Hepatopulmonary or portopulmonary syndrome?

Interaction between the liver and the lung leading to hypoxia has been long recognized, and was earlier described as “hypoxemia of cirrhosis”. This was later termed as the “hepatopulmonary syndrome” (HPS). The condition is characterized by a triad of liver disease, arterial hypoxemia (PaO₂ <70 mmHg or alveolar-arterial gradient >20 mmHg) and intrapulmonary vascular dilations (IPVD), in the absence of primary cardiopulmonary disease.

In this issue of the Journal, two studies on the prevalence of HPS in patients with cirrhosis or cirrhotic and non cirrhotic portal hypertension have been reported. Sood et al did not find any evidence of HPS in the 50 patients with cirrhosis they studied, whereas Anand’s group reported a prevalence of 17.5% in 63 patients with cirrhosis. A small earlier study from the country had shown a prevalence of 6.7% in patients with cirrhosis. In literature, the prevalence has been reported to vary from 13% to 47%.

Hepatopulmonary syndrome can be associated with any stage of liver disease and the degree of hypoxemia does not seem to correlate with the severity of the liver disease. Anand’s group reported a significant association between Child’s grading and HPS, though no correlation was made with the degree of hypoxemia. Although more prevalent in patients with cirrhosis, HPS has also been reported in association with other liver diseases like the Budd-Chiari syndrome and schistosomiasis.

Further, HPS has been reported in non cirrhotic portal hypertension, suggesting thereby that portal hypertension may play a role in the pathogenesis independent of liver dysfunction. A study from Calcutta mentioned an occurrence of 9.5% in patients with non cirrhotic portal fibrosis, a condition with essentially normal liver function. Anand’s group is the first to systematically study patients with extrahepatic portal vein obstruction (who also have normal liver function), though isolated cases have been reported before. They studied small numbers of patients with this condition and non cirrhotic portal fibrosis, and found HPS to be present in 13.3% and 10% of them, respectively. In the light of this evidence, the criteria for HPS need to be modified to a triad of portal hypertension, hypoxemia and intrapulmonary vascular dilations, and it would be more appropriate to term it the “portopulmonary syndrome”.

The salient structural derangement in HPS is widespread vasodilatation of the pulmonary precapillary and capillary vascular bed (IPVD), and direct arteriovenous communications. Areal hypoxemia can result when venous blood does not experience the complete diffusion of oxygen as it perfuses rapidly through dilated vessels that abut normal alveoli, a diffusion-perfusion defect. In this situation, there is no true shunting of blood (type I). In a small subset of patients, the venous blood bypasses the capillary-alveoli interface via direct arterio-venous channels, and hence does not get oxygenated, an “anatomic shunt” (type II). On inspiration of 100% oxygen, a patient with type I HPS shows a dramatic rise in PaO₂. On the other hand, 100% oxygen has little effect on PaO₂ (rise to <300 mmHg) in a patient with direct arterio-venous communication.

One also needs to rule out non vascular pulmonary abnormalities in this group of patients. For example, a different type of shunt can occur in which the alveoli are completely filled with fluid and are not aerated (as in atelectasis). This is considered to be a physiological shunt and again oxygen cannot reach the venous blood and response to 100% oxygen is very poor.

These vascular disturbances could be related to the failure of metabolism or insufficient production of one or several circulating vasoactive substances by the injured liver. In the rat model of common bile duct ligation, Fallon et al demonstrated a significant increase in endothelial nitric oxide synthase content relative to the sham samples in lung homogenates. While NO may play a pivotal role in the pulmonary hemodynamic abnormalities in patients with cirrhosis, its role in the non cirrhotic patient with HPS needs to be elucidated.

Arterial blood gas analysis is an essential component of the diagnostic triad for HPS. Pulmonary function testing rules out intrinsic lung disease. Chest roentgenogram is invaluable to screen for the presence of pulmonary parenchymal diseases and pleural effusion that may contribute to hypoxemia; however, in patients with HPS, bilateral, medium-sized (1.5-3 mm) nodular or reticulo-nodular opacities is a usual finding. High-resolution CT scan is useful in excluding interstitial fibrosis or emphysema as a cause of these opacities. Contrast-enhanced echocardiogram is a sensitive test for the diagnosis of IPVD in patients with HPS. Though Sood et al reported no IPVD on contrast-enhanced echocardiogram in their 50 patients with cirrhosis, Anand et al reported IPVD in about one third of patients with cirrhosis and non cirrhotic portal hypertension. Only about one third to half the patients with IPVD satisfied the criteria for HPS.

No firm conclusions can be made on the prevalence of IPVD in Indian patients based on these studies. Technetium-tagged macroaggregated albumin lung scanning identifies IPVD and anatomic shunts and offers a reasonable means to quantify the degree of vascular dilations. Pulmonary angiography should be reserved...
for patients with severe hypoxemia and a poor response to inspired 100% oxygen, in whom vascular embolotherapy to obliterate arterio-venous communications may be a therapeutic option.\textsuperscript{15}

Hypoxemia in chronic liver disease is multi-factorial and occurs in one third of these patients.\textsuperscript{16} HPS is only one cause of this hypoxemia. Sood \textit{et al}\textsuperscript{17} found that 7% of patients had arterial hypoxemia (PaO_2 < 70 mmHg) and none had any evidence of cardiopulmonary disease as assessed by clinical examination, chest radiography and echocardiography. The exact cause of hypoxemia in the absence of IPVD could have been further evaluated by lung function tests and study of pulmonary hemodynamics.

Portopulmonary hypertension is an important cause of hypoxemia in patients with advanced liver disease. HPS needs to be differentiated from portopulmonary hypertension which is the result of non embolic pulmonarv vasoconstriction/obliteration. Portopulmonary hypertension is associated with high pulmonary artery pressures and pulmonary vascular resistance and is not reversible with liver transplantation.\textsuperscript{20} Premature airway closure can also result from mechanical compression of the smaller airways by blood vessels engorged because of aygous hypertension. Large blood vessels, basal atelectasis due to tense ascites, pulmonary parenchymal disease in metabolic or immune liver disorders, and cardiac involvement in advanced liver disease also result in hypoxemia without IPVD, and these conditions can be excluded using readily available investigations.\textsuperscript{21}

Interest in HPS has been renewed with the observation that HPS reverses with liver transplantation. In fact, HPS is a considered an indication for liver transplantation in patients with cirrhosis irrespective of severity of the liver disease.\textsuperscript{22} It is now being recommended that liver transplantation be performed early in symptomatic patients with HPS as that low PaO_2 (<50 mmHg) and high brain-to-lung ratios (>30%: normal <5%) on technetium scanning do poorly with liver transplantation.\textsuperscript{23,24} Patients who receive liver transplantation for HPS have a higher incidence of postoperative pulmonary complications and it may take up to 15 months for the HPS to reverse.\textsuperscript{24} Patients with type II HPS have a higher mortality with liver transplantation.\textsuperscript{20} Knowledge of the presence of HPS prior to the transplantation thus ensures close monitoring of these patients for pulmonary complications.

In spite of better understanding of the pathophysiology of HPS, certain issues still need to be addressed. What is the natural history of IPVD? What percentage of patients would progress to HPS? What is the pathophysiology of HPS in patients with portal hypertension without liver disease and what is its prevalence in these patients? Is there a correlation between the degree of portal hypertension and the severity of hypoxemia? Finally, there is a need to develop pharmacological therapy to resolve HPS. A recent study in seven patients demonstrated improvement of hypoxemia with the administration of methylene blue.\textsuperscript{25}

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\textbf{References}


JOURNAL ANNOUNCEMENTS

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- Bimonthly schedule of publication
- Article Status Check at the Journal’s website. Authors will now be able to check online the current status of their submissions, at the new Article Status Check facility at www.indianjgastro.com. The Journal’s reference number and an abbreviated article title are featured at the site for reference.