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CASE REPORT

Hepatopulmonary syndrome – a rare cause of hypoxaemia

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Abstract

A 61-year-old man presented with a dry cough and dyspnoea. On examination, persistent hypoxaemia without clinical signs of respiratory distress was observed. After the most common causes of hypoxaemia were ruled out, hepatopulmonary syndrome was suspected because of his medical history of liver cirrhosis. Further diagnostic testing including serial arterial blood gas analysis and contrast enhanced transthoracic echocardiography supported the diagnosis. As liver transplantation is currently the only available curative treatment, the patient was referred to a transplantation centre. Hepatopulmonary syndrome is a rare but severe pulmonary complication of several liver diseases, characterised by arterial deoxygenation and intrapulmonary vascular dilatation. When left untreated it has a high mortality rate. Early recognition may increase survival and lower perioperative transplantation risks. Therefore, when encountering a case of unexplained hypoxaemia in a patient with liver disease, the possibility of hepatopulmonary syndrome should be considered.

Introduction

Hepatopulmonary syndrome (HPS) is a rare but severe pulmonary complication of several liver diseases. It is characterised by the triad of liver disease, arterial deoxygenation and intrapulmonary vascular dilatation (IPVD). The prevalence of HPS in patients with liver disease varies from 4-32%.[1] This depends on the population studied and the diagnostic criteria and methods used. Most patients present with dyspnoea, a non-specific finding which may not be directly recognised as HPS.[2,3] HPS is related to the severity of the underlying liver disease and most commonly observed in liver disease caused by hepatitis B, C or the abuse of alcohol. Child-Pugh and MELD scores are higher in patients with HPS and these scores are associated with increased mortality.[4] In addition, mortality is increased in patients with HPS compared with patients without HPS who have a similar severity of liver disease.[3] Median survival is estimated at 24 months in patients with chronic liver disease and HPS compared with 87 months in patients without HPS. Five-year survival is 23% versus 63% in patients without HPS[2,5] Currently, liver transplantation is the only curative therapy available. Since HPS is reversible or partially reversible after liver transplantation and has a high mortality rate when left untreated, patients diagnosed with HPS are granted high priority on the transplant waiting list regardless of the MELD score. Concurrent with increasing severity of the HPS, the perioperative risks of liver transplantation increase and reversibility decreases.[2,3,6] We present a case and briefly review the pathogenesis, diagnostic considerations and treatment options of HPS based on the currently available evidence.

Case report

A 61-year-old man was admitted to the surgical ward for total hip replacement surgery because of femoral head avascular necrosis. His medical history revealed liver cirrhosis (Child-Pugh B) with refractory ascites in 2011, which was treated with the placement of a transjugular intrahepatic portosystemic shunt (TIPS). Recently, he had also been admitted to the pulmonary ward because of dyspnoea and profound hypoxaemia (pO_2 6.2 kPa and SpO_2 82% without oxygen suppletion). At that time pneumonia and/or an acute exacerbation of COPD seemed most likely. He was treated with antibiotics and supplemental oxygen and quickly recovered. During hospital admission no fever was observed, inflammatory laboratory parameters remained low, and sputum and blood cultures showed no bacterial growth. However, when oxygen suppletion was decreased the hypoxaemia recurred (SpO_2 75-85%). Pulmonary embolism was ruled out by a CT pulmonary angiogram. Because the patient had clinically recovered, despite the severe hypoxaemia, he was discharged home with planned outpatient follow-up.

Before surgery, the oxygen levels fluctuated between 88-94%. During surgery, an oxygen level of 80% was observed without

Table 1. Arterial blood gas (ABG) analysis indicating orthodeoxia

	ABG in outpatient clinic (without supplemental O_2)	ABG lying down (10 litres O_2/min)	ABG sitting upright (10 litres O_2/min)
pH	7.46	7.38	7.42
pCO2 (kPa)	4.0	5.3	4.6
pO2 (kPa)	6.2	8.7	7.4
HCO3 (mmol/l)	21.3	23.3	22.3
SaO2 (%)	82	92	88

clinical signs of respiratory distress. The patient was admitted to the intensive care unit because of persistent hypoxaemia. CT pulmonary angiogram ruled out emboli; there were no signs of pleural fluid or pulmonary consolidation. However, the radiologist observed large crinkled pulmonary vessels and suspected pulmonary hypertension. On additional echocardiography low pulmonary artery pressure was found.

At that time, the combination of persistent hypoxaemia without clinical signs of respiratory distress, the dilated pulmonary vessels, the medical history of liver cirrhosis and the fact that most common pulmonary causes of hypoxaemia had been ruled out, led to the suspicion of hepatopulmonary syndrome.

Diagnostic testing was performed by serial arterial blood gas analysis in supine and upright position. Saturation and blood oxygen levels were higher in supine position compared with upright position indicating orthodeoxia, which supports the diagnosis of hepatopulmonary syndrome *(table 1)*. Contrast enhanced transthoracic echocardiography revealed a right to left shunt of microbubbles appearing within 3-6 heart beats. This finding suggests intrapulmonary vascular dilatation and is pathognomonic of hepatopulmonary syndrome.

A hepatologist in an academic medical centre was consulted and advised screening for liver transplantation. The patient was transferred to a liver transplantation centre. Unfortunately, the work-up showed incurable renal cell carcinoma, and therefore liver transplantation was no longer an option.

Discussion

Pathophysiology

In hepatopulmonary syndrome (HPS), there is dilatation of the pulmonary precapillary and capillary vessels (8-15 µm to 15-160 µm), especially in the lower lobes. Due to this intrapulmonary vasodilatation, arterial deoxygenation occurs by three mechanisms: ventilation-perfusion mismatch, limitation of oxygen diffusion and intrapulmonary shunting.[3,7]

The pathophysiology of the dilatation has not been completely elucidated. Nitric oxide (NO) has been linked to the dilatation because increased NO levels were seen in cirrhotic patients with HPS and NO levels normalised after liver transplantation. Animal studies showed an increase of pulmonary endothelin-B receptors due to shear stress caused by cirrhosis and portal hypertension. Liver injury stimulates release of endothelin-1. Endothelin-1 binds to these receptors stimulating NO synthase, leading to an increased production of NO. In addition, increased phagocytosis of bacterial endotoxin in the lung also promotes the activation of NO synthase. Activated intravascular macrophages also produce haeme oxygenase leading to increased carbon monoxide which also enhances vasodilatation.[2,3,8,9]

Dilatation leads to increased pulmonary blood flow while ventilation remains unchanged, which causes elevated ventilation-perfusion mismatch and arteriovenous shunts. Due to dilatation, the distance for oxygen molecules to traverse to bind haemoglobin is increased. This results in red blood cells exiting the pulmonary capillaries before full oxygenation.[3,5,9,10] Another contributing factor is the hyperdynamic circulation present in patients with cirrhosis. This causes a decrease in transit time of erythrocytes through the alveolar-capillary unit, further compromising oxygen diffusion.[7,9] In addition, the hypoxaemia worsens as a result of the vasoconstrictive response of the blood vessels to hypoxaemia, especially in the lower zones of the lungs where there is less ventilation.[3,10] Finally, patients may have true anatomic arteriovenous shunts, which allow blood to completely bypass alveoli, resulting in a mixture of pulmonary arterial and venous blood, leading to hypoxaemia.[2,3]

There is evidence that not only pulmonary dilatation but also pulmonary angiogenesis causes impaired gas exchange in HPS. In patients with liver cirrhosis, dissemination of gut bacteria through the body takes place due to disruption of gut mucosal barriers and impaired host defence.[11] Angiogenesis may result from accumulation of pulmonary intravascular monocytes due to bacterial translocation, which causes activation of vascular endothelial growth factor contributing to angiogenesis.[2,3]

Clinical symptoms

Platypnoea - an increase in dyspnoea while upright and relief while supine - and orthodeoxia - hypoxaemia exacerbated in the upright position - are characteristic for HPS, although not pathognomonic. Patients can present a variety of other aspecific symptoms. Symptoms concurrent with chronic liver disease may be observed including anorexia, ascites, hepatomegaly, splenomegaly, icterus, clubbing, caput medusa, generalised oedema and asterixis (flapping tremor). Spider naevi are a marker of IPVD and are due to a direct connection between the arterial and venous system.[4,5,8,10]

Diagnosis

There are three diagnostic criteria: liver disease, arterial deoxygenation and IPVD.

In most patients, the diagnosis of liver disease is already established. As diagnostic testing for a variety of liver diseases is beyond the scope of this report, we will not further address it. Arterial deoxygenation can be diagnosed by arterial blood gas analysis. Since orthodeoxia is typically seen in patients with HPS,

serial blood gas analysis with the patient lying down then sitting upright is preferred. Orthodeoxia is defined as a decrease in SaO_2 of ≥4 mmHg or ≥5% from the supine to the upright position. It is a consequence of the increased ventilation-perfusion mismatch and decreased cardiac output when changing from the supine to the upright position and therefore not exclusively seen in HPS. It may also occur in patients with other causes of intrapulmonary shunting and/or ventilation-perfusion mismatch or patients with intracardiac shunting.[7,12]

Furthermore, the severity of HPS is graded based on the PaO_2 in arterial blood gas analysis. This should be drawn with the patient sitting upright at rest on room air. In HPS there is an elevated age-corrected alveolar-arterial (A-a) oxygen gradient ≥15 mmHg (2 kPa) and a PaO_2 of <80 mmHg (10.7 kPa) *(table 2)*.[5,10,13]

Table 2. Grading system for disease severity

Degree of severity	PaO_2
Mild	Partial pressure of oxygen ≥80 mmHg
Moderate	Partial pressure of oxygen ≥60 to <80 mmHg
Severe	Partial pressure of oxygen ≥50 to <60 mmHg
Very severe	Partial pressure of oxygen <50 mmHg <300 mmHg while breathing 100% oxygen

The most sensitive and commonly used test to detect IPVD is contrast-enhanced transthoracic echocardiography.[9,13] It is performed by injecting agitated saline, a mixture of 9 ml physiological saline (NaCl 0.9%) and 1 ml air, creating microbubbles. These microbubbles enter the right atrium, then the right ventricle and pulmonary branches. Under normal circumstances the microbubbles do not cross the pulmonary vascular bed and will not enter the left atrium due to their large size. In case of HPS, microbubbles can cross the pulmonary vascular bed due to intrapulmonary vascular dilatation. For correct diagnosis the number of heart beats has to be counted. When microbubbles are in the left atrium within three cardiac cycles, an intracardiac shunt has to be considered. In case of an intrapulmonary shunt like IPVD, it takes three to six cardiac cycles for microbubbles to enter the left atrium *(video 1)*.[2,7,13,14] Other tests include chest radiographs, lung function tests, high resolution computed tomography (HR-CT), technetium scan and pulmonary angiography. Chest radiographs can show nonspecific bibasilar interstitial changes, but are mostly normal. Lung function tests demonstrate a normal spirometry and lung volumes, but a reduced carbon monoxide diffusion capacity. However, this is not specific for HPS.[8,13] HR-CT may show dilated peripheral pulmonary vessels and an increased pulmonary artery to bronchus ratio, two characteristic findings of IPVD *(figure 1)*.[13,15] This ratio is defined as the diameter of a pulmonary artery divided by the diameter of its accompanying bronchus. It is usually taken as being around 1:1.[16] In technetium-macroaggregated albumin perfusion lung scanning, aggregated albumin particles are injected intravenously. Ordinarily, these particles are trapped in the pulmonary microvasculature. In HPS patients, a fraction passes through due to IPVD and gets trapped in capillary beds in organs such as the brain, kidneys, liver and spleen. This allows the calculation of the shunt fraction, although this scan cannot differentiate intracardiac from intrapulmonary shunting.[2,8,13] Pulmonary angiography is an invasive test and not routinely performed. Based on angiographic patterns, HPS can be classified into two types. Type 1 manifests as an increase in the number of visible vessels with minimal to extensive vascular dilatation. Type 2 demonstrates anatomic arteriovenous communications.[2,13]

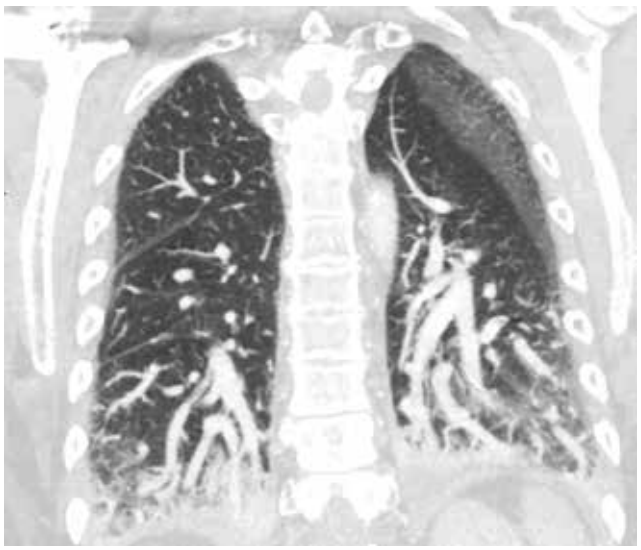

Figure 1. CT pulmonary angiogram of our patient

Treatment

Long-term oxygen therapy is the most recommended therapy in patients with severe or very severe HPS to improve features related to intrapulmonary vascular shunts. In the medical therapeutic options investigated only pentoxifylline and methylene blue have shown some possible benefit, although no clear scientific evidence is available and no randomised trials have been performed.[2,7,8,13] In early case reports it was suggested that the use of a transjugular intrahepatic portosystemic shunt (TIPS), to reduce portal hypertension and improve oxygenation, was associated with a better clinical outcome. However, randomised controlled trials are lacking and more recent case reports suggest that improved oxygenation after TIPS causes a hyperdynamic circulation which may worsen HPS.[7] Liver transplantation is currently the only known effective therapy for HPS and should be considered in patients with severe to very severe hypoxaemia (PaO_2 <60 mmHg).[2,7,8,13] Due to their high pre- and post-transplantation mortality, patients with HPS are prioritised on the transplant waiting list regardless of the MELD score leading to a pre-transplantation mortality rate of 8.8%.[6-8]

Perioperative risks and management

During liver transplantation, it can be challenging to maintain satisfactory oxygen levels, although patients usually respond to 100% inspired oxygen.[17,18] Studies suggest monitoring mixed venous oxygen levels for guidance in the need of initiating venovenous bypass (when SvO_2 falls below 65%).[17,18] Supine positioning, and if necessary, Trendelenburg positioning can increase oxygenation. A study comparing the method of anaesthesia (inhalation versus intravenous) showed no differences in oxygenation 30 minutes after induction.[17]

Postoperative ICU management

Severe post-transplant hypoxaemia is seen in 6-21% of patients. This is defined as a need for 100% inspired oxygen, with PEEP ≥10 mmHg to maintain oxygen levels >85%. This complication has a mortality risk of 45%.[19] Arterial oxygenation is expected to worsen in the hours immediately post-transplant.[17,18] This is due to the abrupt postoperative reversal of pulmonary vasodilatation leading to pulmonary vasoconstriction increasing the ventilation/perfusion mismatch.[17,18] Furthermore, narcotics, sedatives, volume overload and atelectasis may contribute to postoperative hypoxaemia.[17,18] Nayyar et al. proposed an algorithm for the management of severe post-transplant hypoxaemia in HPS based on the available literature. The algorithm recommended therapies including Trendelenburg position, inhaled epoprostenol or nitric oxide, methylene blue, embolisation of abnormal pulmonary vessels and extracorporeal life support.[19]

Prognosis

Improvement of arterial deoxygenation and intrapulmonary vascular dilatation occurs almost universally post-transplant. In >85% of patients liver transplantation results in complete resolution of HPS or significant improvement in gas exchange within the first 6-12 months post-transplant.[7] The 5-year survival rate of patients with HPS after liver transplantation is 76%, which is comparable with cirrhotic patients without HPS undergoing liver transplantation.[6,8]

Conclusion

Hepatopulmonary syndrome is a rare but severe pulmonary complication of several liver diseases in which platypnoea and orthodeoxia are seen. Diagnostic criteria include arterial deoxygenation and intrapulmonary vascular dilatation for which contrast-enhanced transthoracic echocardiography is commonly used to detect dilatation. Liver transplantation is currently the only available curative treatment.

Disclosures

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Video file 1: Contrast-enhanced transthoracic echocardiography (apical four chamber view): microbubbles entering the left atrium within three to six cardiac cycles after entering the right atrium.

https://www.njcc.nl/njcc-d-17-00050-lamers