

Screening of Hepatopulmonary Syndrome (HPS) with CEUS and Pulse-Oximetry in Liver Cirrhosis Patients Eligible for Liver Transplant

A.I. Suceveanu¹, L. Mazilu¹, D. Tomescu², N. Ciufu¹, I.R. Parepa¹, A.P. Suceveanu¹

¹Clinical Emergency Hospital, Ovidius University of Constanța, Romania

²Department of Anaesthesia and Intensive Care, Fundeni Clinical Institute, Bucharest, Romania

“Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

“Nicolae Testemițanu” University of Medicine and Pharmacy, Moldova

Rezumat

Screening-ul sindromului hepatopulmonar (HPS) prin CEUS și puls-oximetrie la pacienții cu ciroză hepatică eligibili pentru transplant hepatic

Scop: Prevalența sindromului hepatopulmonar (HPS), complicație severă a cirozei hepatice (CH), variază între 4% și 47% și alterează rezultatele singurei variante terapeutice curative, transplantul hepatic (OLT). În studiul prezent ne-am propus să stabilim existența unei corelații între modificările cardiace și pulmonare, decelate cu ajutorul ecografiei cardiace cu substanță de contrast (CEUS) și a puls-oximetriei, astfel încât să oferim o variantă de diagnostic precoce a HPS și în consecință să optimizăm momentul în care pacienții beneficiază maximal de OLT.

Metodă: Au fost considerați cu risc de HPS toți pacienții care au prezentat la examinarea CEUS o creștere întârziată a contrastului la nivelul ventriculului stâng, la cel puțin 3 bătăi sistolice, după apariția contrastului în ventriculul drept. Am corelat rezultatele CEUS cu cele ale puls-oximetriei, considerând ca diagnostic pozitiv de HPS, asocierea modificărilor CEUS cu cele ale puls-oximetriei ($\text{SaO}_2 < 95\%$).

Rezultate: Din cei 186 de pacienți diagnosticați cu CH, 56 de pacienți (30,10%) au prezentat o creștere întârziată a contrastului la nivelul ventriculului stâng. Puls-oximetria a înregistrat $\text{SaO}_2 < 95\%$ și $\text{PaO}_2 < 70$ mmHg la 62 de pacienți (33,33%).

Indicele Pearson a semnalat o bună corelație între modificările cardiace și pulmonare diagnosticate de CEUS, respectiv puls-oximetrie ($r=0,99$), în diagnosticul HPS.

Concluzii: Două metode non-invazive, simple și rapide, CEUS și puls-oximetria, pot diagnostica cu ușurință HPS, o complicație fatală a CH, și pot ghida recomandările de tratament, alegând momentul optim în care pacienții să beneficieze maximal de terapia chirurgicală.

Cuvinte cheie: sindrom hepatopulmonar, CEUS, puls-oximetrie, transplant hepatic

Abstract

Background and aim: The prevalence of hepatopulmonary syndrome (HPS) in the setting of cirrhosis ranges between 4%-47%. We aimed to detect a correlation between heart and lungs findings on contrast-enhanced ultrasound (CEUS) and pulse-oximetry, in order to early detect HPS and thus to improve patients referral to orthotopic liver transplantation (OLT).

Methods: We considered at risk for HPS all patients with delayed left ventricle (LV) enhancement of the contrast agent, at least 3 systolic beats after it appears in the right ventricle (RV). We correlated CEUS results with pulse-oximetry findings, considering to have a positive HPS diagnosis in all patients with both CEUS findings and $\text{SaO}_2 < 95\%$.

Results: From 186 patients diagnosed with liver cirrhosis, 56 patients (30.10%) had delayed LV enhancement of the contrast agent. Pulse-oximetry showed alterations, such as $\text{SaO}_2 < 95\%$ and $\text{PaO}_2 < 70$ mmHg in 62 patients (33.33%). Pearson index showed a good correlation between lung and heart CEUS findings and pulse-oximetry ($r=0.99$) in HPS diagnosis.

Corresponding author:

Andra Suceveanu, MD
Department of Gastroenterology
Clinical Emergency Hospital of Constanta
Romania, Tomis Blvd. no. 145, 900591
E-mail: andrasuceveanu@yahoo.com

Conclusions. Two non-invasive, simple and rapid methods such as CEUS and pulse-oximetry can easily diagnose HPS, a highly fatal complication of liver cirrhosis, and can also guide the future treatment by speeding up OLT recommendations.

Key words. hepatopulmonary syndrome, CEUS, pulse-oximetry, liver transplant

Introduction

Respiratory signs and symptoms are common in patients with liver cirrhosis, no matter the stage of the disease. Intrapulmonary vascular complications of liver cirrhosis have two distinct etiologies and consist of hepatopulmonary syndrome (HPS) and portopulmonary hypertension. HPS appears when intrapulmonary blood shunting impairs arterial gas exchange (1). Portopulmonary hypertension occurs when pulmonary arterial constriction leads to increased pulmonary arterial pressure (2). The latter is less common than HPS, but either pulmonary complication increases morbidity and mortality in patients with liver cirrhosis. HPS is defined by a widened alveolar-arterial oxygen gradient (age corrected) in room air, with or without hypoxemia. It results from intrapulmonary vascular dilatations in the presence of hepatic dysfunction and/or portal hypertension (3-5). A key factor in the diagnosis of HPS is the exclusion of other causes than HPS that may be involved in cirrhosis presenting with hypoxemia (cardiopulmonary abnormalities, pulmonary atelectasis, pneumonia, ascites, pulmonary edema or hepatic hydrothorax) (6). The ERS Task Force (3) has proposed a classification system that uses arterial oxygen tension (PaO_2) to stage the severity of HPS. Staging the severity of HPS is important as a means of predicting survival and determining the timing and risks of orthotopic liver transplantation (OLT) (7).

The prevalence of HPS in the setting of cirrhosis ranges between 4%-47% and its presence increases the mortality rate, especially when hypoxemia is present (8,9). In a recent prospective multicenter study, mortality was significantly increased and quality of life (QoL) significantly decreased among patients with HPS compared to patients without HPS (10). OLT is the only curative therapeutic intervention for HPS, the benefits of medical treatment being controversial (11). There is data supporting this affirmation, although the mechanism of how the pulmonary vasculature is remodeled after transplantation is not clearly understood. What is known is that at least 85% of all cases of patients with HPS undergoing OLT experience significant improvement or complete resolution in hypoxemia (12). Still, survival is worse for those patients with more severe hypoxemia and significant intrapulmonary shunting. Unfortunately the mortality after OLT is significantly increased in HPS patients with a 1-year survival rate of 71% noted in one cohort study (12,13). OLT approach to HPS is the best treatment option and fully complete the management of HPS. The ERS Task

Force on Pulmonary-Hepatic Vascular Disorders recommends as a firm indication for OLT if $\text{PaO}_2 \geq 50 - < 60$ mmHg and consideration of OLT on an individual basis if $\text{PaO}_2 < 50$ mmHg (3). Pulse-oximetry based screening protocols are used to identify hypoxemia in cirrhotic patients, but more accurate clinical methods to early diagnose HPS would be helpful for further assessment of HPS presence (14).

Aim

Due to the fact that currently there are no reliable clinical predictors, nor clearly established diagnostic guidelines for HPS (10), our study aimed to detect a correlation between contrast-enhanced ultrasound (CEUS) findings on heart and pulse-oximetry, in order to early detect HPS. Applying this approach, we aimed to improve patient's recommendations for OLT in early stage of pulmonary complication of the liver disease, knowing that mortality after OLT is markedly increased and proportional with the HPS severity (15).

Methods

The diagnosis of HPS is based on the triad of chronic liver disease, an increased alveolar-arterial oxygen gradient, and evidence of right-to-left intrapulmonary shunt (IPS) (16). The presence of IPS can be confirmed by contrast-enhanced echocardiography (CEUS) (17), technetium-99m-labeled macroaggregated albumin (Tc-99m MAA) scanning (18) or pulmonary arteriography.

In our study we correlated transthoracic CEUS findings with pulse oxymetry as a screening test for detecting IPS in 186 patients diagnosed with liver cirrhosis between 2009-2012 in Gastroenterology Department of Clinical Emergency Hospital of Constanta County. All patients performed chest x-ray and if necessary pulmonary function tests (to rule out common intrinsic pulmonary disorders such as chronic obstructive pulmonary disease). We used agitated saline solution as contrast agent, in order to produce microbubbles with a mean diameter of up to $10 \mu\text{m}$, which were then injected through a peripheral vein. Unlike blood, microbubbles resonate at a frequency similar to clinical transducer frequencies, which make ultrasounds to be reflected. Under normal circumstances, only right heart chambers are opacified and the microbubbles are trapped in the pulmonary capillaries (mean diameter, $8 \mu\text{m}$). The presence of contrast in the left chamber suggests an arteriovenous connection. In patients with intracardiac right-to-left shunts, a small amount of contrast is usually recorded in the left chambers within 1 or 2 cardiac cycles after its appearance in the right side chambers (early shunt). On the contrary, late arrival of contrast in the left atrium after a time delay of 4-8 cardiac cycles is diagnostic of IPS (delayed shunt), and is due to the time required for passage through the pulmonary circulation (17). Measurement of SaO_2 was performed with a portable pulse oximeter. In all patients, the measurements were performed at ambient O_2 partial pressure in supine position. We considered at risk for HPS all patients with delayed left ventricle (LV) enhancement of the contrast agent,

at least 3 systolic beats after it appears in the right ventricle (RV). We correlated CEUS results with pulse-oximetry findings, considering to have a positive HPS diagnosis in all patients with both CEUS findings (as shown before) and $\text{SaO}_2 < 95\%$.

Results

The demographic data of 186 patients diagnosed with liver cirrhosis enrolled into the study and the statistic analysis suggested following results: most of patients were male (115/186); mean age was 63.10 years; the etiology of liver cirrhosis was alcohol use in 30%, viral hepatitis B (VHB) in 23% of patients, viral hepatitis C (VHC) in 18% of patients, and criptogenetic etiology for the rest of 29% of patients; the diagnosis of liver cirrhosis was based on clinical, biochemical, ultrasound and upper endoscopy criteria; the patients with liver cirrhosis were classified according to the Child-Pugh classification as follows: A (21%), B (52%) and C (27%) (Table 1).

From the total of 186 patients studied, 83 (44.62%) presented respiratory symptoms; some of them (28.91%) had also ascites and pleural effusion. The major respiratory symptoms reported were dyspnea in 61 patients (32.79%), followed by cough in 48 patients (25.80%). Clinical examination showed distal cyanosis in 59 cases (31.72%), clubbing in 67 cases (36.02%) and spider angioma in 73 cases (39.24%). All patients diagnosed with HPS presented dyspnea (Table 2).

Pulse-oximetry showed alterations, such as $\text{SaO}_2 < 95\%$ and $\text{PaO}_2 < 70$ mmHg in 61 patients (32.79%). From 186 patients diagnosed with liver cirrhosis, with or without respiratory signs and/or symptoms (dyspnea, clubbing, distal cyanosis, cough and/or spider angioma) referred to CEUS examination, 56 (30.10%) had delayed LV enhancement of the contrast agent (Fig. 1, 2). PaO_2 was less than 70 mmHg in 56 (100%) of HPS patients versus 6 (10.71%) of non-HPS patients ($P < 0.0001$). Pearson index showed a good correlation between heart CEUS findings and pulse-oximetry ($r=0.99$) in HPS diagnosis.

Discussions

HPS was defined as a triad of portal hypertension, intra-pulmonary vascular dilatation or shunting, and hypoxemia (19). Hypoxemia was defined by PaO_2 cutoff level of less than 70 mmHg in an arterial blood sample. We used this cutoff level of PaO_2 in arterial blood to pick up patients for further evaluation by CEUS, knowing that these patients

Table 1. Characteristics of the study patients

Variable	Results
Mean age (yrs)	63.10 ± 10.71 (interval 36-85; 95%CI, 61.55-64.65)
Sex (M/F)	115/71
Etiology of liver disease	
Alchool	56 (30.10%)
VHB	43 (23.11%)
VHB + alchool	29 (15.59%)
VHC	35 (18.81%)
VHB+VHD	14 (7.52%)
Unknown	9 (4.83%)
Liver cirrhosis classification	
Child-Pugh A	38 (20.43%)
Child-Pugh B	97 (52.15%)
Child-Pugh C	51 (27.41%)

with PaO_2 of more than 70mmHg were unlikely to have HPS (20).

In the current study, among 186 patients with liver cirrhosis, 56 patients (30.10%) met the clinical, laboratory and radiological criteria of HPS. HPS shows a wide variability in prevalence in different studies, ranging from 4 to 47% among cirrhotic patients (21), depending on the diagnostic criteria and the cutoff levels used for hypoxia. In our study, dyspnea was the most prevalent clinical feature in HPS patients. It was present in 100% of HPS patients and it was similar to other studies (20,22,23). However ascites by elevating the diaphragm and impairing the ventilation/perfusion match might lead to mild hypoxemia and dyspnea in cirrhotic patients without HPS (22). Dyspnea ($n=61$), clubbing ($n=67$), and spider angioma ($n=73$) were the most specific clinical features in our study. Our results are similar with other studies (5,22,24) who detected that patients with HPS had significantly higher incidence of dyspnea (100%), clubbing (76.11%) and spider angioma (71.23%). In the current study cyanosis showed a higher incidence in HPS patients (83.05%) and this is consistent with previous studies (20,22,25). Lee et al (25) concluded that only cyanosis could reliably distinguish between shunt positive and shunt negative patients. Spider angioma also showed a higher incidence in HPS patients (71.23%) and our results are similar to those of Hira et al (20), who concluded that the presence of spider angioma significantly correlated with intra-pulmonary vascular dilatation. Dyspnea had the highest sensitivity (100%) in HPS cases

Table 2. Clinical features in liver cirrhosis patients

Symptoms/signs	No. (%)	HPS positive	HPS negative	P value
Dyspnea	61 (32.79%)	56 (100%)	5	<0.0001
Cough	48 (25.80%)	28 (58.33%)	20	0.1527
Distal cyanosis	59 (31.72%)	49 (83.05%)	10	<0.0001
Spider angioma	73 (39.24%)	52 (71.23%)	21	<0.0001
Clubbing	67 (36.02%)	51 (76.11%)	16	<0.0001



Figure 1. Contrast echocardiogram. Panel 1: apical four-chamber view before injection of contrast agent (saline solution); Panel 2: apical four-chamber view after contrast injection showing opacification of the right atrium (RA) and RV. Panel 3 and 4: apical four-chamber view showing bubbles within the left atrium (LA) and LV, 4 and then 5 systolic beats after its appearance in the right heart

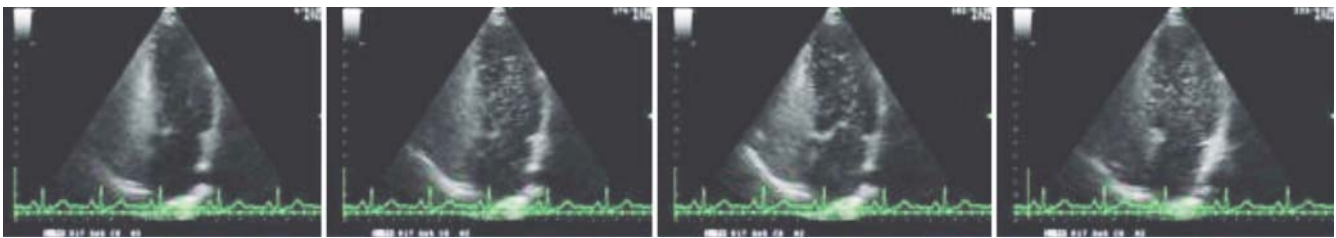


Figure 2. Contrast echocardiogram. Panel 1: apical four-chamber view after contrast injection (agitated saline) showing opacification of the RA and RV. Panel 2, 3 and 4: apical four-chamber view showing the bubbles within the LA and LV (5, 6 and 7 systolic beats after its appearance in the right chambers)

followed by spider angioma (92.85%), clubbing (91.07%), and cyanosis (87.50%). In our study PaO₂ was less than 70 mmHg in 100% of HPS patients versus 10.71% of non-HPS patients, in which pulmonary function tests were used to diagnose chronic intrinsic pulmonary disease. All patients with positive CEUS findings had arterial PaO₂ < 70 mmHg and were qualified for the diagnosis of HPS. CEUS was proved by previous investigators to be a useful sensitive and specific screening test for HPS even in early stages of liver dysfunction and even in whom the lung scintigraphy was still negative (26). The diagnosis of IPS can also be made by Tc-99m MAA scintigraphy, which shows abnormal extrapulmonary tracer activity, demonstrating a lack of captured albumin in the pulmonary capillaries. Tc-99m MAA scan is particularly recommended in cirrhotic patients with intrinsic lung disease because of its higher specificity (27). The only privilege of lung scintigraphy over CEUS is quantitation of the degree of shunting in relation to cardiac output (28). Some authors suggested transesophageal CEUS as a gold standard (29,30). However, others claimed that transthoracic CEUS was as accurate as transesophageal CEUS in determining the presence of right to left shunt. Proper timing of left atrial opacification by microbubbles during the cardiac cycle was considered a distinguishing step in the transthoracic CEUS between intracardiac and intrapulmonary shunting (31). Transesophageal CEUS might have higher sensitivity than transthoracic CEUS because it allows the contrast to be seen when entering from the pulmonary veins (32,33). However, transthoracic CEUS is diagnostic in the majority of cases. In addition, esophageal varices are relatively common in these patients, and this is considered a relative contraindication to perform transesophageal CEUS (34). Current data shows no

benefits from medical therapy for HPS, but no randomized trials have been performed yet; OLT is the only effective treatment for HPS (10). Complete resolution of HPS should occur in patients surviving OLT. CEUS is of great value to examine shunting reversibility during follow-up, because is reliable and non-invasive (35).

Conclusion

Our study showed a good correlation between lung and heart CEUS findings and pulse-oximetry in HPS diagnosis. Two non-invasive, simple and rapid methods, such as CEUS and pulse-oximetry can easily diagnose HPS, a highly fatal complication of liver cirrhosis, and can also guide the future management by speeding up OLT recommendations, knowing that as HPS severity increases, survival after OLT declines.

Conflicts of interest

None to declare.

Authors contribution

First 2 authors with equal scientific contributions.

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