Value of contrast echocardiography for the diagnosis of hepatopulmonary syndrome

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Abstract The hepatopulmonary syndrome must be suspected in patients with end-stage liver disease and refractory hypoxemia. We report a case of a 49-year-old woman with hypoxemia and cirrhosis referred to the cardiac ultrasound laboratory in the evaluation of liver transplantation. Contrast-enhanced echocardiography with intravenous injection of agitated saline solution was crucial to obtain the definitive diagnosis. This imaging modality has proven to be a valuable tool in detecting intrapulmonary right-to-left shunt. The present case emphasizes the usefulness of contrast echocardiography in the diagnosis of a noncardiac disease with important prognosis implications.

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The diagnosis of hepatopulmonary syndrome (HPS) is based on the triad of chronic liver disease, gas exchange abnormalities with significant hypoxemia and/or an increase of alveolar–arterial oxygen gradient, and evidence of right-to-left intrapulmonary shunt (IPS). Its prevalence ranges between 17% and 47% among patients with end-stage hepatic disease. The natural history of the HPS is characterized by a progressive deterioration, which leads to severe dyspnea and a high mortality rate after 4–5 years from the beginning of the respiratory symptoms. Liver transplantation (LT) is considered the only effective treatment in most of these patients. The presence of IPS can be confirmed by contrast-enhanced echocardiography, technetium-99m-labeled macroaggregated albumin (Tc-99m MAA) scanning or pulmonary arteriography.

We report the case of a patient referred to the echocardiography laboratory to confirm a suspected HPS as part of a complete evaluation before an LT.

Case report

A 49-year-old woman with chronic hepatic disease due to alcoholic cirrhosis and a history of 1-year progressive dyspnea was referred to the echocardiography laboratory. Physical examination was normal except for labial cyanosis. The electrocardiogram was normal and the chest roentgenogram displayed no significant abnormalities. Pulmonary function tests were within normal limits. Arterial blood gas analysis revealed hypoxemia (oxygen saturation of 92%, PaO₂ 58 mmHg, and PCO₂ 27 mmHg) and significant orthodeoxia (desaturation in an upright posture: oxygen saturation of 88%, PaO₂ 51 mmHg, and PCO₂ 27 mmHg). Standard transthoracic echocardiography (TTE) showed normal left ventricular size and function, normal mitral and aortic valves, normal left ventricular filling pattern and the estimated pulmonary artery pressure was 28 mmHg. To disclose IPS, 10 ml of agitated saline solution were injected via the right antecubital vein. Bubbles were first seen in the right atrium; 5 cycles later, bubbles appeared in the left atrium (Fig. 1), which is consistent with IPS. Tc-99m MAA scans showed normal
ventilation. However, abnormal activity of the radiotracer was seen in the brain, spleen and kidneys, a finding suggestive of a right-to-left shunt. Pulmonary arteriography ruled out cirrhosis-associated pulmonary hypertension and did not show direct arteriovenous communication.

**Discussion**

Diffusion–perfusion impairment relates to the mechanism of hypoxemia associated with intrapulmonary vascular dilatations in the setting of HPS.\(^3\) Recent studies on experimental models of HPS have identified a sequence of hepatic and pulmonary endothelial alterations that lead to nitric oxide- and carbon monoxide-mediated intrapulmonary vasodilatation.\(^7\)

Contrast echocardiography is considered the most useful screening test for detecting IPS.\(^2\) The contrast agent used is agitated saline solution injected through a peripheral vein. It is a safe method as long as there is no visible free air in the injection system. Gelatine solutions which give brighter contrast have been used as well.\(^8\) Unlike blood, microbubbles resonate at a frequency similar to clinical transducer frequencies, which make ultrasounds to be reflected.\(^5\) Under normal circumstances, only right heart chambers are opacified and the microbubbles (mean diameter of up to 10 \(\mu\)m) are trapped in the pulmonary capillaries (mean diameter, 8 \(\mu\)m).\(^2,5\) The presence of contrast in the left chamber suggests an arteriovenous connection. Three levels of shunting can be identified: atrial septal defect, ventricular septal defect with Eisenmenger’s and IPS.\(^5\) 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. On the contrary, late arrival of contrast in the left atrium after a time delay of 4–8 cardiac cycles is diagnostic of IPS, and is due to the time required for passage through the pulmonary circulation.\(^2,5\) Transoesophageal echocardiogram (TEE) might have higher sensitivity than TTE because it allows the contrast to be seen entering from the pulmonary veins.\(^8,9\) However, TTE is diagnostic in the majority of cases. In addition, the presence of esophageal varices, which is considered a relative contraindication to the performance of TEE,\(^10\) is relatively common in these patients. Therefore, a contrast TTE should be performed first, and only if it is normal, a contrast TEE should be considered. In general, TEE has been reported as a low-risk procedure with an overall incidence of minor side effects and complications of 2.8%.\(^10\) TTE using the Doppler-detected tricuspid regurgitation is also an accurate method in detecting severe pulmonary hypertension, which is an important contraindication for LT.\(^11\)  

![Figure 1](https://academic.oup.com/ehjcimaging/article-abstract/8/5/408/2398169)
The diagnosis of IPS can also be made by Tc-99m MAA scanning, 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. Pulmonary arteriography is considered the standard in the diagnosis of shunts, but several reports suggest that contrast-enhanced echocardiography is more sensitive when the arteriovenous fistulas are very small or diffuse. In our case, pulmonary arteriography was normal. The usefulness of the ECG in the HPS is limited. It has been shown that a prolonged Q-T interval is often present in chronic liver disease but further research should address the prognostic and therapeutic significances of the prolonged Q-T interval in cirrhosis.

According to the previous reports, complete resolution of HPS frequently occurs in patients surviving LT. TTE, being non-invasive, is of great value to examine the reversibility of the shunting during follow-up.

In conclusion, HPS should be ruled out in a patient with refractory hypoxemia and chronic hepatic disease. Our case illustrates that saline contrast echocardiography plays an important role in this context.

References