Shortness of breath due to portopulmonary hypertension and hepatopulmonary syndrome: diagnostic challenges and complex management approach in frail patients

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A 60-year-old woman with a background of frailty, non-alcoholic fatty liver disease (NAFLD), cirrhosis and type 2 diabetes mellitus (T2DM), presented with worsening shortness of breath and a drop in oxygen saturation on sitting and standing up. Her chest X-ray demonstrated evidence of upper lobe venous diversion. Given the hypoxia, she had a computed tomography pulmonary angiography (CTPA) to rule out a pulmonary embolism. The only finding from the CTPA was pulmonary hypertension in the absence of any clots in the lungs. An ultrasound of the abdomen confirmed portal hypertension with splenomegaly and a cirrhotic liver, therefore, an initial diagnosis of portopulmonary hypertension and hepatopulmonary syndrome was made.

The patient declined an agitated saline contrast echocardiography. Based on frailty she was not deemed to be a suitable candidate for a liver transplant and was discharged with a package of care alongside home oxygen therapy with periodic review in the gastroenterology clinic. She was assessed as stable with no new concerns while on home oxygen and diuretics.

This case highlights challenges in diagnosing and managing patients with cirrhosis, portopulmonary hypertension and hepatopulmonary syndrome with a background of complex comorbidities and frailty.

KEYWORDS: shortness of breath, portopulmonary hypertension, hepatopulmonary syndrome, cirrhosis, non-alcoholic fatty liver disease

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Introduction

Out of all of the ‘999’ (emergency) calls to the ambulance service (in the UK), about 8% are due to an acute shortness of breath. It remains the third most common type of emergency call. It stems from a wide range of aetiologies, the most serious being a patient who has a pneumothorax (air in the pleural cavities) or pulmonary emboli (clot in the pulmonary arteries or its tributaries). The drop in the oxygen saturation, with an increased respiratory rate and effort demands urgent assessment and investigation followed by prompt management as these conditions are potentially reversible in many situations.

Hepatopulmonary syndrome (HPS) is a relatively less common condition that affects patients with advanced and chronic liver disease. Classically, patients suffer with worsening shortness of breath in an upright position known as platypnoea, together with a drop in oxygen saturation known as orthodeoxia. The cause for the drop in oxygen levels is thought to be due to microscopic intrapulmonary venous dilatations (IPVD) of blood vessels in the lungs. Hence, HPS is defined by a triad of decreased arterial oxygenation, IPVD and portal hypertension on the background of chronic liver disease.

The cause of IPVD is thought to be multifactorial and may relate to increased production with or without decreased clearance of vasodilators. Increased bacterial translocation and toxin release from portal hypertension with release of vasodilator mediators (like nitrous oxide (NO) and tumour necrosis factor-alpha (TNF-alpha)) result in pulmonary vasodilatation and angiogenesis along with a failure to clear circulating pulmonary vasodilators resulting in ventilation-perfusion mismatch and an associated increased arterial–alveolar (A-a) gradient. Furthermore, high-output cardiac failure with reduced capillary exposure time for red blood cells results in significant hypoxaemia on sitting or standing.

Portopulmonary hypertension (POPH) refers to portal hypertension in association with pulmonary hypertension. Contrary to HPS, it is the imbalance between the vasoconstrictors and vasodilators, with overall dominant humoral vasoconstrictor effect in the lung while the dilator effect dominates the systemic circulation with associated symptoms of breathlessness.

Endogenous prostacyclin (vasodilator) imbalance versus thromboxane (vasoconstrictor from Kupffer cells) and nitrous oxide (NO) vasodilator versus vasoconstrictor endothelin-1 (ET-1) have all been implicated in the pathophysiology, bypassing liver metabolism and portal circulation as a consequence of portal hypertension causing portal-systemic shunting. Accumulation of serotonin that is not metabolised by the liver has been suggested to be associated with smooth muscle hypertrophy and hyperplasia causing pulmonary vascular wall thickening leading to
increased pulmonary arterial pressure resulting in increased right-sided heart failure.\textsuperscript{11}

**Case report**

A 60-year-old woman with multiple comorbidities presented to the emergency department with worsening shortness of breath, tiredness and fatigue. She had a background of non-alcoholic fatty liver disease (NAFLD), cirrhosis, type 2 diabetes mellitus (T2DM), atrial fibrillation, ischaemic heart disease, asthma, hypertension, stable mild cerebrovascular accident, hypertension, chronic kidney disease, possible undiagnosed chronic obstructive pulmonary disease (COPD; 30-pack-year history) and severe frailty (Rockwood–Dalhousie frailty score 6). She lived at home with her family, mostly housebound, and required a chair lift to go to the bedroom upstairs. On examination, she was found to have bilateral pitting pedal oedema extending to the mid-thigh. Her oxygen saturation was 92\% on air when lying down which dropped to 83\% on air when sat upright or trying to mobilise, and was accompanied with an increase in the respiratory rate.

Cardiology examination revealed an ejection systolic murmur in the aortic area, radiating to the carotids (suggesting aortic stenosis), a split-second heart sound with a loud second heart sound in the pulmonary area (suggesting pulmonary hypertension) and jugular venous extension along the sternal angle. Her abdominal examination revealed hepatomegaly with an irregular margin, and a palpable spleen with shifting dullness. Her chest X-ray showed upper lobe venous diversion, compatible with congestive cardiac failure (CCF; Fig 1).

The blood infection markers, cardiac markers (serial troponins), iron studies and urine dipstick were all within normal ranges while her calculated Child–Pugh score was class ‘C’ (Table 1). She was started on high-flow oxygen (4 L/min) and a furosemide intravenous infusion of 200 mg per 24 hours. Her spironolactone dose was increased from 100 mg to 200 mg orally once a day (OD). Her blood glucose levels were monitored and managed using a variable rate insulin infusion. Her D-dimer assay was 2.57 μg/mL FEU (0–0.5) and her calculated Wells score was 9.0 (high-risk group 40.6\% chance of pulmonary embolism (PE) in an ED population). Computed tomography pulmonary angiography (CTPA) was requested to rule out PE as a cause of shortness of breath in the absence of consolidation on chest X-ray and normal infection markers. Although it did not show evidence of a PE, imaging confirmed pulmonary hypertension, with increased

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diameter of the pulmonary outflow tract compared with the aortic outflow tract (Fig 2).

The patient had an abdominal ultrasound that demonstrated a bulky liver with an irregular outline and diffusely heterogenous coarsened echotexture throughout, with splenomegaly of 130 mm (Fig 3). A CT of the abdomen confirmed cirrhosis with splenomegaly and ascites consistent with portal hypertension.

The patient underwent echocardiography to assess her ejection fraction and rule out any cardiac abnormality that may be contributing to her symptoms based on the cardiomegaly and upper lobe venous diversion seen on her X-ray. The operator noticed difficulty in visualising the right-sided heart function (Fig 4).

A request was made to complete an agitated saline contrast echocardiography aiming to use intravenous microbubbles of a size more than 10 μm in diameter, which normally should be obstructed by pulmonary capillaries if the size is more than 8 μm. However, initially the investigation had to be rebooked due to poor cannulation and, later, the patient declined further testing and requested a conservative approach. A diagnosis of POPH along with hepatopulmonary syndrome was made on a background of cirrhosis related to a long history of NAFLD. The patient was switched to oral furosemide 40 mg twice a day, spironolactone dose was tapered down to 100 mg OD and oxygen at 2–4 L/min. She had short trial of sildenafil 25 mg orally OD, but that did not improve her symptoms.

Her case was discussed in the multidisciplinary team meeting with representation from the gastroenterology, respiratory, cardiology and endocrinology teams. Based on her multiple comorbidities, frailty and calculated Child–Pugh score of class C, she was not a suitable candidate for liver transplantation and was discharged home with a package of care and home oxygen, with regular 6-monthly gastroenterology clinic follow-up. Three years post-discharge, she remained stable with no new concerns, continuing with home oxygen and diuretics with an improvement in her calculated Child–Pugh score to class A (Table 1). Her bloods tests, including kidney function tests are monitored by her general practitioner on a monthly basis.

Fig 2. Computed tomography of the chest showing pulmonary outflow tract diameter of 29.6 mm (blue arrow) compared with a smaller aortic root diameter of 26 mm (red arrow), suggestive of probable pulmonary hypertension.

Discussion
HPS consists of liver dysfunction on a background of chronic liver disease, hypoxaemia and IPVD. Contrast-enhanced echocardiography using agitated saline is the gold standard technique for the diagnosis of HPS. Usually, agitated saline...
produces microbubbles that are too large (more than 8 μm) to cross pulmonary capillaries and, therefore, normally confined to the right side of the heart. In HPS, the microbubbles pass through the pulmonary circulation as a consequence of a dilated vascular bed and can be visualised in the left atrium following three to six cardiac cycles. Other conditions where the microbubbles pass through to the left side of heart are intracardiac shunts, however, the transfer occurs earlier within the first and third heartbeat.  

Flückiger first mentioned a patient with cirrhosis and cyanosis in 1884 but Kennedy and Knudson first coined the term ‘HPS’ in 1977. Krowka et al later described HPS as we know it today. Previously, HPS was considered a contraindication to liver transplantation. However, Krowka et al challenged this, as they observed a post-liver transplantation survival rate of 70%, and demonstrated transplantation led to reversal in hypoxaemia. This outcome, combined with the lack of effective medical treatment enabled HPS to become an indication for liver transplantation. Four degrees of severity have been described, based on levels of hypoxaemia (Table 2).  

Various investigations are utilised towards diagnosing HPS. Pulse oximetry remains the cheapest and most rapid way to assess arterial oxygenation saturation. Arguedas et al published a prospective cohort study with a group of 127 patients listed for liver transplant evaluation comparing pulse oximetry versus contrast echocardiography in detection of HPS, which found pulse oximetry revealed 100% sensitivity and 88% specificity in detecting levels of hypoxaemia lower than 60 mmHg (7.99 kPa). Additionally, they showed a pulse oximetry value of less than or equal to 94% detected all patients with a partial pressure of oxygen <60 mmHg (7.99 kPa) with an increased specificity of 93%. Lastly, they have shown higher pulse oximetry thresholds reliably identified HPS patients with less severe hypoxaemia, although with a lower specificity.  

Chest X-ray may demonstrate interstitial markings, which was more commonly seen in patients with HPS. Single photon emission computed tomography (SPECT) combined with computed tomography (CT), known as SPECT-CT, has been used in two HPS patients in the past for the location of IPVD. Other investigations used to aid diagnostic evaluation include pulmonary arteriography and lung function tests. The technetium macroaggregated albumin scan (99mTc-MAA) is yet another mode of detecting the presence of IPVD using tagged albumin detection at extrapulmonary sites. Fukushima et al have published two case studies that remain the only previous data suggesting improvement in Child–Pugh score from C to A and improvement of liver function tests after 1 year of being on home oxygen therapy. POPH is now recognised as one of the leading causes of pulmonary arterial hypertension. It may occur with or without chronic liver disease, however, prognosis remains poor. Medical treatment (including vasodilators, diuretics and liver transplant) have been proposed as appropriate modes of management. For patients awaiting liver transplant or unsuitable for transplantation, long-term oxygen therapy remains the cornerstone of the management.  

Child and Turcotte published scoring criteria for potential patients for portosystemic shunt surgery in 1964. The variables included serum levels of bilirubin and albumin, degree of ascites, encephalopathy, and nutritional status of patients. This prognosis stratification was classified as class A (best), B (moderate) or C (worst). Pugh et al modified this to replace nutrition status with prothrombin time and used it towards assessing patients undergoing surgical treatment for oesophageal varices in 1973. Over time, it was used also to assess outcome of surgery in general and for stratification of patients on the waiting list for liver transplant. It is also empirically now used to assess and stratify patients with chronic liver disease in day-to-day clinic and ward settings with overall 1- and 2-year prognosis (Table 3).  

We report a patient, who remained stable after 3 years of diagnosis of combined hepatopulmonary syndrome and POPH on a background of NAFLD and cirrhosis. She was previously
Although liver transplantation is now considered in patients presenting with both HPS and POPH, long-term oxygen therapy may have a significant role in improving patient quality of life and morbidity in frail patients with multiple comorbidities. It would be interesting to see more case reports on this topic as further case studies may shed light on whether a conservative approach is associated with safer outcomes over 5 and 10 years.

Key points

- Although liver transplantation is now considered in patients presenting with both HPS and POPH, long-term oxygen therapy may have a significant role in improving patient quality of life and morbidity in frail patients with multiple comorbidities.
- Pulse oximetry remains the cheapest and most rapid way to reliably assess arterial oxygenation saturation in patients with HPS and portopulmonary syndrome.

References


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