Novel predictors of intrapulmonary vascular dilatations in cirrhosis : extending the role of pulse oximetry and echocardiography

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Abstract

Background and study aims : **Intrapulmonary vascular dilatations (IPVDs) are a criterion for the diagnosis of hepatopulmonary syndrome in patients with liver cirrhosis. We aimed to show that IPVDs are more common than suspected in a heterogenous cirrhotic population and to identify new diagnostic parameters.**

Patients and methods : **Forty-three consecutive patients with cirrhosis admitted to our Gastroenterology department were included in this prospective study. History, physical examination, ECG and, when warranted, pulmonary function tests and chest radiograph were used to exclude patients with significant cardiac or pulmonary disease. Contrast enhanced transthoracic echocardiography (CEE) was used to determine the presence of IPVDs. Pulse oximetry readings were taken in the supine and standing positions.**

Results : **We found 12 patients with IPVDs. Statistical analysis proved the correlation between IPVDs and systolic pulmonary artery pressure (sPAP) (p = .049), right ventricle wall width (RVW) (p = .013) and E/A ratio (p = .034) but not left atrial or ventricular diameter. Orthodeoxia was also present more frequently in patients with positive CEE. The difference between supine and standing oxygen saturation (ΔSat) proved a fair diagnostic test for detecting IPVDs, with an area under the receiver operated curve (AUROC) of 0.823.**

Conclusions : **Our study shows that RVW, sPAP, E/A and orthodeoxia determined by pulse oximetry are valuable novel predictors of IPVDs, encouraging the routine use of pulse oximetry and echocardiography in cirrhotic patients.** (Acta gastroenterol. belg., **2013**, 76, **241-245**).

Key words : pulse oximetry, contrast enhanced echocardiography, cirrhosis, hepatopulmonary syndrome, cirrhotic cardiomyopathy.

Introduction

Intrapulmonary vascular dilatations, a necessary criterion for diagnosing HPS, have generally been studied in patients awaiting liver transplant (1,2). However, IPVDs have also been found in cirrhotics without any oxygenation abnormalities (3) thus prompting the use of the term subclinical HPS (4,5), the significance of which is yet unknown. Some recent studies (6) have suggested the use of increased cardiac output indicators such as left atrium or ventricular volume in screening for HPS. These findings seem to indicate a link between cardiac function in cirrhosis and the development of IPVDs. Lately, attention has also been given to the better understanding of cirrhotic cardiomyopathy (CCM), but so far there have been no attempts at discovering if CCM could have any connection to IPVDs and HPS.

Defined by electrocardiographic anomalies and diastolic insufficiency unmasked during strenuous effort, CCM (7,8) was long believed to be an extension of the deleterious effect of alcohol on heart tissue. New insight into the role of diastolic dysfunction (9) in cirrhosis has led to the need for a deeper understanding of interrelations between liver, heart and pulmonary vessels dysfunction in cirrhosis.

The pathogenetic basis of IPVDs, like that of many complications of liver cirrhosis, is not well established, although the existence of common molecular mechanisms at the root of these alterations is conceivable. Nitric oxide production increase in liver cirrhosis seems one of the more likely options as it might be a common trait linking complications such as HPS and CCM (10,11,12,13). This potential link between less understood complications of cirrhosis prompted our search for further echocardiographic evidence.

Studying a heterogeneous population and not just liver transplant candidates allowed for a broader view of the prevalence and impact of IPVDs in the clinical setting. The fact that our study focused on IPVDs rather than HPS circumvented current difficulties in HPS definitions and was meant to better serve the evaluation of possible links between cardiac dysfunction and pulmonary vascular alterations in cirrhosis.

Methods

We enrolled 54 consecutive patients with cirrhosis diagnosed using clinical, ultrasonic and biochemical findings in a prospective observational study. The Child-Pugh score was used to assess the stage of cirrhosis. Thorough history was collected and physical examination and ECG were performed on all patients. Clinical judgement was used in ordering lung function tests and chest radiographs in patients with suspected comorbidities that would cause exclusion from the study. 11 patients were excluded (6 refused CEE, 1 had a history of recurrent pulmonary thrombembolism and pulmonary hypertension, 1 had silicosis, severely altered chest radiograph and lung function tests, 1 had severe aortic stenosis and mitral valve prolapse, 1 had severe mitral stenosis and 1 had patent foramen ovale).

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In order to detect IPVDs CEE on an Aloka ProSound Alpha 7 was performed in all 43 patients by injecting 9 mL of agitated saline mixed with 1 mL of air. The same operator performed all examinations. Delayed appearance (more than 3 heart cycles after opacification of the right atrium) of microbubbles in the left heart was considered indicative of IPVDs. In the absence of right-left intra or extra-cardiac communication microbubbles (> 10 μm in diameter) are visible in the right heart but never in the left atrium due to the absorption of the air during passage through the normally narrow pulmonary capillaries. A difference of less than 3 cardiac cycles between right and left atrium opacification was considered diagnostic of septum defect and represented an exclusion criterion. Diameters of the cardiac chambers, RVW, cardiac valve insufficiency, interventricular septum width, mitral valve E/A ratio (MV E/A) with Valsalva maneuver (to differentiate normal from pseudonormal pattern), tricuspid annular plane systolic excursion (TAPSE), left ventricular ejection fraction (LVEF) and sPAP were assessed by ultrasonography. E/A ratio could not be determined in two subjects due to atrial fibrillation. Oxygen saturation in the supine and standing positions were determined 5 minutes apart by using an Aespire pulse oximeter.

Statistical analysis was performed using SPSS 16.0 and the usual criteria of statistical significance were employed ($p < .05$, means and standard deviations were provided, Mann Whitney U was performed for nonparametric variables). The study complied with the principles of the declaration of Helsinki and was approved by the Hospital Ethics Committee ; informed consent was obtained from all patients.

Results

Of the 43 patients included 18 were women and 25 men. The mean age was 57 years (SD = 10.7 years). In this group the prevalent cause of cirrhosis was ethanol (18 patients-41.9%) followed by HCV (12 patients-27.9%), and mixed etiology due to both ethanol and viral infection : HBV or HCV (11 patients-25.6%). One subject had cirrhosis due solely to HBV and one had liver disease of unknown etiology. According to Child class severity the study population was evenly distributed : 12 patients had a Child A severity class, 16 were Child B and 15 were Child C.

CEE revealed IPVDs in 12/43 (27.9%) patients. The presence of IPVDs did not seem to be influenced by Child class ($p = .429$) or age.

The means and standard deviations for the cardiac structure and functional parameters of the entire study population are presented in table 1.

Left ventricle ejection fraction showed normal systolic function in all subjects (mean 61.23 %, SD = 3.73%). The E and A fractions of ventricular filling did not independently correlate with IPVDs, but higher E/A ratio was associated with right-left shunting (mean E/A = 1.34 in those with and E/A = 0.94 in those without IPVDs ; $p = .034$, Mann Whitney U). Patients with IPVDs also had increased sPAP (mean 29.08 vs. 26.35 mmHg, $p = .049$) and a thicker right ventricle wall (7.77 vs. 6.59 mm $p = .013$) compared to those with negative findings on CEE. However, right ventricle diameter did not vary significantly between the two groups. We also did not find TAPSE, left ventricle end-diastolic diameter (LV), interventricular septum width (IVS) to be statistically different in patients with and without IPVDs (Table 2).

The mean saturation determined by pulse oximetry was similar in supine position (S_1) in patients with or without positive CEE (97 % versus 97.33%). While lower orthostatic saturation (S_2) showed an interesting trend approaching statistical significance (93.25 % in IPVDs+ versus 97.55% in IPVDs- ; $p = .052$), oxygen saturation in standing position was not shown to vary according to the presence of right-left shunting (Table 3).

Orthodeoxia was significantly associated with the presence of IPVDs (mean $\Delta Sat = 4.08$ in patients with shunting versus -0.55 in those without ; $p < 0.001$, Mann Whitney U). The difference between supine and standing saturation (ΔSat) proved to be a fairly good diagnostic test for the detection of IPVDs, with a calculated AUROC of 0.823 (CI 95% 0.675-0.970) (Fig. 1). A cut-off value

Table 1. — **Measured echocardiography indices in all patients with mean, lowest and highest registered values and respective standard deviations. (RV-right ventricle diameter, RA-right atrium diameter, LV-left ventricle diameter, LA-left atrium diameter, RVW-right ventricle wall thickness, IVS- interventricular septum, TAPSE-tricuspid annular plane systolic excursion, sPAP-systolic pulmonary arterial pressure, LVEF- left ventricle ejection fraction)**

	Minimum	Maximum	Mean	Standard deviation
RV (mm)	23	40	31.65	3.57
RA (mm)	22	56	38.39	5.21
LV (mm)	28	57	47.76	5.63
LA (mm)	30	54	40.70	5.50
RVW (mm)	5	10	6.92	1.19
IVS (mm)	8.5	15	11.80	1.50
E/A	.5	2.25	1.04	.42
TAPSE	18	36	25.57	3.80
sPAP (mmHg)	17	44	27.11	5.52
LVEF (%)	50	70	61.23	3.73

Table 2. — **Echocardiography indices (mean and standard deviation) in patients with and without IPVDs. No significant differences were documented between cirrhotic patients with and without intrapulmonary vascular dilatations regarding left and right heart chamber diameters, left ventricle ejection fraction, interventricular septum width or tricuspid annular plane systolic excursion. Thicker right ventricular wall, higher sPAP and E/A fraction values correlated well with the presence of IPVDs in cirrhotic patients**

	Patients without IPVDs	Patients with IPVDs	P value
LV	47.64 mm (SD = 5.53)	48.08 mm (SD = 6.12)	NS
LA	40.82 mm (SD = 5.47)	40.41 mm (SD = 5.80)	NS
RV	31.12 mm (SD = 3.55)	33 mm (SD = 3.38)	NS
RA	37.64 mm (SD = 5.43)	40.33 mm (SD = 4.20)	NS
RVW	6.59 mm (SD = 0.88)	7.77 mm (SD = 1.48)	**0.013**
sPAP	26.35 mmHg (SD = 5.84)	29.08 mmHg (SD = 4.16)	**0.049**
E/A	0.94 (SD = 0.34)	1.31 (SD = 0.51)	**0.034**
LVEF	61.32 % (SD = 3.6)	61 % (SD = 4.22)	NS
IVS	11.8 mm (SD = 1.7)	11.81 mm (SD = 1.31)	NS
TAPSE	26.03 mm (SD = 3.29)	24.5 mm (SD = 4.7)	NS

Table 3. — **Mean saturations and standard deviations of pulse oximetry measurement of oxygen saturation in patients with and without IPVDs (S_1-oxygen saturation in the supine position, S_2-oxygen saturation on standing, ΔSat-difference between the supine and upright saturation levels). While oxygen saturation in the supine position is not significantly different between the two groups, saturation on standing reveals a statistically significant trend and the difference between the supine and upright saturation levels correlates extremely well with the presence of IPVDs in cirrhotic patients**

	IPVDs absent	IPVDs present	P value
S_1	97% (SD = 2.32)	97.33% (SD = 2.83)	NS
S_2	97.55% (SD = 1.99)	93.25 (SD = 7.92)	**0.052**
ΔSat = S_1-S_2	-0.55 % (SD = 1.98)	4.08% (SD = 5.26)	**< 0.001**

of 1 had a specificity of 83.8% and a sensitivity of 66.7% for detecting IPVDs, while a cut-off value of 2 had a specificity of 94% but a sensitivity of only 60%.

20 patients complained of dyspnea, 3 of whom reported platypnea. Dyspnea was more frequent in patients with IPVDs (p = .046) and was not influenced by the presence of ascites, while all subjects with platypnea showed a positive CEE. There was no significant correlation between severity class and low oxygen saturation or presence of IPVDs.

Discussion

The presence of IPVDs was determined in 27.9% of the patients in our study and was not influenced by sex, age, Child severity class or etiology. This is significant because it demonstrates a high prevalence rate in the general cirrhotic population and encourages active detection of these patients.

There is a lot of controversy (14) regarding the significance of IPVDs in cirrhosis. It has been shown that IPVDs are not necessarily reflected through hypoxic disturbances and that positive CEE cannot by itself diagnose HPS. There are some articles (15) that suggest the use of the term subclinical HPS as adequate in the case of IPVDs not associated with oxygenation defects in HPS. Classically, HPS (16) requires the fulfillment of 3 criteria : extra cardiac right-left shunting, oxygenation defect and portal hypertension but so far diagnostic guidelines have not been universally approved despite the convincing and seemingly conclusive effort of the TASK force (17).

While the oxygenation defect associated with IPVDs is best assessed by alveolar-arterial gradient we have used pulse oximetry because it is easier to reproduce, non-invasive, acceptable to the patient and a proven substitute for arterial blood gas analysis in this case (18). Pulse oximetry has been shown to be an extremely valuable screening tool highly predictive for HPS (19,20,21). The decrease in oxygen saturation (SpO_2) on changing from a supine to a standing position is a simple and efficient way of detecting possible pulmonary arterial blood oxygenation deficits in the cirrhotic patient.

Our study confirms that pulse oximetry is valuable in screening for IPVDs. Calculating the difference between supine and standing SpO_2 has demonstrated high speci-

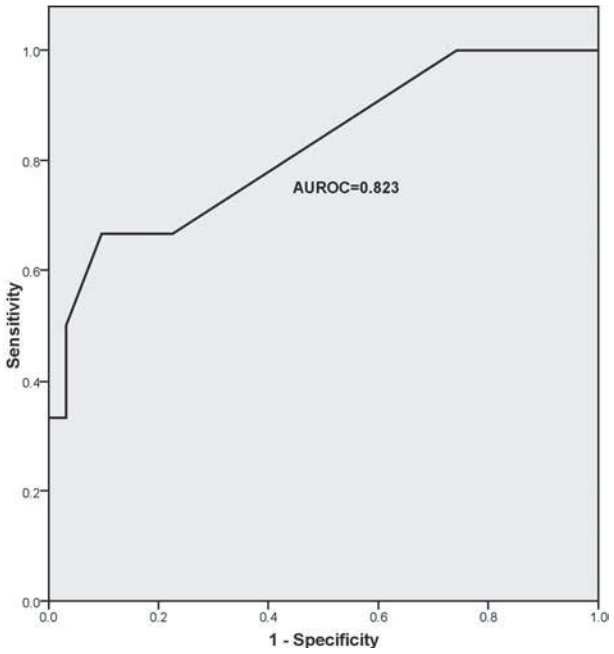

Fig. 1. — ROC curve, sensitivity and specificity of the difference between supine and standing oxygen saturation determined by pulse oximetry in the detection of IPDVs in cirrhotic patients. The difference between saturations is a fairly good predictor for the detection of IPVDs, with a calculated AUROC of 0.823 (CI 95% 0.675-0.970).

ficity and fair sensitivity for different cut off points, as well as an AUROC of 0.823. Patients with IPVDs had similar oxygen saturation in the supine position to those without IPVDs, but on standing their SpO_2 decreased by a mean of 4% to a mean of 93%.

To our knowledge this is the first study to demonstrate the use of calculating the difference between supine and standing SpO_2 in the detection of IPVDs. Moreover, we have found that among patients with orthodeoxia only 3 complained of platypnea while none of the patients without IPVDs had platypnea. This is in accordance with previous observations that consider platypnea as a specific but not very sensitive symptom of HPS.

We have decided to look into novel as well as established echocardiographic parameters in order to detect effects of the hyperdinamic circulation in the cirrhotic heart.

Left atrial volume (LAV) has been shown to correlate with HPS (22,23) in cirrhosis and a recent study proposes left ventricle enlargement and mitral valve insufficiency as markers of HPS (6). While LA size is definitely an indicator of diastolic burden (24) we have not found LA diameter to be related to the existence of IPVDs. This could be explained by the fact that the LA is an asymmetrical cavity and its dimension is sometimes erroneously estimated by measuring only one diameter.

We have found a single study (25) that shows alteration in the function and dimensions of the right ventricle and atrium in patients with HPS. Our results do not concord with those of Karabulut et al. and this may be due to our broader inclusion criteria (we studied all IPVDs and not only those associated with hypoxemia and we chose not to exclude patients with left ventricle dysfunction).

Despite arguments about its accuracy (26), assessment of pulmonary artery pressure by echocardiography has been shown to be a good estimation (27) of actual pressure as determined by right heart catheterization. This is important in the context of the severely ill cirrhotic patient who is not an optimal candidate for invasive investigations. We have found that slightly higher ultrasonographically determined sPAP correlates with right-left shunting. Higher sPAP in patients with IPVDs could reflect the recruitment and dilatation of pulmonary small vessels due to diastolic dysfunction of the left ventricle in these patients. A possible confounding factor in this setting is portopulmonary hypertension, a condition increasingly diagnosed in cirrhosis, which is suspected when the echocardiographic estimated value of sPAP is over 50 mmHg and considered unlikely when the respective value is below 36 mmHg (28,29). None of our patients had an sPAP of over 50 mmHg which is the lower limit for likeliness of portopulmonary hypertension, only 3 had sPAP values of 36 mmHg or above and while one of those also presented IPVDs he did not have any other signs, clinical or echocardiographic, to support this diagnosis.

As noted above there was no correlation between left cardiac chambers diameters and IPVDs although a higher MV E/A ratio seems to be indicative of the presence of right-left shunting. E/A alteration is thought to be an early sign of CCM (30) and it has been hypothesized that diastolic dysfunction precedes and sometimes evolves into systolic dysfunction in cirrhosis.

A more comprehensive study of the diastolic function in the cirrhotic heart is compulsory for validation, but our findings could provide a connection between pulmonary vascular anomalies and cardiac dysfunction. Since in our study patients with IPVDs were also found to have slightly higher sPAP and increased RVW it can be argued that in this case there is an increased haemodynamic burden on the right heart eliciting an adaptative structural and functional response. While E/A ratio is not the preferred test for diastolic dysfunction it is still considered to have good accuracy (31) and our finding of higher E/A ratio in patients with compared to those without IPVDs could reflect advanced diastolic dysfunction in the pseudonormalization phase. Whether any of these suppositions is valid must be further investigated but, whatever the answer, it seems that diastolic dysfunction of the left ventricle and IPVDs are more intimately connected than previously thought (32).

Improvements can be made to our protocol and more accurate parameters such as E/E', pulmonary vein signals, and strain imaging or LAV can be used in order to better estimate the consequences of left ventricular diastolic dysfunction. Also, ABG analysis and stress testing in all patients seem to be the next logical step as they are

necessary in the diagnosis of HPS and CCM respectively. Nonetheless our findings are valuable insofar as they support an intriguing new outlook on the connections between complications of liver cirrhosis.

Our study shows a high prevalence of IPVDs in a heterogenous population thus prompting the need to increase awareness of this condition among doctors treating patients with cirrhosis. Pulse oximetry and echocardiography proved to be tests of choice in the initial workup and the novel predictors proposed could help in an easier and more complete characterization of IPVDs and HPS.

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