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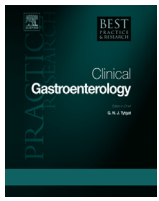

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Liver in cardiopulmonary disease

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A B S T R A C T

Hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PoPH) are two fascinating and incompletely understood pulmonary vascular conditions seen in the setting of cirrhotic patients. Of the two HPS is more common and is primarily caused by pulmonary vasodilatation resulting in hypoxaemia and hyperdynamic circulation. PoPH is less common and conversely, pulmonary vasoconstriction and vascular remodelling occurs resulting in increased pulmonary vascular resistance. However, both conditions can co-exist and it is usually PoPH which develops in a patient with pre-existing HPS. Although these two pulmonary conditions are not common complications of chronic liver diseases, the treatment options are mainly limited to liver transplantation. Cirrhotic cardiomyopathy is closely related to haemodynamic changes in portal hypertension. The key features are normal cardiac pressures at rest, with reduced ability to compensate for physiological or iatrogenic stresses such as drug therapy or TIPSS. There is no effective therapy and outcomes after liver transplantation are variable.

Hepatopulmonary syndrome (HPS)

Definition

HPS is characterised by a defect in oxygenation secondary to pulmonary vasodilatation in the setting of liver disease. It is defined by a triad of liver dysfunction and/or portal hypertension (cirrhotic/

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non-cirrhotic) associated with intrapulmonary vascular dilatations resulting in impaired pulmonary gas-exchange. European respiratory society (ERS) consensus defined an alveolar–arterial oxygen gradient (AaPO2) ≥15 mmHg (≥20 mmHg if >64 years old) as pathological [1]. It further delineated severity into mild (partial pressure of oxygen [PaO2] ≥ 80 mmHg), moderate (PaO2 ≥60 to <80 mmHg), severe (PaO2 ≥50 to <60 mmHg) or very severe (PaO2 <50 mmHg). These partial pressures of oxygen are taken in a standardised position, preferably sitting, at rest and on ambient air. Measuring AaPO2 is more sensitive than PaO2 as the former does not take into account of the compensatory factors like reduced levels of arterial carbon dioxide and hyperventilation, commonly seen in cirrhosis [2].

HPS is usually diagnosed in patients with cirrhosis, but neither cirrhosis nor portal hypertension are essential for the diagnosis. It has been reported in chronic non-cirrhotic hepatitis [3], Budd–Chiari syndrome [4], non-cirrhotic portal hypertension [5] and even in acute liver diseases, such as fulminant hepatitis [6] and ischaemic hepatitis [7].

Prevalence

Because of the lack of consensus in the past regarding the diagnostic criteria, in particular to the degree of gas-exchange abnormality, the prevalence rates described are variable. Indeed in one study involving the same cirrhotic group using various cut offs, the prevalence varied from 19% to 32% [8]. At present there are no multicentre prospective studies available but limited data suggests a prevalence of 10–17% in the overall cirrhotic group [9].

Pathophysiology

Although the mechanisms responsible for the vascular changes in HPS are poorly understood, the consistent and unique striking pathological feature in HPS is gross dilatation of the pulmonary pre capillary and alveolar beds, along with an absolute increase in the number of dilated vessels (Fig. 1). In fact, this was first described by Berthelot in 1966 who demonstrated in an autopsy study that marked pulmonary vasodilatation and increased vessels may play a role in this condition [10].

As a result of the vasodilatation there is increased and rapid blood flow in the alveolar capillary beds, particularly at the lung bases because of gravitational effects. Therefore, patients with HPS demonstrate characteristic orthodeoxia (hypoxia worsened by sitting or standing and improved on lying flat). Furthermore, vasodilatation leads to increased distance oxygen has to travel from the alveolus resulting in a 'functional diffusion barrier'. In more severe cases shunting from arteriovenous communications has also been demonstrated resulting in hypoxaemia. Hence, ventilation perfusion mismatches, diffusion limitation and shunting appear to be the key physiological mechanisms seen in HPS (Fig. 1).

So far studies, mainly from animal models, show that increased production of nitric oxide (NO) and endothelin (ET) 1 via ETb receptors are primarily responsible for pulmonary vasodilatation [11] (Table 1).

Finally, it is thought that pulmonary angiogenesis also plays a role in impaired gas-exchange [12]. This is supported by persistence of hypoxia in a proportion of patients after liver transplantation and improvement in the hypoxia by blocking the vascular endothelial growth factor dependent signal pathways [13]. It is thought that genetic factors may also play a role in this phenomenon [14].

Clinical features and investigations

Dyspnoea is often the presenting symptom in a patient with HPS and chronic liver disease. However it is a non-specific symptom and conditions like ascites and hepatic hydrothorax seen in advanced liver disease are more commonly associated with dyspnoea. A more specific symptom is platypnoea (dyspnoea worsens from supine to erect position). This is also reflected in blood gas measurements as orthodeoxia.

Finger clubbing is seen in about 50% of patients with HPS. In fact presence of finger clubbing, cyanosis, spider nevi and severe hypoxaemia in a patient with chronic liver disease is highly suggestive of HPS [15].