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Literature Review

Portopulmonary Hypertension (Literature Review)

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Abstract

Portopulmonary hypertension is a form of pulmonary arterial hypertension that develops as a complication of portal hypertension. The specific gravity of liver cirrhosis as a cause of portal hypertension is about 75%, which means that a significant proportion of patients with portopulmonary hypertension have liver cirrhosis, therefore, these patients are potentially candidates for liver transplantation. Although this complication is not common, it is extremely important to distinguish portopulmonary hypertension from other causes of pulmonary arterial hypertension, since an increase in mean pulmonary arterial pressure > 35 mmHg is associated with a 50-100% mortality rate during waiting and after liver transplantation. There are no clear recommendations for the treatment of this complication in patients with portal hypertension, since there are not enough clinical trials in this group of patients. A significant number of obstacles can limit the adequate treatment of patients with portopulmonary hypertension and explain the lower survival rate of this group of patients compared with other types of pulmonary arterial hypertension. Until recently, only one randomized controlled trial included patients with portopulmonary hypertension, and most of the treatment data came from relatively small observational studies. Currently, the treatment of portopulmonary hypertension includes therapy specific for pulmonary arterial hypertension regardless of its cause, and in some cases such therapy is necessary to facilitate successful liver transplantation.

Keywords: Portopulmonary Hypertension; Pulmonary Arterial Hypertension; Liver Cirrhosis; Portal Hypertension; Mean Pulmonary Arterial Pressure; Transthoracic Echocardiography; Liver Transplantation

Introduction

Portopulmonary hypertension (PoPH) is a rare, severe complication of liver disease characterized by increased vascular resistance and remodeling of small pulmonary arteries, which in turn leads to right ventricular failure and a significant reduction in life expectancy [1]. PoPH is a subtype of pulmonary arterial hypertension and occurs in individuals with portal hypertension due to chronic liver disease or extrahepatic causes. The incidence of POPH varies from 5% to 10% of the total number of cases of pulmonary arterial hypertension [2].

The combination of pulmonary arterial hypertension with portal hypertension was first described by Mantz and Craige as early as 1951 in a 53-year-old man with portal vein thrombosis and development of a porto-caval shunt with a dilated pulmonary artery. The prevalence of PoPH among patients with portal hypertension and cirrhosis, and portal hypertension without liver cirrhosis is 2-6% and 1-2%, respectively [3]. Thus, for the occurrence of PoPH, a prerequisite is the presence of portal hypertension, which can be associated with both cirrhosis and other pathologies, for example, portal vein thrombosis, hepatic schistosomiasis, and other causes, while the prevalence of PoPH not related neither with the severity of portal hypertension nor with the severity of liver disease [4]. However, some studies have shown higher rates of PoPH among patients with end-stage liver disease who underwent liver transplantation (LT) [5]. This fact may indicate a greater risk of develop-

ing POPH in this population. Most studies have shown no association between the etiology of portal hypertension or chronic liver disease and the development of PoPH [6]. In contrast, some studies have found that PoPH is more often associated with autoimmune cirrhosis and less often with cirrhosis associated with hepatitis C [7]. Another study reported that alcohol and hepatitis C were the most common etiological factors associated with the development of PoPH [8]. Most studies have shown the same incidence of PoPH in both men and women, but some studies report the female sex as a risk factor for this complication [4,6]. Because PoPH is based on an abnormality of the pulmonary vasculature associated with liver disease, it is often confused with hepatopulmonary syndrome. However, hepatopulmonary syndrome is characterized by vasodilation and hypoxemia, while PoPH is characterized by vascular obstruction and/or vasoconstriction, resulting in pulmonary arterial hypertension (PAH).

Due to the relatively low morbidity, the pathogenesis of PoPH remains not fully understood. Factors influencing the development of PoPH include genetic predisposition, thromboembolism in the portal vein system, inflammation, hyperdynamics of the pulmonary circulation and imbalance of vasoconstrictive and vasodilator mediators due to a decrease in metabolism in the affected liver [9]. The latter is considered the main and generally recognized by many scientists mechanism in the pathogenesis of PoPH development.

This review describes the causes, mechanisms of development, diagnostic criteria for POPH, presents a classification according to the severity depending on the pressure in the pulmonary artery, describes diagnostic methods, provides an overview of clinical trials of drugs for the treatment of PAH and PoPH.

Pulmonary hypertension (PH) is divided into five groups (1 through 5) (Table 1). Group 1 (also known as PAH has multiple causes, one of which is POPH. Given the low prevalence of PoPH among patients with pulmonary arterial hypertension (5-10%), PoPH is a diagnosis of exclusion when there is no alternative cause in a patient with coexisting portal hypertension PAH [10].

The main mechanisms of the pathogenesis of PoPH development are poorly understood and continue to be an area of active research. Liver cirrhosis and portal hypertension lead to intrahepatic vasodilation and the formation of portosystemic shunts, which are

1. PAH
Idiopathic
Hereditary
Induced by drugs and toxins
Associated with portal hypertension
Congenital heart disease
Connective tissue disease
HIV infection
Schistosomiasis
2. PH associated with left heart disease
3. PH associated with lung disease
4. PH due to obstruction of the pulmonary artery
5. PH with unclear or multifactorial mechanism
Hematological disorders
Systemic and metabolic disorders
Complicated congenital heart defects

Table 1: Classification of pulmonary hypertension.

thought to contribute to the pathogenesis of PoPH in a variety of ways. Thus, liver fibrosis leads to portal hypertension, increased resistance to blood flow in the liver and the expansion of internal vessels. Splanchnic vasodilation leads to an increase in total circulation and a deviation of blood flow from the liver to the heart through portosystemic shunting, which in turn leads to a general hyperdynamic state. At the same time, damage to the pulmonary endothelium and underlying smooth muscle leads to irreversible vascular remodeling, which ultimately leads to the development of PH. The increased intrahepatic resistance to blood flow associated with cirrhosis leads to an increase in the pressure gradient in the portal vein and portosystemic collateralization due to reperfusion/expansion of existing vessels and the formation of new vessels [11]. Portosystemic shunting allows blood to bypass the liver and thus avoid the metabolism of vasoactive substances in the liver. Such vasoactive substances are serotonin, interleukin-1, endothelin-1, glucagon, secretin, thromboxane B2 and vasoactive intestinal peptide. Elevated plasma concentrations of these mediators have been found in patients with portal hypertension. An imbalance of the above vasoactive substances in the pulmonary vasculature leads to vasoconstriction and an increase in pulmonary vascular resistance. The tension of the vascular wall from constantly high flows leads to trauma of endothelial cells and activation of genes that are

involved in the process of vascular remodeling and, theoretically, play a role in various forms of pulmonary arterial hypertension [12,13]. Exposure and damage to the underlying smooth muscle of the artery leads to proliferation of smooth muscle and thickening of the inner, middle and adventitia membranes of the pulmonary vasculature. The thickening of the arterial wall, in turn, can lead to sluggish pulmonary blood flow, platelet aggregation, and blood clots, which can recanalize over time. Autopsy data from patients with PoPH confirm that the end stage of this process is thickening of the medial part of the intima, plexiform lesions and fibrous venular obstruction [14]. This combination of vascular lesions results in persistently increased pulmonary vascular resistance, which distinguishes POPH from other causes of increased mean pulmonary artery pressure in patients with portal hypertension.

The role of genetic predisposition in the development of PoPH is discussed. Signaling through morphogenetic protein type 2 (BMPR2) has been shown to play a key role in the development of familial PAH due to mutations in the gene encoding this receptor, which was found in 15-40% of cases of idiopathic pulmonary arterial hypertension [15]. However, unlike idiopathic pulmonary arterial hypertension, PoPH does not show mutations in the BMPR2 receptor gene. The main role in the development of pulmonary hypertension associated with portal hypertension is assigned to bone morphogenic protein type 9 (BMP9). This protein is a circulating factor produced by hepatic stellate cells, through which BMPR2 signals are transmitted, which in turn has a protective effect by slowing down liver fibrosis [16]. Recent studies have shown that PoPH patients have significantly lower circulating BMP9 levels compared to control patients with severe liver disease and no evidence of pulmonary hypertension [17]. BMP9 levels were also significantly lower in PoPH patients compared to PAH patients of a different etiology [18]. Moreover, selective enhancement of endothelial BMPR2 by exogenous BMP9 has been shown to alter pulmonary arterial hypertension in many experimental models [19]. Thus, the pooled results of the studies confirm that BMP9 and BMPR2 are likely to play a role in the pathogenesis of PoPH.

Another theory for the occurrence of PoPH is thromboembolism from the portal vein system. According to this theory, thrombi from the portal circulation pass through the portosystemic shunts and reach the pulmonary circulation, resulting in PAH. In order to confirm this theory, a large number of autopsies were studied, but the results of the study could not confirm this theory, since a significant number of blood clots were not found simultaneously in the portal and pulmonary vascular beds [20], while some histopathological findings suggest that blood clots in the pulmonary artery sometimes seen in PoPH, usually occur *in situ* [21].

A sufficient number of theories of the occurrence of PoPH have been proposed, but the main theory is the imbalance of vasoconstrictive and vasodilator mediators due to a decrease in metabolism in the affected liver.

There are no specific complaints for PoPH. The most common clinical symptom of PoPH is shortness of breath during exercise. Other symptoms, such as fatigue, increased heart rate, loss of consciousness due to a drop in blood pressure, or chest pain, are less common. In mild PoPH, clinical data indicating pulmonary hypertension may even be completely absent. Mild hypoxemia is a common finding when examining patients with PoPH and, conversely, symptoms such as severe dyspnea, severe hypoxemia, cyanosis are more characteristic of hepatopulmonary syndrome, and are rare in PoPH. On physical examination, common symptoms of POPH include a second-tone accent on the pulmonary artery, gallop rhythm, and systolic murmur indicating tricuspid insufficiency. Bloating of the jugular veins, ascites, and edema of the lower extremities — symptoms suggestive of decompensated cirrhosis are often associated with patients with PoPH [22].

Instrumental research methods such as ECG can show signs of right ventricular hypertrophy, right atrial enlargement and right heart displacement. X-rays of the lungs are usually normal or with signs of enlarged pulmonary arteries and cardiomegaly. Lung function tests may be normal or indicate lower lung diffusion capacity [23]. Although all of the above instrumental methods can be useful, according to the recommendations of the American Association for the Study of the Liver (AASLD), the most accurate method for suspecting PAH associated with portal hypertension is transthoracic echocardiography. This research method allows assessing the systolic pressure in the right ventricle (RVSP). Further, confirmation of the diagnosis is based on catheterization of the pulmonary artery (right heart), which includes the measurement of pulmonary arterial pressure, cardiac output and pulmonary vascular resistance [24].

Thus, all patients with unexplained dyspnea and/or hypoxemia and all patients undergoing LT assessment should be evaluated

using transthoracic echocardiography to decide on further evaluation [25]. An elevated RVSP requires further hemodynamic evaluation by right heart catheterization (RHC) to confirm an increase in mean pulmonary arterial pressure (mPAP) and rule out other causes of pulmonary hypertension. The AASLD currently recommends RCH in patients with RVSP ≥ 45 mmHg. and/or other evidence of elevated mPAP on transthoracic echocardiography. At the same time, at the Mayo Clinic, the target group of patients for RHC was defined as a group of patients with RVSP ≥ 50 mmHg [26].

RHC detects PAH that is characterized by certain hemodynamic abnormalities, such as: mPAP> 25 mm Hg. Art., pulmonary vascular resistance (PVR)> 3 units. Woods, pulmonary artery wedge pressure (PAWP) <15 mmHg. Depending on the mPAP indices, a classification of POPH has been proposed (Table 2).

PAH	mPAP
Mild	25 ≤ mPAP <35 mmHg
Moderate	35 ≤ mPAP <45 mmHg
Severe	≥ 45 mmHg

Table 2: PAH classification.

However, the above indicators are very inaccurate in the diagnosis of PAH associated specifically with portal hypertension. Not all patients with elevated mPAP have PAH. A high blood flow condition occurs in many cirrhotic patients, which can lead to an increase in mPAP, but the PVR remains normal. Left-sided volume overload can also lead to an increase in mPAP, but PVR also remains normal, and PAWP, on the contrary, increases. All patients with PAH need careful evaluation and exclusion of other conditions associated with PAH, such as left ventricular failure, heart valve disease, interstitial and obstructive pulmonary disease.

Thus, PoPH is a rare and rather difficult condition to diagnose, requiring invasive research methods such as transthorocal echocardiography and RHC. However, exclusion of PAH associated with portal hypertension should be considered in all LT candidates, especially those with hypoxemia, due to the high mortality in the perioperative period. The importance of screening for PoPH has been established by Krowka., *et al*. in a retrospective review of reports and case series that looked at the relationship between the presence of untreated PoPH and cardiopulmonary mortality in LT patients [27]. The study included 43 patients with PoPH (confirmed by RHC) who did not receive treatment prior to LT. Patients were grouped according to the severity of pulmonary hypertension, depending on the value of mPAP, (see table. 2). The results of the study were as follows: in the groups of patients with severe and moderate PAH, 100% and 50% of patients died due to cardiopulmonary complications, respectively (the majority died during hospitalization after transplantation). About mortality in patients with mild (mPAP <35 mmHg) PAH was not reported. As a result of this and other studies, routine screening for pulmonary hypertension is strongly recommended for all patients undergoing screening for forthcoming LT.

After the results of this basic study showed that PoPH patients with higher mPAP scores have a higher risk of death due to LT, the question arose as to whether drug treatment could reduce some of these risks. Treatment of PoPH before or instead of LT remains challenging due to insufficient research and the lack of well-defined algorithms for action based on evidence-based databases. Previous randomized controlled trials of drugs specific for the treatment of pulmonary hypertension in patients with PoPH were limited by concerns about the adverse events on the liver of specific drugs for the treatment of PAH [28].

A retrospective analysis of data on PoPH treatment has shown the ambiguity of the results from different clinical trials. Some studies have shown improvements in hemodynamics and outcomes, while others, in contrast, show no clinically significant results. A recent prospective cohort study from the French Register of Pulmonary Hypertension examined data on 637 patients with PoPH, 90% of whom received PAH-specific treatment [29]. Patients included in the study showed a significant improvement in functional class and hemodynamic parameters. A prospective study of ambrisentan (the ANGEL study) enrolled 31 patients with PoPH [30]. The results of this study showed an improvement in hemodynamic parameters (PVR, mPAP, cardiac index) and functional class. From these prospective studies, it can be concluded that PAH-targeted therapy has a beneficial effect on hemodynamics and functional outcomes, but the effect on mortality before and after LT remains unclear.

The vast majority of randomized controlled trials of specific PAH therapy did not include PoPH patients. An exception is the PATENT-1 study, which included 443 patients with PAH of different etiology in Group 1 (see Table 1). All patients were randomized to

receive either placebo or two different doses of riociguat [31]. This study is notable in that it included 13 PoPH patients, 11 of whom received the highest dose of study drug (2.5 mg per day). The primary endpoint of the PATENT-1 study was 6-min walk distance (6MWD), which was significantly improved in the 2.5 mg riociguat group. Secondary hemodynamic scores (PVR, mPAP, and cardiac index) and functional scores (functional class, Borg dyspnea score, and time to clinical deterioration) were also significantly improved in the riociguat 2.5 mg daily group. The PATENT-2 study was a continuation of the PATENT-1 study, in which all eligible patients from the first study received riociguat and were followed up for 2 years. PATENT-2 showed sustained improvement in functional class and 6MWD [32]. A recently published subgroup analysis of 13 PoPH patients included in PATENT-1 and PATENT-2 showed similar improvements in functional class, 6MWD and PVR [33]. Importantly, riociguat was well tolerated by PoPH patients.

Finally, the PORTICO study is the first randomized controlled trial of specific PAH therapy in PoPH patients, the results of which were published in 2019. The study included 85 patients with PoPH. Patients were randomized to receive either macitentan or placebo for 12 weeks. The study results showed that the macitentan group experienced a 35% reduction in PVR from the primary endpoint [34]. Although there were significant improvements in some secondary endpoints (mPAP and cardiac index), there were no significant improvements in functional class and 6MWD. It should be noted that macitentan was well tolerated in this population without liver side effects. A significant limitation of the PORTICO study was that it excluded all patients with known poor survival associated with end-stage liver disease (Child-Pugh class C and patients with a MELD score> 19).

Research results show clinically significant effects of specific PAH therapy, however, it is still unclear whether a decrease in PVR in patients with PoPH can lead to more significant results for patients (improved functional ability, improved quality of life, reduced mortality). However, the studies taken together indicate that PAH treatment can improve hemodynamics and functional outcomes in patients with POPH given that the drugs are well tolerated by patients with liver disease and PoPH. It is speculated that PoPH treatment could help patients become a suitable candidate for LT, ultimately extending life expectancy. In the absence of specific guidelines for the treatment of PoPH, clinicians should follow the general principles of PAH treatment, while paying particular attention to the unique characteristics of patients with PoPH. More research is needed to determine the characteristics of specific PAH therapy in the PoPH patient population.

Conclusion

- The frequency of occurrence varies from 5% to 10% of cases of the total number of cases of pulmonary arterial hypertension.
- The main theory of the occurrence of PoPH is the theory of imbalance of vasoconstrictive and vasodilator mediators due to a decrease in metabolism in the affected liver.
- No clinical symptoms specific to PoPH. The most common clinical symptom of PoPH is exertional dyspnea.
- The most accurate method for suspecting PAH associated with PoPH is transthoracic echocardiography.
- Systolic pressure in the right ventricle> 45 mmHg according to the AASLD is an indication for catheterization of the right heart.
- Hemodynamic abnormalities, such as: increased mPAP> 25 mmHg, increased pulmonary vascular resistance (PVR)> 3 units. Woods and a decrease in pulmonary capillary wedge pressure <15 mmHg. correspond to the presence of PAH and require detailing etiology of this condition.
- The exclusion of PAH associated with portal hypertension should be performed in all patients who are candidates for LT, especially those with hypoxemia, due to the high mortality in the perioperative period.
- There is no specific PAH therapy associated with PoPH, so treatment does not differ from PAH therapy regardless of etiology.
- PAH treatment can improve hemodynamics and functional outcomes in PoPH patients and may help become a suitable candidate for LT, ultimately extending life expectancy.

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