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Correlation Between Transthoracic Contrast-Enhanced Ultrasound and Pulse Oximetry in Hepatopulmonary Syndrome Diagnosis

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Abstract

The prevalence of hepatopulmonary syndrome (HPS) in the setting of cirrhosis ranges between 4 and 47% and its presence increases the mortality rate, especially when hypoxemia is present. Our study aim was to fix whether there is a correlation of results between two simple and non-invasive procedures such as transthoracic contrast-enhanced ultrasound (CEUS) and pulse oximetry, used for early detection of HPS in patients with liver cirrhosis, having as endpoint the improvement in their outcome. The rapid lung enhancement and delayed left ventricle enhancement of the saline solution, after at least three systolic beats during CEUS and pulse oximetry showing a $\text{SaO}_2 < 95\%$, were correlated and considered positive for the diagnosis of HPS. One hundred and sixty-five (44%) of the total of 375 patients diagnosed with liver cirrhosis enrolled in the current study, with or without respiratory symptoms (dyspnea, clubbing, distal cyanosis, cough and/or spider angioma), showed positive criteria for HPS diagnosis during CEUS. $\text{SaO}_2 < 95\%$ and $\text{PaO}_2 < 70$ mmHg were found in 123 patients (33%) during pulse oximetry investigation. Pearson correlation index showed a good correlation between lung and heart CEUS findings and pulse oximetry ($r = 0.97$) for HPS diagnosis. CEUS and pulse oximetry results correlate and rapidly diagnose HPS, a highly fatal complication of liver cirrhosis (LC), guiding the future treatment by speeding up orthotopic liver transplant OLT recommendations to improve the survival rates.

Keywords: transthoracic contrast-enhanced ultrasonography, pulse oximetry, liver cirrhosis, hepatopulmonary syndrome, hypoxemia

1. Introduction

The hepatopulmonary syndrome (HPS) represents a complication of liver cirrhosis characterized by a gross dilatation of the pulmonary precapillary and capillary vessels, an increase in the number of dilated vessels, portopulmonary anastomoses, pleural and pulmonary arteriovenous shunts. It can be diagnosed when the triad represented by liver disease, impaired oxygenation and intrapulmonary vascular abnormalities, referred to as intrapulmonary vascular dilatations (IPVDs) coexist [1]. The prevalence of pulmonary complications associated with liver cirrhosis ranges between 4 and 47%, worsening the evolution and prognosis, especially when hypoxemia is present [2, 3]. According to the medical literature focused on the current topic, 23% of patients with HPS have an average survival rate around 24 months, compared to 63% of patients without HPS. Survival can be further worsened in case of comorbidities or advanced age [4]. Respiratory signs and symptoms are common in patients with liver cirrhosis, no matter the stage of the disease. Intrapulmonary vascular complications of liver cirrhosis consist of hepatopulmonary syndrome (HPS) and portopulmonary hypertension. HPS appears when intrapulmonary blood shunting impairs arterial gas exchange [5], and portopulmonary hypertension occurs when pulmonary arterial constriction leads to increased pulmonary arterial pressure [6]. The latter, although rare, can cause pulmonary complication, which worsens the morbidity and mortality in patients with liver dysfunction. The outcome of patients with advanced liver disease, complicated with pulmonary involvement, can be influenced even in the setting of orthotopic liver transplant, due to chronic hypoxemia installed during the evolution of cirrhosis influencing the prognosis. A key factor in the diagnosis of HPS is the exclusion of causes other than HPS that may be involved in cirrhosis and characterized by hypoxemia (cardiopulmonary abnormalities, pulmonary atelectasis, pneumonia, ascites, pulmonary edema or hepatic hydrothorax) [7]. The challenge for physicians working in the field of hepatology is to raise the idea of establishing new methods for a conventional, rapid and simple diagnosis of pulmonary involvement during the evolution of liver cirrhosis, in order to improve as much as possible the outcome of possible curative treatment.

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 [8, 9].

The development of pulmonary vascular dilatation has as pathogenic mechanism a pulmonary overproduction of endogenous nitric oxide (NO) [10]. According to studies focused on the topic in the last two decades, a theory can be formulated according to which endothelin-1 and tumor necrosis factor- α may play a role in pulmonary microvascular tone modulation [11, 12]. The contributing factors to the process of pulmonary microvascular dilatation in HPS include angiogenesis, vascular remodeling, pulmonary arteriovenous shunts and portopulmonary venous anastomoses [13, 14].

Trough this pathogenic mechanism, the rapid or direct passage of mixed venous blood into the pulmonary veins is responsible for the pulmonary vascular dilatation. The mismatch of ventilation-perfusion sequence produces a deficit in the blood oxygenation. The inhibition of hypoxic vasoconstriction produces an increased blood flow and preserved alveolar ventilation.

The alveolar-arterial oxygen tension difference— ≥ 15 , or ≥ 20 mmHg for patients aged >64 is considered as a very sensitive index of early arterial deoxygenation in HPS, and this difference being overload before arterial oxygen tension becomes abnormally low [8]. On the other hand, the alveolar-capillary interface is too wide to allow for complete equilibration of carbon monoxide with hemoglobin, thus being translated in reducing the diffusing capacity of the lungs for carbon monoxide.

Patients complain of symptoms correlated not only with the subsequent liver disease, but also with the respiratory signs and symptoms, usually revealing dyspnea and cyanosis. The management of these patients requires the exclusion of other causes for such respiratory symptoms, because chronic obstructive pulmonary disease and pulmonary fibrosis can coexist in approximately 30% of patients with HPS [15]. Dyspnea (“platypnea”) and hypoxemia (“orthodeoxia”) are characteristically worsened in the upright position and improved by lying supine, resulting from a gravitational increase in blood flow through dilated vessels in the lung bases [16].

According to the pathogenic definition, the diagnosis of HPS requires evidence of pulmonary vascular dilatation and hypoxemia, with no cardiopulmonary disease history. To stage the severity of the disease, it is required to investigate the arterial blood gas tension at rest, while breathing room air and in the sitting position. A sensitive and non-invasive tool for the detection of pulmonary vascular dilatation is the contrast-enhanced transthoracic echocardiography after injection of hand-agitated normal saline. During the first pass, microbubbles are physiologically trapped and absorbed by alveoli, and they should not be seen in the left atrium. The passage of saline microbubbles through abnormally dilated lung vessels requires more than three cardiac cycles to reach left heart chambers [17]. In contrast, the immediate enhancement of saline microbubbles in the left atrium raises the suspicion of an intracardiac right-to-left shunt [18]. The alternative to CEUS investigation is scintigraphic perfusion scanning, which uses the technetium-99-labeled albumin macroaggregates >20 μm in diameter. The uptake of tc-99-labeled albumin macroaggregated in other organs occurs in case of right-to-left shunt, while the trapping of albumin macroaggregates in pulmonary circulation is characteristic for HPS [19].

The present management of HPS lacks of efficient therapy solutions, until the OLT is available. Starting from the pathogenic mechanism, physicians investigated several classes of drugs such as β -blockers, cyclo-oxygenase inhibitors, systemic corticosteroids, cyclophosphamide, inhaled NO, and NO inhibitors, but without a real benefit in oxygenation improvement or pulmonary vascular dilatation. The only efficient treatment in case of severe and refractory hypoxemia is the oxygen supplementation, with complete resolution in more than 80%, according to study results [8, 20]. The presence of HPS offers exception points in MELD scoring and an advantage for patients to occupy better places on waiting lists for OLT [21]. Without OLT, the prognosis for HPS is poor, with mortality around 41% of patients over a mean period of 2.5 years [22]. The literature data do not provide reliable clinical predictors or diagnosis guidelines for the outcome of HPS [23].

A retrospective cohort analysis of data submitted to the United Network for Organ Sharing studied the effects of room-air oxygenation of patients with HPS and the pre- and post-transplantation outcomes. Patients with HPS were given MELD exception points and prioritized

for liver transplantation due to their high pre- and post-transplantation mortality. Comparing the overall survival rates of patients with and without HPS, transplant recipients with more severe hypoxemia had increased risk of death after liver transplantation. The overall mortality was significantly lower among waitlist candidates with HPS (hazard ratio = 0.82; 95% CI: 0.70–0.96), having the OLT before the deterioration of tissue oxygenation and liver dysfunction, due to exception MELD points given, which provided an advantage for a rapid transplant [24].

The aim of our study was a possible correlation between contrast-enhanced ultrasound (CEUS) findings on heart and pulse oximetry, in order to early detect HPS, as a prognostic factor for orthotopic liver transplant (OLT) success [25].

2. Methods

Demographic data, etiology and severity scores were recorded. For the diagnosis of HPS, we used the classical triad: presence of chronic liver disease, an increased alveolar-arterial oxygen gradient, and evidence of right-to-left intrapulmonary shunt (IPS) [26]. In order to determine the HPS diagnosis, we used the classical charts provided by the guidelines for transplant candidates (**Table 1**). The diagnosis of liver cirrhosis was based on clinical, biochemical, ultrasound, and upper endoscopy criteria. The patients with liver cirrhosis were classified according to MELD scores, considering exception points according to international recommendations. The contrast-enhanced echocardiography (CEUS) [27], technetium-99m-labeled macroaggregated albumin (Tc-99m MAA) scanning [28], and pulmonary arteriography are the current imagistic tools to diagnose the IPS. We correlated transthoracic CEUS findings with pulse oxymetry as a screening test for detecting IPS in 375 patients diagnosed with liver cirrhosis between December 2009 and June 2016 in Gastroenterology Department of Clinical Emergency Hospital “St Apostle Andrew” of Constanta County.

Criteria	Data requirements
Strict HPS criteria	<p>Alveolar-arterial gradient ≥ 15 mmHg, or ≥ 20 mmHg if age older than 60 years</p> <p>Intrapulmonary shunting on transthoracic echocardiogram or $>6\%$ shunt fraction on macroaggregated albumin scan</p> <p>No evidence of severe restrictive or obstructive pulmonary disease</p>
Hypoxia/hypoxemia+ IP shunts	<p>Hypoxemia defined as:</p> <ul style="list-style-type: none"> • $\text{PaO}_2 < 70$ mmHg on room air or • Pulse oximetry $\leq 96\%$ (room air or supplemental O_2) <p>Intrapulmonary shunting (right \rightarrow left bubbles on echocardiogram after three cardiac cycles and/or free text stating “intrapulmonary shunting”)</p> <p>No evidence of concurrent cardiopulmonary disease</p>

Table 1. Inclusion criteria defining OLT waitlist candidates with HPS based on exception narrative data [28].

All patients were examined by chest X-ray and pulmonary function tests (to rule out common intrinsic pulmonary disorders such as chronic obstructive pulmonary disease). We used as a contrast agent of hand-agitated saline solution, in order to produce microbubbles with a mean diameter of up to 10 μm 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 the right heart chambers are opacified, and the microbubbles are trapped in the pulmonary capillaries (mean diameter, 8 μm). The presence of contrast in the left chamber suggests an arteriovenous connection. In patients with intracardiac 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 for HPS (delayed shunt) and is done by the time required for passage through the pulmonary circulation [27]. 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 have chosen a SaO_2 value of $<95\%$ in order to detect all HPS patients with a $\text{PaO}_2 < 70$. The correlation of rapid lung enhancement and delayed left ventricle enhancement of the saline solution, after at least three systolic beats in the left ventricle during CEUS and pulse oximetry showing a $\text{SaO}_2 < 95\%$ was considered positive for the diagnosis of HPS [29].

3. Results

A total of 375 patients diagnosed with liver cirrhosis were enrolled in our study. The majority of patients were male (251/375). The average age was 66.04 years (SD 8.81). The etiology of liver cirrhosis was alcohol abuse in 39% (146/375) of patients, viral hepatitis B (VHB) in 28% (105/375) of patients, viral hepatitis C (VHC) in 21% (79/375) of patients, and the rest of 12% (45/375) having uncommon etiologies. Severity in MELD score divided our patients in three groups according to which we could fix the prognosis and the need of transplantation (**Table 2**).

According to present international recommendations, we decided upon exception points for those patients meeting the criteria for MELD exception: patients with $\text{PaO}_2 < 60$ mmHg on room air at rest in the sitting position, arterial blood gas result provided, patients with pulmonary vascular dilatation documented by a positive transthoracic contrast echocardiography, patients with absence of significant alternative pulmonary disease to explain severe hypoxemia (chest X-ray, pulmonary function tests, and chest computed tomography reports), patients with moderate or severe pulmonary function tests changes or significant chest X-ray abnormalities or MAA scan positive for intrapulmonary shunting) (**Table 3**). From the total of 375 patients studied, 165 (44%) presented respiratory symptoms. Pulse oximetry showed alterations, such as $\text{SaO}_2 < 95\%$ and $\text{PaO}_2 < 70$ mmHg in 123 patients (33%). From 375 patients diagnosed with LC, with or without present respiratory signs and/or symptoms (dyspnea, clubbing, distal cyanosis, cough and/or spider angioma) referred to CEUS examination, 105 (28%) had rapid lung enhancement and delayed left ventricle enhancement of the contrast agent (**Figures 1–3**). PaO_2 was less than 70 mmHg in all 105 HPS patients (100%) versus 12 (14.76%) of non-HPS patients ($P < 0.0001$). Pearson correlation index showed a good correlation between lung and heart CEUS findings and pulse oximetry ($r = 0.97$) in HPS diagnosis.

Variable	HPS (no, %)	Non-HPS (no, %)
Mean age (IQR)	66.04 ± 8.81 (95% CI, 58.44–74.85)	63.10 ± 10.71 (95% CI, 61.55–64.65)
Gender		
Males	128 (50.99)	123 (49.00)
Females	59 (47.58)	65 (52.41)
Race		
Caucasians	92 (87.61)	243 (90)
Blacks	2 (1.90)	1 (0.37)
Asians	11 (10.47)	26 (9.62)
Ethnicity		
Romanian	51 (48.57)	173 (64.07)
Turcs/tatars	8 (7.61)	19 (7.03)
Moldavians	4 (3.80)	9 (3.33)
Macedonians	31 (29.52)	42 (15.55)
Other	11 (10.47)	27 (10)
Primary diagnosis		
HCV	27 (25.71)	52 (19.25)
HBV	31 (29.52)	74 (27.40)
Alcohol	39 (37.14)	106 (39.25)
HVD	5 (4.76)	18 (6.66)
Autoimmune	2 (1.90)	4 (1.48)
NASH/cryptogenetic	1 (0.95)	9 (3.33)
Other rare causes	–	5 (1.85)
MELD score, median (IQR)	14 (11–22)	16 (11–24)
MELD score categories		
<15	47 (44.76)	156 (57.77)
15–20	34 (32.38)	76 (28.14)
>20	14 (13.33)	38 (14.07)
MELD exceptions		
PaO ₂ < 60 mmHG (22 pts)	5 (4.76)	–
PaO ₂ = 51–55 mmHG (24 pts)	4 (3.80)	–
PaO ₂ < 50 mmHG (26 pts)	1 (00.95)	–
History of ascites	84 (80.00)	229 (84.81)
History of liver decompensations	74 (70.47)	172 (63.70)

Table 2. Baseline clinical and demographic characteristics of HPS and non-HPS patients.

PaO ₂	Exception points for MELD scoring for HPS
56–59 mmHg	22 MELD points
51–55 mmHg	24 MELD points
<50 mmHg	26 MELD points

Table 3. Allocation of exception points for HPS in MELD scoring system [28].

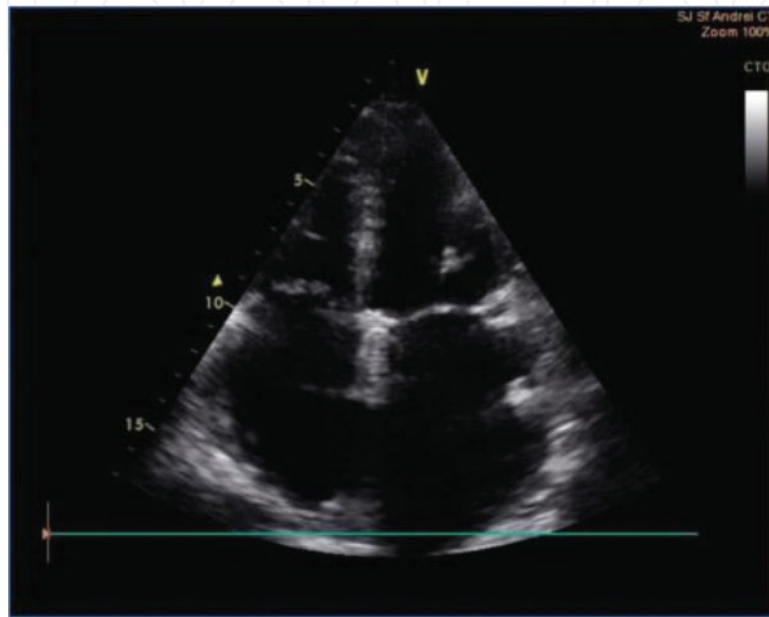


Figure 1. Contrast-enhanced echocardiogram. Apical four-chamber view before contrast injection.

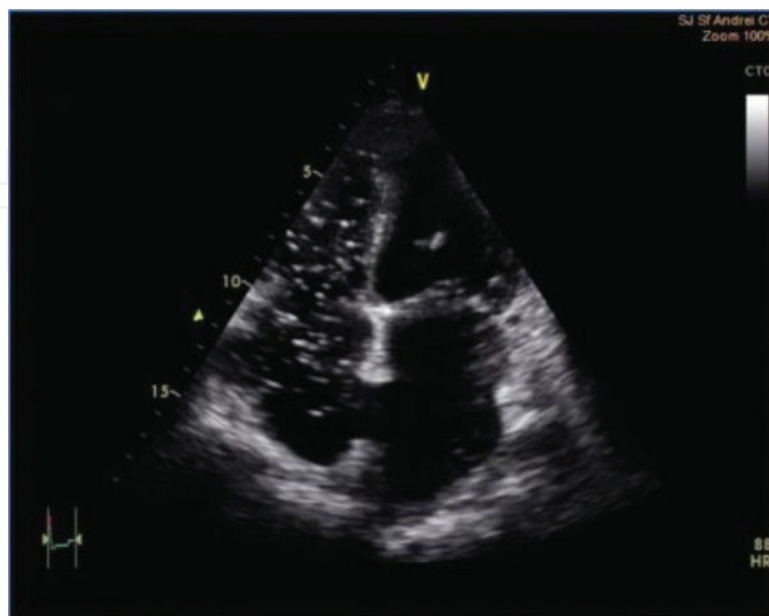


Figure 2. Contrast-enhanced echocardiogram. Apical four-chamber view after contrast injection (agitated saline) showing the presence of bubbles in the right chambers and no bubbles in the left chambers after the first systola.

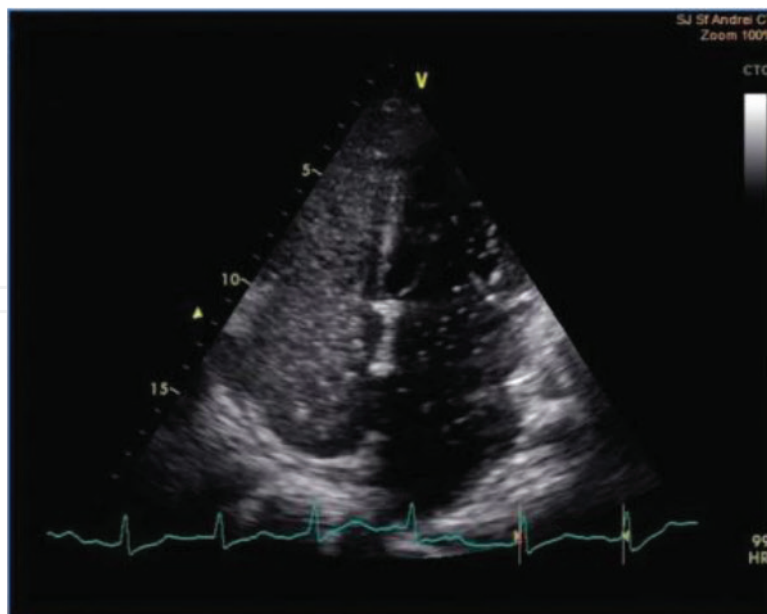


Figure 3. Contrast-enhanced echocardiogram. Apical four-chamber view after contrast injection (agitated saline) showing the presence of bubbles in the right heart chambers and the appearance of bubbles in the left heart chambers, late, after the fourth systole.

4. Discussion

HPS was defined as a triad of portal hypertension with or without hepatic dysfunction, intrapulmonary vascular dilatation or shunting, and hypoxemia [30]. Hypoxemia was defined by PaO_2 cutoff level of less than 70 mmHg in an arterial blood sample to pick up these patients for further evaluation by CEUS. This arterial PO_2 cutoff level was suggested by previous researchers [31], who found that patients with PaO_2 of more than 70 mmHg were unlikely to have HPS.

In the current study, among 375 patients diagnosed with liver cirrhosis, 105 patients (28%) met the clinical, laboratory and imaging criteria of HPS. HPS shows a wide variability in prevalence in different studies, ranging from 4 to 47% among cirrhotic patients [1, 4, 32], depending on the diagnostic criteria and the cutoff levels used for hypoxia. In our study, PaO_2 was less than 70 mmHg in 100% of HPS patients versus 12% 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 $\text{PaO}_2 < 70$ 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 [33]. Some authors suggested transesophageal CEUS as a gold standard [34, 35]. However, others argued that transthoracic CEUS has the same accuracy 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 [36]. Transesophageal CEUS might have higher sensitivity than transthoracic CEUS

because it allows the contrast to be seen when entering from the pulmonary veins [37, 38]. However, transthoracic CEUS is diagnostic in the majority of cases. In addition, esophageal varices are relatively common in these patients, and this can be considered as a relative contraindication in transesophageal CEUS performing [29, 39].

According to their correlated results, the transthoracic CEUS and pulse oximetry could be inserted in the algorithm of liver cirrhosis staging, in order to select those patients in need for a more rapid indication of OLT. Both methods provide data regarding the pulmonary dysfunction during liver cirrhosis evolution, improving the outcome after OLT, especially in HPS patients with moderate or severe hypoxemia. The presymptomatic stage of HPS can be correctly diagnosed using the combination of these two methods, making the algorithm of liver cirrhosis staging more accurate.

5. Conclusion

Our study showed a good correlation between lung and heart CEUS findings and pulse oximetry in HPS diagnosis. When correlated, these two simple, non-invasive, low-cost and rapid methods can easily diagnose HPS, a highly fatal complication of liver cirrhosis, which can worsen the outcome of patients even after OLT.

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