Hepatopulmonary syndrome: Clinical perspectives

ASHIS MUKHOPADHYA, GEORGE M. CHANDY

ABSTRACT
Hepatopulmonary syndrome consists of a triad of chronic liver disease, pulmonary gas exchange abnormalities and pulmonary vascular dilatation in the absence of detectable cardiopulmonary disease. Patients usually present with symptoms of liver disease and the clinical recognition of this condition is a challenge. Newer non-invasive tests facilitate the diagnosis. Therapeutic strategies for this condition are still dismal. Liver transplantation is a possible curative option for a subgroup of patients with hepatopulmonary syndrome.

INTRODUCTION
The challenge of managing liver disease includes the management of the myriad effects it has on other organ systems. Pulmonary complications of chronic liver disease are less common but definitely relevant clinically. These are a result of disruption of pulmonary mechanics and the ventilation-perfusion system. Most of these patients do not present with pulmonary complaints, but about 80% present with complaints related to the underlying liver disease. The usual manifestation in the early stages is exertional dyspnoea, but as the disease progresses, tachypnoea, dyspnoea at rest, platypnoea and cyanosis can occur. Diseases that affect both the liver and the lung can also have pulmonary manifestations (Table I). Alcoholics are often smokers and it is not uncommon to find co-existing alcohol-related liver disease and smoking-related lung disease.

In hepatopulmonary syndrome (HPS), liver dysfunction plays no role in determining the severity of the pulmonary disorder. The degree of hypoxaemia does not correlate with worsening laboratory tests such as total bilirubin, serum albumin and prothrombin time. However, HPS seems to be more common in patients with Child's C grade of liver disease. Hepatopulmonary syndrome is defined as a triad of chronic liver disorder, pulmonary gas exchange abnormalities leading to arterial hypoxaemia and widespread pulmonary vascular dilatation. This definition has been partially challenged by the finding of HPS in other conditions such as non-specific hepatitis, non-cirrhotic portal hypertension, portocaval and splenorenal shunts. It is also believed that HPS can occur in patients with pleural effusion or smoking-related lung disease.

PATHOPHYSIOLOGY

Structural changes
Rydell and Hoffbauer were the first to demonstrate numerous postmortem arteriovenous intrapulmonary anastomoses in a young patient with cirrhosis. The degree of hypoxaemia does not correlate with worsening laboratory tests such as total bilirubin, serum albumin and prothrombin time. However, HPS seems to be more common in patients with Child's C grade of liver disease. Hepatopulmonary syndrome is defined as a triad of chronic liver disorder, pulmonary gas exchange abnormalities leading to arterial hypoxaemia and widespread pulmonary vascular dilatation. This definition has been partially challenged by the finding of HPS in other conditions such as non-specific hepatitis, non-cirrhotic portal hypertension, portocaval and splenorenal shunts. It is also believed that HPS can occur in patients with pleural effusion or smoking-related lung disease.

Table I. Pulmonary abnormalities associated with chronic liver disease

<table>
<thead>
<tr>
<th>Pulmonary disease</th>
<th>Pathological manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diseases affecting both lungs and liver</td>
<td>Obstructive airway disease</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Obstructive airway disease</td>
</tr>
<tr>
<td>Alpha 1-antitrypsin deficiency</td>
<td>Intrapulmonary shunting</td>
</tr>
<tr>
<td>Sarcoïdosis</td>
<td>Restrictive lung disease</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Decreased thoracic volumes</td>
</tr>
<tr>
<td>Mechanical effect of ascites and pleural effusion</td>
<td>Decreased diffusing capacity</td>
</tr>
<tr>
<td>Hepatopulmonary syndrome</td>
<td>Restrictive lung disease</td>
</tr>
<tr>
<td>Pulmonary vascular dilatations</td>
<td>Shift in oxyhaemoglobin dissociation curve</td>
</tr>
<tr>
<td>V/Q mismatch</td>
<td>Portopulmonary anastomosis</td>
</tr>
<tr>
<td>Reduced DLco</td>
<td></td>
</tr>
</tbody>
</table>

Primary sclerosing cholangitis
Suppurative bronchiectasis

Drug toxicity

The fact is also borne out by antemortem pulmonary angiography, which often demonstrates spidery dilatation of arteries or, in severe cases, diffuse dilatation of large and small vessels and even discrete arteriovenous communications.

In a small number of patients, the portal venous system anastomoses with both the superior vena caval system and pulmonary venous system through mediastinal, paraoesophageal andazygos vascular channels. It has been postulated that if the pressure gradient between the portal and pulmonary veins exceeds 22 mmHg, portopulmonary shunting would occur.
Clinical pulmonary hypertension is an uncommon complication, occurring in less than 1% of patients with cirrhosis who have portal hypertension. A majority of patients with cirrhosis have low or normal pulmonary vascular resistance and pulmonary artery pressure. Thus, this entity is of no consequence in HPS.

Summarizing the findings from various studies one can surmise that significant structural disorganization exists in HPS, which allows admixture of mixed venous blood, rapidly or directly, with the pulmonary venous blood. This jeopardizes adequate oxygenation of the pulmonary arterial blood and results in hypoxaemia.

Physiological changes
The structural defects seen in HPS lead to arterial hypoxaemia. However, various physiological mechanisms have also been postulated to explain this finding: changes in the affinity of oxyhaemoglobin; alveolar capillary diffusion limitations for oxygen; ventilation–perfusion (V/Q) inequalities and intrapulmonary shunts.

Affinity of oxyhaemoglobin. In 1938, Keys and Snell found a consistent shift of the oxyhaemoglobin dissociation curve to the right in cirrhotic patients. The decreased affinity of haemoglobin for oxygen appears to be related to an increased concentration of 2,3-diphosphoglycerate within the red blood cell. However, the contribution of this shift is minimal when compared with the degree of hypoxaemia that is commonly seen.

Impaired alveolar capillary diffusion. A common finding seen in patients with HPS, and confirmed by a reduced carbon monoxide diffusion capacity (DL\textsubscript{CO}), is that of impaired alveolar capillary diffusion of gases. The postulated causes are a high cardiac output and pulmonary vasodilatation. In patients with a high cardiac output, the transit time across the pulmonary gas exchanging units is short. This limits effective oxygenation. With dilated capillaries, the oxygenation is inadequate in the centre of these vessels as the distance is increased.

\[ V/Q \text{ mismatch} \]

The effect of V/Q relationship on pulmonary gas exchange has been studied using the multiple inert gas elimination technique. One of the main causes of arterial hypoxaemia in cirrhotics is a V/Q mismatch. Pulmonary vasodilatation in patients with liver disease leads to hypoxaemia as this results in increased perfusion of lung units with low V/Q ratios.

Due to hydrostatic effects, this mismatch tends to occur more frequently in the lung bases and leads to orthodeoxia. Pulmonary vasodilatation results in increased basilar blood flow. As the lung bases have more true intrapulmonary shunts, more shunting occurs in the upright position, resulting in more hypoxaemia. As the disease progresses, the number of true intrapulmonary shunts, that is, the units which are perfused but not ventilated (V/Q=0), increases. The difference between true shunts and a V/Q mismatch can be judged by the response to 100% oxygen by the multiple inert gas elimination technique.

Krowka and Cortese used the presence of true intrapulmonary shunts to classify HPS: Type 1 as those without shunts and Type 2 as those with shunts. This classification is clinically relevant when assessing the outcome of liver transplantation. It has been shown that hypoxaemia reverts to normal in patients with Type 1 HPS, whereas it may persist for months in those with Type 2.

PATHOGENESIS

The key events preceding HPS are worsening liver function and the development of portal hypertension. Both these events result in widespread vasodilatation. The pathogenesis is summarized in Fig. 1.

The exact cause of vascular and pulmonary vascular disturbance has not been elucidated. It could be related to the inability of the liver to metabolize circulating vasoactive substances, or as a result of such substances bypassing the liver due to the presence of portosystemic anastomoses. Numerous putative vasodilators have been proposed.

Glucagon levels have been found to be elevated in rat models with portal hypertension and portosystemic shunting, but the circulating levels failed to show a relationship with the degree of vasodilatation. No such relationship was seen in patients with HPS. The infusion of somatostatin, an inhibitor of glucagon release, did not affect the gas exchange abnormalities in these patients. Prostacyclin probably contributes to vasodilatation by depressing hypoxia-related pulmonary vasoconstriction.

Nitrous oxide (NO) is a ubiquitous biological agent that has evinced interest as the probable pathogenic agent causing a hyperdynamic circulation in cirrhosis and HPS. NO synthase exists in inducible and constitutive isoforms. Endotoxaemia is a common finding in cirrhotic patients and this can induce NO synthase in peripheral blood vessels or indirectly through cytokine. This is borne out by increased levels of exhaled NO in cirrhotic patients with HPS as compared to those without HPS and control patients. It has also been shown that higher levels of exhaled NO are present in patients with unstable cirrhosis compared to those with stable cirrhosis. The levels of NO are also inversely correlated with the pulmonary vascular resistance. All these findings suggest a significant role of NO in the pathogenesis of HPS.

DIAGNOSIS

Pulmonary tests
The primary complaint of patients with HPS is exertional dyspnoea. In severe cases, they may have resting dyspnoea and platypnoea. Clinical examination of the chest is usually unremarkable. Pulmonary function tests show normal lung volumes except when the condition is complicated by pleural effusion. Diffusion capacity (DL\textsubscript{CO}) can be abnormal and can show resting hypoxaemia as well as an abnormal alveolar–arterial gradient. Orthodeoxia (>10% reduction of PaO\textsubscript{2} on movement from the supine to the standing position) is present in 80%–90% of patients with HPS.

Diagnostic imaging

Contrast echocardiography. This is the simplest method to confirm the diagnosis of HPS. This test involves the formation of microbubbles generated from agitated normal saline or indocyanin green. These bubbles pass through the pulmonary blood vessels
from the right side of the heart through the lung into the left atrium. Most bubbles should be absorbed in the first pass through the pulmonary capillary bed. Delayed detection of microbubbles suggests a pulmonary vascular shunt as opposed to immediate detection of microbubbles in a right-to-left cardiac shunt. Further confirmation can be obtained by transoesophageal echocardiography, which can actually demonstrate the passage of these bubbles through the intrapulmonary shunts.

Technetium99 macroaggregated albumin lung scanning. This method can also be used to detect and quantify the degree of intrapulmonary shunting in HPS. In normal circumstances (in the absence of intrapulmonary shunts) all the lung perfusion scanning material is concentrated in the pulmonary vasculature and does not escape the capillary bed. Due to intrapulmonary shunts the capillary bed is bypassed and deposits can be picked up by nuclear scanning in the brain, kidneys, liver, etc. This not only documents a bypass, it also quantifies the extent to which shunting has occurred.

Pulmonary angiography. This invasive technique should usually be used as a last option. It is important to note that Type I HPS patients may have a normal pulmonary angiogram. Thus, angiography should be restricted to patients with severe hypoxaemia. The characteristic picture comprises spidery dilatation of small branches of the pulmonary artery and arteriovenous shunts. Two distinct patterns have been described on pulmonary angiography—diffuse and discrete. However, a poor response to inhaled 100% oxygen can be seen in both diffuse abnormalities as well as in large discrete lesions.

THERAPEUTIC OPTIONS

Various modalities of treatment have been attempted in HPS. Theoretically, these agents cause widespread pulmonary vasoconstriction and should reverse the pathological changes. Recent studies with almetrine bimesylate, prostaglandin inhibitors and somatostatin analogues have shown these to be of no use. Therapeutic procedures such as embolization of small vessel therapeutic procedures such as embolization of small vessel pulmonary arteries in HPS have shown some promise in improving oxygenation.

Liver transplantation

There has been a sea change in the role of liver transplantation for the treatment of HPS. Initially, HPS was a contraindication for liver transplantation, but the successful improvement of oxygenation in patients with chronic liver disease after transplantation indicates that this may now very well be an indication. This improvement is not always universal. This was exemplified in a recent review of the literature, which had 13 failures after liver transplantation out of a total of 41 cases with HPS. The question that is to be asked now, in the light of the current knowledge, is not whether to do liver transplantation but when to do it.

The lack of controlled studies in this area greatly hampers our knowledge and practice. Krowka et al. recently reviewed 81 paediatric and adult patients with HPS who underwent liver transplantation. The post-transplant mortality was 16% and was correlated with the severity of hypoxaemia. The 69 survivors had a mean (SD) PaO2 of 54.2 (13.2) mmHg while the non-survivors had a mean (SD) PaO2 of 44.7 (7.7) mmHg. Patients with a pretransplant PaO2 <50 mmHg had a higher mortality (30%) compared to those with a PaO2 >50 mmHg (3%). It has been postulated that the severity of hypoxaemia should determine which patients require a liver transplantation.

CONCLUSION

Hepatopulmonary syndrome is a triad of chronic liver disease, pulmonary gas exchange abnormalities and pulmonary vascular dilatation. Its pathophysiology is incompletely understood. The success of liver transplantation in ameliorating symptoms and abnormalities of gas exchange gives an opportunity for understanding this complex syndrome. Managing patients with HPS will continue to be a challenge.

REFERENCES


---

**Attention Subscribers**

The subscriptions for *The National Medical Journal of India* are being serviced from the following address:

The Subscription Department  
*The National Medical Journal of India*  
All India Institute of Medical Sciences  
Ansari Nagar  
New Delhi 110029

The subscription rates of the journal are as follows:

<table>
<thead>
<tr>
<th></th>
<th>One year</th>
<th>Two years</th>
<th>Three years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indian</td>
<td>Rs 500</td>
<td>Rs 900</td>
<td>Rs 1300</td>
</tr>
<tr>
<td>Overseas</td>
<td>$80</td>
<td>$140</td>
<td>$200</td>
</tr>
</tbody>
</table>

**Personal subscriptions paid from personal funds are available at 50% discounted rates.**

Please send all renewals and new subscriptions along with the payment to the above address. Cheques/Demand Draft should be made payable to *The National Medical Journal of India*. Please add Rs 20 for outstation cheques.

If you wish to receive the Journal by registered post, please add Rs 60 per annum to the total payment and make the request at the time of subscribing.