

## Severe Arterial Hypoxemia in Liver Cirrhosis

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### Introduction

The clinical symptoms in liver cirrhosis arise from portal hypertension. The classic signs and symptoms include ascites, bleeding from esophageal varices, and encephalopathy. Moreover, many patients with cirrhosis and portal hypertension develop peripheral vasodilatation and a hyperdynamic circulation with the presence of arteriovenous communications, increased blood volume, and activation of vasodilating systems such as the nitric oxide system.<sup>1,2</sup> The hyperdynamic syndrome comprises increased heart rate, cardiac output, and plasma volume, and reduced systemic vascular resistance and arterial blood pressure. These compensatory reactions are mainly brought about by activation of potent vasoconstricting systems such as the renin-angiotensin-aldosterone system and the sympathetic nervous system. This situation has led to the appearance of new clinical entities, such as the hepatopulmonary syndrome,<sup>1</sup> which is a pulmonary vascular disorder that complicates hepatic diseases, most frequently liver cirrhosis, and is responsible for morbidity and mortality in patients awaiting liver transplantation, primarily due to the adverse effects of hypoxemia.<sup>1,3</sup> Knowledge about the relationship between hepatopulmonary syndrome and liver cirrhosis dates back to 1884, when Flückiger first described it, based on observation of a woman with cyanosis, clubbing, and cirrhosis.<sup>4</sup> However, any acute or chronic liver disease can coexist with hypoxemia due to pulmonary vascular dilatation. Therefore, portal hypertension is not required for the syndrome to manifest.<sup>2</sup>

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The authors declare no conflicts of interest.

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Hepatopulmonary syndrome consists of a triad of hepatic dysfunction, hypoxemia ( $P_{aO_2} < 70$  mm Hg), and extreme vasodilatation in the form of intrapulmonary vascular dilatations. It may be further characterized by an elevated alveolar-arterial oxygen difference ( $P_{(A-a)O_2}$ ), intrapulmonary shunt (diagnosed via lung-perfusion scintigraphy with technetium-99m macroaggregated albumin, or via contrast-enhanced echocardiography), and the absence of arterial carbon dioxide retention.<sup>5</sup>

A lung-perfusion scintigram can indicate the shunt fraction from the right-kidney scintigraphic count, corrected for attenuation. The fraction is expressed as a percentage of the injected dose, with the right-to-left shunt expressed as 10 times that value, assuming the right kidney received 10% of the cardiac output (kidney-dose method). The kidney-lung method calculates the right-kidney count as a proportion of the lung counts.<sup>6</sup>

Another modality to investigate thoracic shunt is contrast-enhanced echocardiography. Saline is agitated to produce microbubbles ( $\geq 15 \mu\text{m}$  in diameter) and the agitated saline is injected intravenously. Under normal circumstances the microbubbles are trapped in the pulmonary microvasculature and then absorbed. In patients with intracardiac or intrapulmonary shunt the microbubbles appear in the left-side cardiac chamber. Differentiation between intracardiac and intrapulmonary shunt is based on the timing of when the bubbles reach the left heart chamber. In intracardiac right-to-left shunt the bubbles appear in the left heart chamber within 3 heartbeats after they appear in the right heart chamber. In intrapulmonary shunt the bubbles appear in 4–6 heartbeats.<sup>7,8</sup> The severity of hepatopulmonary syndrome can be classified by the degree of  $P_{(A-a)O_2}$ .

Rodríguez-Roisin et al described the degrees of severity from mild ( $P_{(A-a)O_2} \geq 15$  mm Hg,  $P_{aO_2} \geq 80$  mm Hg) to very severe ( $P_{(A-a)O_2} \geq 15$  mm Hg,  $P_{aO_2} \leq 50$  mm Hg).<sup>9</sup> However, there is no relationship between the severity or presence of hepatopulmonary syndrome and the severity of liver disease, on the basis of the Child-Turcotte-Pugh classification system or the Model for End-Stage Liver Disease scoring system.<sup>3</sup> Because of differences in  $P_{aO_2}$  and  $P_{(A-a)O_2}$  measurement techniques during the adminis-

tration of 100% oxygen, on the basis of our literature review, we believe no accurate comparison can be made of  $P_{aO_2}$  and characterization of hepatopulmonary syndrome severity.<sup>3,7</sup>

Despite these disadvantages, the suggestion to consider progressive hypoxemia in the presence of hepatopulmonary syndrome as an indication for liver transplantation has been raised from a pulmonary perspective, for several reasons, including substantial mortality (33–40%) during the fairly brief time span, insufficient response to oxygen therapy, and ineffective medical therapies to improve oxygenation.<sup>2,3,5,9</sup>

### Case Summary

A 69-year-old woman with a medical history of alcoholic liver cirrhosis, complicated by grade II esophageal varices and polycythemia, was referred to the emergency room with abdominal pain. The liver cirrhosis was established in 2005 via abdominal ultrasonography and scored 8 with the Model for End-Stage Liver Disease.<sup>10</sup> A large intra-abdominal mass was also found, most likely originating from the uterus. However, the patient had refused further investigation of that mass.

In 2006 she had a  $P_{aO_2}$  of 49 mm Hg while breathing room air. Polycythemia (hemoglobin 212 mg/dL, hematocrit 54%) was due to a high erythropoietin level (34.7 mU/mL; normal value corrected for hematocrit 5–17 mU/mL). With phlebotomy the hemoglobin level was corrected to normal. The high erythropoietin level was thought to originate from an erythropoietin-producing adenoma in the intra-abdominal mass. An abdominal computed tomogram showed signs of a stomach perforation, liver cirrhosis, and a large uterus myomatosus. A median laparotomy revealed a uterus myomatosus of 30 cm in length and a ventral stomach perforation. The perforation was affixed and the large uterus was removed. Macroscopy and microscopy confirmed a large uterus myomatosus and no signs of adenoma.

Postoperatively a  $P_{aO_2}$  of 51 mm Hg and an arterial oxygen saturation of 82% was measured without complaints while the patient was breathing room air. She was admitted to the intensive care unit for further postoperative care and investigation. During admission a decrease in arterial oxygen saturation, from 80% to 71%, was noted in the upright posture, which improved on recumbency, demonstrating orthodeoxia. However, arterial hypoxemia ( $P_{aO_2}$  50 mm Hg, arterial oxygen saturation 82%) persisted despite 100% oxygen via nonrebreather mask. Chest radiograph and computed tomogram of the thorax did not explain the hypoxemia. Calculated shunt fraction was 35%, and  $P_{(A-a)O_2}$  while on 30 min of 100% oxygen via nonrebreather mask was 640 mm Hg. Dynamic technetium-99m macroaggregated albumin perfusion scintigraphy showed

an enlarged venous return via the vena azygos, and a right-to-left shunt fraction of 30–35% uptake in both kidneys and brain (Fig. 1). We used the mean of measurements obtained via the kidney-dose and kidney-lung methods.

Contrast-enhanced echocardiography showed air bubbles in the left heart after 6 cardiac cycles, which confirmed an intrapulmonary shunt (Fig. 2).

After removal of the uterus myomatosus, the erythropoietin level remained high (hemoglobin 189 mg/dL, hematocrit 0.49%, and erythropoietin 38.7 mU/mL; reference erythropoietin value corrected for hematocrit 5–17 mU/mL).

Our patient was discharged from the intensive care unit with a diagnosis of hepatopulmonary syndrome with secondary polycythemia due to chronic arterial hypoxemia. Supplemental oxygen therapy had been started on admission to the intensive care unit, but she refused further oxygen therapy because of lack of benefit and absence of symptoms. She had stopped alcohol abuse before admission. After discharge, our patient returned to our emergency room several times with complaints caused by abdominal distention due to ascites. Ultrasound-guided drainage was performed each time to improve her quality of life. She was not evaluated for orthotopic liver transplantation because she was more than 65 years old.

### Discussion

Our patient's diagnosis of hepatopulmonary syndrome with severe chronic hypoxemia was made with contrast-enhanced echocardiography and technetium-99m macroaggregated albumin perfusion scintigraphy. Contrast-enhanced echocardiography is the preferred screening test for hepatopulmonary syndrome.<sup>11</sup> Apart from establishing a shunt, contrast-enhanced echocardiography cannot quantify a shunt or differentiate between intrapulmonary vascular dilatation and direct arteriovenous communication, so, although contrast-enhanced echocardiography is highly sensitive for hepatopulmonary syndrome, it lacks specificity. Also, in patients with concomitant intrinsic lung diseases, the contribution of hepatopulmonary syndrome to arterial desaturation cannot be determined via contrast-enhanced echocardiography.<sup>12</sup> To overcome the disadvantages of contrast-enhanced echocardiography, technetium-99m macroaggregated albumin lung-perfusion scintigraphy is used to diagnose hepatopulmonary syndrome.

The pathogenesis of hepatopulmonary syndrome remains unknown. All patients with hepatopulmonary syndrome have intrapulmonary vascular dilatations, which can result from failure of the diseased liver to clear circulating pulmonary vasodilating substances, the formation of a vasodilator by the liver, or possibly inhibition of a vasoconstrictive substance by the liver.<sup>2</sup> Most likely, decreased hepatic clearance of various vasodilatory substances (in-

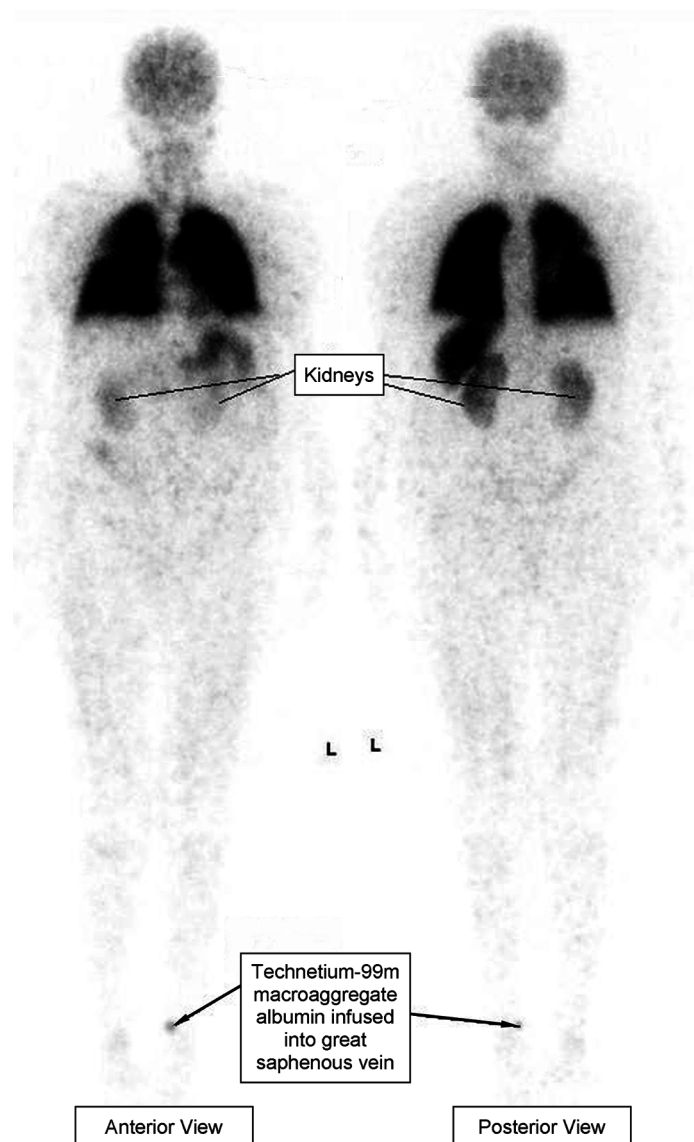


Fig. 1. Scintigraphy shows the uptake of technetium-99m macroaggregated albumin in the brain, lungs, and kidneys.

cluding vasoactive intestinal peptide and other substances synthesized by intestinal bacteria) results in widespread dilatation.<sup>4</sup>

Our patient tolerated her severe hypoxemia well. Possible mechanisms for her tolerance include the secondary polycythemia, the hyperdynamic syndrome in hepatopulmonary syndrome (increased heart rate, cardiac output, and plasma volume, and reduced systemic vascular resistance and arterial blood pressure), and tissue adaptation over time.<sup>2,7</sup> In addition, long-term exposure to normobaric hypoxia decreases oxygen sensitivity of peripheral chemoreceptors, resulting in less frequent and lower-amplitude afferent signals to the sensory cortex.<sup>13,14</sup>

The European Respiratory Society Task Force<sup>8</sup> proposed a classification system that uses  $P_{aO_2}$  to stage the severity

of hepatopulmonary syndrome (Table 1). Staging the severity of hepatopulmonary syndrome is important for predicting survival and determining the timing and risks of orthotopic liver transplantation.<sup>15</sup> However, as mentioned above, there is no relationship between severity or presence of hepatopulmonary syndrome and severity of liver disease.<sup>3</sup> An earlier literature review found that mortality was 30% within 3 months in patients with pre-transplantation  $P_{aO_2} \leq 50$  mm Hg.<sup>3</sup> Because liver transplantation remains the only established effective therapy for hepatopulmonary syndrome, based on the total resolution or substantial postoperative improvement in gas exchange in  $> 85\%$  of reported patients,<sup>3</sup> screening for hepatopulmonary syndrome is suggested in (asymptomatic) patients with signs of or established liver cirrhosis.

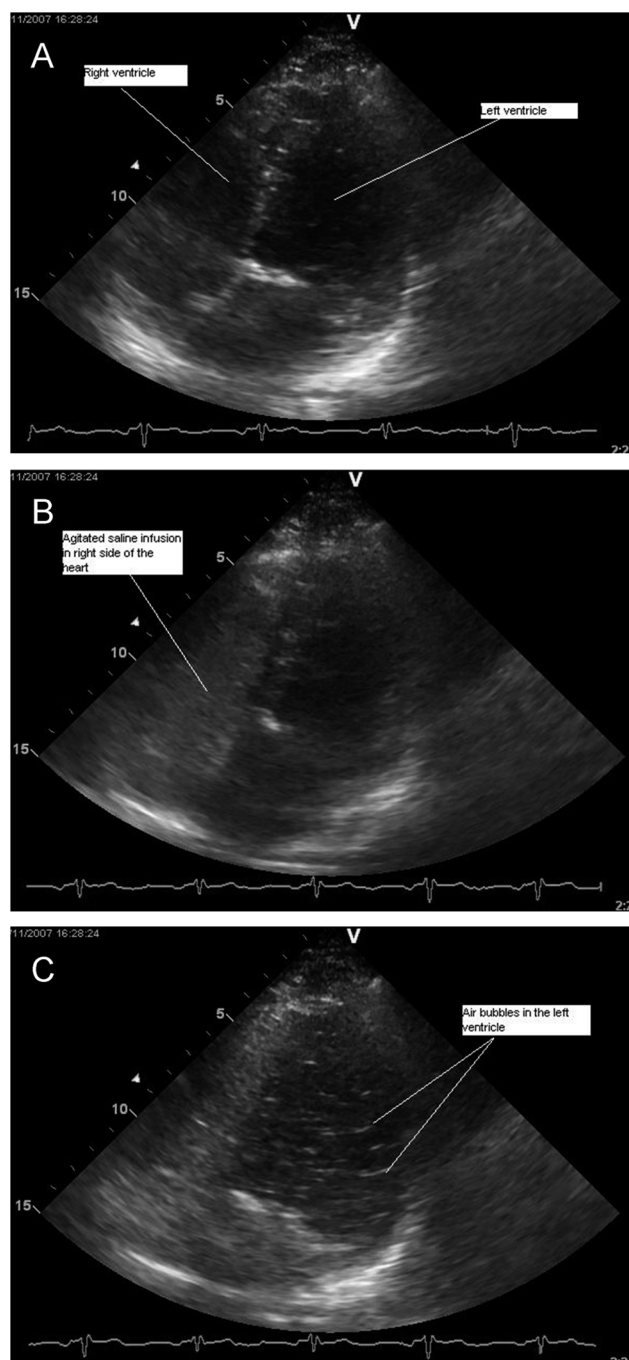


Fig. 2. Contrast-enhanced transthoracic echocardiography with agitated saline. A: Reference 4-chamber view of the heart. B: Right-side shows bubbles in agitated saline infused via the left brachial vein. C: Bubbles in agitated saline in the left heart after 6 cardiac cycles.

Our patient had severe arterial hypoxemia without symptoms due to hepatopulmonary syndrome in the presence of liver cirrhosis. Possible mechanisms for her tolerance of the severe hypoxemia include the secondary polycythemia, the hyperdynamic syndrome, tissue adaptation over

Table 1. European Respiratory Society Task Force Classification System for Hepatopulmonary Syndrome

Severity	P <sub>aO<sub>2</sub></sub> (mm Hg)
Mild	60–80
Moderate	50–60
Severe	<50

time, and decreased oxygen sensitivity of peripheral chemoreceptors. Because severe hypoxemia is correlated to high mortality in pretransplantation patients, screening is suggested for hepatopulmonary syndrome.

Hepatopulmonary syndrome is characterized by a defect in oxygenation, induced by pulmonary vascular dilatation, most frequently complicating liver cirrhosis, and consists of a triad of hepatic dysfunction, hypoxemia, and extreme vasodilatation. Hallmark in the diagnosis is intrapulmonary shunt. Our patient had established liver cirrhosis, hypoxemia (P<sub>aO<sub>2</sub></sub> 51 mm Hg on room air), polycythemia due to persistent high erythropoietin (34.7 mU/mL), and lack of oxygen therapy.

Diagnosis of hepatopulmonary syndrome was made via contrast-enhanced echocardiography and technetium-99m macroaggregated albumin scintigraphy. Our patient refused oxygen therapy because of lack of benefit and the absence of symptoms. She was not evaluated for orthotopic liver transplantation because of her refusal of an operation and because she was more than 65 years old.

### Teaching Points

Severe arterial hypoxemia can occur without symptoms in patients with liver cirrhosis. Hypoxemic patients should be screened for hepatopulmonary syndrome because of the risk of mortality in pre-transplantation patients.

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