.8–5.7). If left atrial enlargement is defined as LAD/BSA > 2.3 cm/m², the prevalence of left atrial enlargement was also greater in patients with IPS (21 vs 5%; Odds ratio = 4.2; 95% CI: 3.1–5.5). The same scenario was repeated for LAD/BMI as 19% of patients with IPS and 5% of those without IPS have LAD/BMI > 0.172 (Odds ratio = 3.8; 95% CI: 3–5.1).

Ranges of cardiac output in liver transplant candidates

By application of 5th, 50th and 95th percentile, ranges of cardiac output was calculated in two subgroups of patients with liver cirrhosis. In each percentile, cardiac output is greater in patients with IPS compared with those without IPS (Table 3).

Figure 1 Contrast-enhanced echocardiographic finding of intrapulmonary right to left shunt in a patient with liver cirrhosis. (A) One beat after the initial appearance of contrast in the right atrium. There is no contrast in the left atrium. (B) Three beats later; severe left ventricular opacification is seen.
Relationship between left atrial size and IPS

Receiver-operator curve was generated in a multi-variable model to assess the strength of left atrial size for the prediction of IPS. After adjustment for BSA and BMI, left atrial enlargement was the strong predictor of IPS (area under the curve $\approx 0.66$, 95% CI: 0.64–0.69) but when controlling for cardiac output, left atrial size was not an independent predictor of IPS.

Discussion

In the present study, left atrial enlargement, as assessed by M-mode echocardiography, was found to be a simple and feasible parameter to detect IPS in patient with liver cirrhosis. On the other hand we found that cardiac output is significantly greater in patients with IPS compared with those without IPS. It must be kept in mind that although left atrial enlargement is correlated to IPS, but when controlling for cardiac output, it is not an independent marker of IPS. In fact, we found that patients with IPS have greater cardiac output compared with those without IPS, whereas left atrial enlargement which reflects only one aspect of increased cardiac output is an independent marker of IPS. What is the mechanism(s) responsible for increased cardiac output in patients with IPS? It is known that patients with liver cirrhosis may have increased cardiac output.16 Systemic vascular dilatation is the main mechanism for increased cardiac output in these patients.16,17 Several mechanisms have been postulated as causes for such vascular dilatation.17 Recent studies have emphasized the role of nitric oxide in the vasodilatation of liver cirrhosis.17 Intrapulmonary vascular dilatations are extra-hepatic complications of chronic liver disease that can result in intrapulmonary right-to-left shunt.1–3 The same mechanism, mentioned above for systemic vasodilatation, is responsible for development of intrapulmonary vascular dilatation in liver cirrhosis.4 Therefore, in the presence of systemic vasodilatation, one would expect simultaneous intrapulmonary vascular dilatation. Hemodynamic manifestation of the systemic vasodilatation is increased cardiac output whereas echocardiographic manifestation of intrapulmonary vascular dilatation is IPS. Therefore, with amalgamation of the above data, one would expect IPS in a cirrhotic patient with increased cardiac output. This scenario is supported by our echocardiographic study which demonstrated that cardiac output is significantly greater in patients with IPS compared with those without IPS. It must be emphasized that the main finding of this study is that in the context of liver cirrhosis cardiac output is significantly greater in patients with IPS compared with those without IPS. It must be emphasized that the main finding of this study is that in the context of liver cirrhosis cardiac output is significantly greater in patients with IPS compared with those without IPS. The relationship between left atrial enlargement, which reflects only one aspect of the increased cardiac output, and IPS is the most important finding of the present study and, as noted earlier, left atrial enlargement can be used as a simple and feasible parameter for detection of IPS. To the best of our knowledge, association of the cardiac output with IPS in patients with liver cirrhosis has not been reported previously.

Conclusion

It is concluded that, in the context of liver cirrhosis, patients with intrapulmonary right to left shunt have greater cardiac output compared with those without shunt. Left atrial enlargement, which reflects only one aspect of increased cardiac output, is an indirect marker of IPS and greater left atrial

| Table 1 | Characteristics of the liver transplant candidates, positive IPS subgroup, and negative IPS subgroup |
|--------------------------|----------------------------------|--------------------------|
| Variables                 | Total population ($n = 92$)        | With IPS ($n = 39$)        | Without IPS ($n = 53$)        | P-value |
|                          | Mean   | SD    | Mean   | SD    | Mean   | SD    |
| Age, years               | 58     | 6.1   | 56     | 6.3   | 59     | 6.2   | NS    |
| Women, %                 | 51     | –     | 50     | –     | 52     | –     | NS    |
| BSA, m$^2$               | 1.32   | 0.21  | 1.33   | 0.22  | 1.24   | 0.23  | NS    |
| BMI, kg/m$^2$            | 21.64  | 3.16  | 21.94  | 3.11  | 21.23  | 3.17  | NS    |
| LAD, cm                  | 4.18   | 0.41  | 4.58   | 0.54  | 4.37   | 0.63  | $<0.01$ |
| C.O, L/min               | 5.27   | 0.67  | 5.68   | 0.83  | 4.75   | 0.76  | $<0.01$ |

IPS, intrapulmonary right to left shunt; SD, standard deviation; BSA, body surface area; BMI, body mass index; LAD, left atrial dimension; C.O, cardiac output.

| Table 2 | Ranges for left atrial dimension, with and without indexing, in liver transplant candidates |
|--------------------------|----------------------------------|----------------------------------|
| Measurement              | IPS                              | Percentile                       |
|                          | 5%     | 50%    | 95%    |
| LAD, cm                  | Positive | 3.00  | 3.90   | 4.70   |
| LAD, cm                  | Negative | 2.81  | 3.49   | 4.20   |
| LAD/BSA, cm/m$^2$        | Positive | 1.57  | 2.00   | 2.63   |
| LAD/BSA, cm/m$^2$        | Negative | 1.49  | 1.87   | 2.30   |
| LAD/BMI, cm/kg/m$^2$     | Positive | 0.102 | 0.134  | 0.178  |
| LAD/BMI, cm/kg/m$^2$     | Negative | 0.100 | 0.131  | 0.172  |

IPS, intrapulmonary right to left shunt; LAD, left atrial dimension; BSA, body surface area; BMI, body mass index.

| Table 3 | Ranges for cardiac output in liver transplant candidates |
|--------------------------|----------------------------------|----------------------------------|
| Measurement              | IPS                              | Percentile                       |
|                          | 5%     | 50%    | 95%    |
| Cardiac output, L/min    | Positive | 5.11  | 5.43   | 6.12   |
| Cardiac output, L/min    | Negative | 4.33  | 4.84   | 5.26   |

IPS, intrapulmonary right to left shunt.
dimension is associated with the presence of intrapulmonary right to left shunt.

References