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Hepatopulmonary Syndrome: A Brief Review

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Hepatopulmonary syndrome (HPS) is a pulmonary complication of liver disease characterized by arterial hypoxemia. Mechanisms related to this event are diffusion-perfusion flaw, ventilation-perfusion (V/Q) mismatch, and direct arteriovenous shunts. Diagnosis of HPS is based on the presence of liver disease or portal hypertension, increased alveolar-arterial (A-a) PO_2, and intrapulmonary vascular dilatations (IPVD). Lung transplantation (LT) remains the most effective therapy for HPS. In spite of its poor prognosis, we could improve the quality of life and survival rate of patients.

Key words: Hepatopulmonary syndrome, liver cirrhosis, liver disease, lung disease, portal hypertension.

INTRODUCTION

Hepatopulmonary syndrome (HPS) is a pulmonary complication of liver disease characterized by arterial hypoxemia. This condition often manifests in adult patients with terminal liver disease, having a prevalence of 4% to 32% [1]. It is distinguished by three specific clinical entities consisting of liver disease and/or portal hypertension, disturbance of alveolar-arterial oxygen gradient, and intrapulmonary vascular dilatations (IPVD) [2].

The relationship between pulmonary disorder and liver disease has been recognized for more than 100 years. Despite years of research, diagnosing HPS is still difficult due to the existence of other comorbidities and unclear clinical presentation. Moreover, the only proven therapy for HPS is liver transplantation (LT) [3, 4]. Thus, early diagnosis of HPS is needed to put the patients in priority list for LT. For these reasons, a physician looking to diagnose and manage patients with HPS will need extensive knowledge and broad clinical experience. This review will briefly explain updates from the definition to the management of HPS.

DEFINITION AND PREVALENCE

Kennedy and Knudson were the first to describe cyanosis which emerged four years following porto-caval shunt surgery in a cirrhosis patient, a condition which would later be called HPS. It is defined by the existence of liver disease, disturbance of arterial oxygenation marked by elevated room air alveolar-arterial oxygen gradient [$P(A\text{-}a)O_2$]$\geq$15 mmHg or $\geq$ 20 mmHg if the patient's age$\geq$ 65 years or arterial partial pressure oxygen (PaO_2) < 80 mmHg during room air breathing without other identifiable cause, and IPVD diagnosed by contrast transthoracic echocardiography or other accepted modality [1, 2]. However, it is now known that HPS could manifest in patients with portal hypertension despite having no liver cirrhosis. Moreover, many studies have failed to establish a clear link between the severity of liver disorder and the presence of HPS. Consequently, clinical symptoms such as dyspnea, cyanosis, digital clubbing, orthodeoxia, and platypnea will have more diagnostic value in establishing a more reliable definition [5, 6].

The estimated prevalence of HPS is 4% to 32% among chronic liver disease patients. The cause of this wide range of prevalence is the variation of diagnostic criteria and study populations used in related studies. Abrams *et al.* detected IPVDs in 38% of cirrhosis patients using biopsy in conjunction with microbubble transthoracic echocardiography (MTTE), but only 17.5% of cirrhosis patients had an arterial oxygenation defect as detected by blood gas analysis. However, other studies found a wide range of IPVDs prevalence (13-80%) in LT candidates [7]. These studies had also found that mild IPVDs without any ab-

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normality in arterial oxygenation were more frequent than previously expected in cirrhosis patient. The European Respiratory Task Force had proposed the staging of HPS according to the level of PO_2. HPS is considered to be mild when PO_2 ≥80 mmHg, moderate when PO_2 60-79 mmHg, severe when PO_2 ≥80 mmHg, and very severe when PO_2< 50 mmHg [1, 2].

ETIOLOGY AND PATHOPHYSIOLOGY

The definitive cause of HPS has not been clearly determined. Some clinical studies have suggested that reduced pulmonary vascular tone and advanced liver disorder are the main causes. Other studies have also found that exhaled NO level is elevated in cirrhotic patients with HPS compared to control, providing a clue of the role elevated pulmonary nitric oxide (NO) production has in causing HPS. Another contributing factor in elevated NO levels is the increased expression of inducible NO synthase (iNOS) due to increase in phagocytosis caused by bacterial endotoxin. This event could occur in portal hypertension, which will eventually result in intestines perfusion disturbance and increased rate of gram-negative bacteria and enteral endotoxin translocation. Moreover, it also induced the release of vasoactive mediators including NO [1, 6, 8, 9].

Plasma endothelin-1 (ET-1) could give rise to NO-associated vasodilatation through activation of endothelin B receptors (ET_BR) on endothelial cells. ET-1 levels were found to be elevated in cirrhosis and IPVD cases [9]. Macrophages could also induce vasodilatation due to heme oxygenase (HO-1) production that resulted in increased production of carbon monoxide (CO) [11]. Furthermore, gene polymorphisms also played a role in angiogenesis that had been linked with advanced HPS [12].

The aforementioned conditions lead to diffusion-perfusion flaw, ventilation-perfusion (V/Q) mismatch, and direct arteriovenous shunt. Diffusion-perfusion flaw is caused by an increase of alveolar capillary diameter that expanded the binding space between oxygen molecules with hemoglobin. The combination of the aforementioned conditions with increased cardiac output and reduction of transit time that was usually shown in cirrhosis caused the red blood cells to leave the pulmonary capillaries before oxygen equilibrium was reached. V/Q mismatch is also caused by vascular dilatations. It could also be aggravated by hypoxic pulmonary vasoconstriction. Lastly, direct arteriovenous shunt could lead to hypoxemia due to mixture of arterial and venous blood [1, 9].

Studies using HPS animal model lung functions have identified a number of pathological changes consisting of decreased tidal volume, minute ventilation, lung airway resistance, and mean inspiratory flow, accompanied by elevated chest wall pressure dissipation and viscoelastic pressure. The amount of collagen volume in the vasculature was elevated by 29% in HPS animal models. In addition, cirrhotic patients also showed an increased level of lipopolysaccharide (LPS). Cirrhotic animal models that had been given extra LPS revealed abnormalities of lung anatomy and functions, such as reduction of cell density, expanded alveoli wall, constricted alveoli space, and obliteration of type 1 cell membrane solidity, along with a series of inflammatory reactions and interstitial pulmonary edema. These impairments lead to extensive dilatation of alveolar capillaries and increased permeability of vasculature [13].

CLINICAL CHARACTERISTIC AND DIAGNOSIS

Progressive dyspnea especially on activity is the most frequent complaint in HPS patients. LT candidates with HPS who described dyspnea amount to 48% in contrast to LT candidates without HPS or other lung disorder that amount to 29% (P = 0.007). Other symptoms or clinical signs associated with HPS were orthopnea, platypnea, cyanosis, and digital clubbing. It was also found that cyanosis in liver disease patients with HPS amount to 10% compared to 1% in liver disease patients without HPS (P = 0.007). Moreover, digital clubbing was also more prevalent in a similar population (17 *vs* 7%, P = 0.03) [1]. Even though the aforementioned symptoms and clinical signs were not specific for the diagnosis of HPS, their presence may lead to an increased V/Q mismatch as the consequence of predominant vasodilation, especially in the basal parts of the lung [14, 15]. Direct arteriovenous shunt and V/Q mismatch thus contributed to the occurrence of orthodeoxia. Spider angiomata and neurological complications could also be seen in HPS patients [16].

Diagnosis of HPS is based on the presence of liver disease or portal hypertension, increased $P(A-a)O_2$, and IPVD. Blood gas analysis showed an

increase of age-regulated A-a PO_2 with or without hypoxemia. In addition, chest radiograph and other pulmonary function tests have to be done in order to exclude other possible pulmonary cause [1, 2, 6, 17]. The screening modalities used to assess IPVD are MTTE and technetium-labeled macroaggregated albumin (MAA) scan. MTTE is considered as the gold standard for diagnosing IPVD because the test is relatively less invasive and more sensitive compared to MAA scan. Even though transoesophageal contrast echocardiography may have a higher sensitivity to identify HPS, it had a lot of setbacks, such as the need for sedation, the risk of esophageal variceal bleeding, and a higher cost [18]. In addition to differentiating between intracardiac and intrapulmonary shunting, MTTE also had another advantage to detect pulmonary hypertension. Other tests such as pulmonary angiography and chest computerized tomography could show benefit in particular conditions, such as when large arteriovenosus shunt was suspected [1, 2]. While clinical symptoms may not be definitive, a good history taking and comprehensive physical examination should help in establishing diagnosis.

Some recent studies have shown the potential of a more simple, non-invasive screening modality to detect HPS, such as pulse oximetry. The pulse oximetry method was associated with 100% sensitivity and 88% specificity. By measuring the difference between supine and standing oxygen saturation, HPS could be detected with an oxygen saturation cutoff of <96% [19, 20].

TREATMENT

At present, LT remains the most effective therapy for HPS. A number of methods have been tested to halt the progression of HPS. Nitric oxide inhalation, low consumption of L-arginine using methylene blue, aspirin, antibiotic usage to reduce intestines bacterial translocation, somatostatin, indomethacin, garlic, and transjugular intrahepatic portosystemic shunt (TIPS) have not shown any particular benefit as long-term treatment of HPS [1, 2, 21, 22]. According to theory, the use of TIPS could reduce portal hypertension and improve oxygenation. Wallace *et al.* had studied a series of successful cases of HPS managed by TIPS. They conclude that TIPS could be considered as a management option for HPS patients, in patients contraindicated for LT, in patients where dyspnea were progressive and incapacitating, and as a bridge to transplantation. However, the use of TIPS remained controversial due to the lack of large randomised controlled trials and unfavourable in most clinical settings [23].

The established 5-year survival rate was 23% for HPS patients and 67% for patients without HPS. Another study showed that 33%-40% of HPS patients died within 2.5-4 years. Approximately 85%-100% of patients with HPS undergoing LT have an improvement in oxygenation within 1 year. Nevertheless, in some severe cases of hypoxemia, improvement may not be reached in only one year. These cases usually have a worse prognosis and a longer length of hospital stay [24-26].

One of the recent management options for life-threatening hypoxemia in HPS patients is extracorporeal membrane oxygenation (ECMO). This method has the capacity to support gas exchange and haemodynamics. Monsel *et al.* reported the use of EECMO in preparation of LT in patients with refractory hypoxemia caused by a combination of acute respiratory distress syndrome (ARDS) and HPS. The preliminary data showed that ECMO allowed the performing of successful LT by controlling gas exchange. Their research provided the basis to test ECMO on a large number of patients. Auzinger *et al.* also reported the successful case of using ECMO for severe refractory hypoxemia after LT in HPS patients. It could facilitate early ventilator weaning, thus prevented the need for the prolonged use of sedation and reduced complication associated with interventions. However, the effectiveness of ECMO must still be proven by future mulitcenter trials [28, 29].

For patients on the LT waiting list, it is extremely important to screen them for HPS besides their Model for End-Stage Liver Disease (MELD) scores as their survival rate was expected not to be as high as their non-HPS counterpart. However, data regarding the clinical features of HPS that might influence exception to the MELD scoring system were still limited. In the United States, Organ Procurement Transplant Network (OPTN)/United Network for Organ Sharing (UNOS) suggested that patients with PaO_2<60 mmHg on room air in sitting position should receive an increase in their MELD score and they should get a 2 to 3 point increase every 3 months during their waiting period. It was indicated that patients who had LT this way exhibited a better survival rate and that post-LT mortality was not dependent on severity of hypoxemia at the time of HPS diagnosis. In the largest cohort study of HPS patients reported

to date, Goldbert *et al.* provided the proof that LT is feasible in patients with HPS and resulted in a similar post-LT survival rate compared to non-HPS recipients [30, 31].

One of the major complications in LT is severe hypoxemia in the early postoperative period as patient in this population often resulted in death. However, the condition is poorly defined. Nayyar *et al.* reviewed 27 studies and defined severe hypoxemia as hypoxemia requiring 100% fraction of inhaled oxygen to maintain a saturation of 85%. They also found that there was a liability in patients with very severe preoperative hypoxemia, defined as $PO_2 \leq 50$ mmHg, for having an increased risk of developing the complication. This suggested the need for increased preoperative attention for severe hypoxemia among high-risk patients [32].

CONCLUSION

HPS is a serious complication of liver and/ orlung disease. At present, the main stay effective therapy to HPS is still LT. Therefore, an early diagnosis regarding HPS has to be done as soon as possible. Study to find a more effective diagnosis and therapeutic modality needs to be done more thoroughly. With accurate diagnosis, we could make a prioritized list of LT for HPS patients. In spite of its poor prognosis, we could improve quality of life and survival rate of patients.

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Sindromul hepatopulmonar este o complicaţie pulmonară a bolii hepatice caracterizată prin hipoxemie. Mecanismele implicate sunt modificări ale capacităţii de difuzie, defectele de ventilaţie-perfuzie şi şunturile directe arterio-venoase. Diagnosticul afecţiunii se bazează pe prezenţa bolii hepatice sau a hipertensiunii portale, creşterea gradientului de oxygen alveolo-arterial şi dilatările vasculare pulmonare. Transplantul renal rămâne singura terapie eficientă pentru această patologie. Deşi prognosticul acestei afecţiuni este rezervat, calitatea vieţii şi supravieţuirea pacienţilor poate fi îmbunătăţită.

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