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''Porto-pulmonary hypertension: A comprehensive review''

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Summary Porto-pulmonary hypertension (PoPH) is a rare but threatening vasculopathy, defined by the presence of pulmonary arterial hypertension (PAH) in the setting of portal hypertension. Although most commonly observed in cirrhotic patients, those with non-cirrhotic portal hypertension are also at risk of developing it. Little is known about the mechanisms by which PAH develop in patients with portal hypertension, but genetic factors, pulmonary vascular wall shear stress, and a dysregulation of vasoactive, proliferative and inflammatory mediators might be involved. PoPH is estimated to occur in 3 to 10% of patients with end-stage liver disease, although its frequency is not related to the severity of liver dysfunction or the degree of portal hypertension. Moderate-to-severe PoPH portends an extremely poor prognosis. Presentation is highly variable, therefore a high index of suspicion is required to establish the diagnosis. PoPH should be screened by transthoracic echocardiography (TTE) in cirrhotic patients presenting with dyspnoea as well as in all patients being evaluated for liver transplantation (LT) regardless of their symptoms. If TTE shows elevated pulmonary pressures, patients should undergo right heart catheterisation, which is required for the definitive diagnosis of PoPH. Without LT, the overall 5-year mortality in PoPH patients is 70%, but it should not be considered an indication

Abbreviations: BNP, B-type natriuretic peptide; ET, endothelin; LT, liver transplantation; MELD, Model for End-stage Liver Disease; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PASP, pulmonary artery systolic pressure; PH, pulmonary hypertension; PoPH, porto-pulmonary hypertension; PVR, pulmonary vascular resistance; PAOP, pulmonary arterial occlusion pressure; RCT, randomised clinical trial; REVEAL, Registry to Evaluate Early and Long-term; RHC, right heart catheterization; RVSP, right ventricular systolic pressure; TPG, trans-pulmonary gradient; TTE, two-dimensional transthoracic ecocardiography.

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for LT. Moderate-to-severe PoPH contraindicates LT, since it is associated with a prohibitively increased intra and postoperative mortality. However, there is now evidence supporting the use of PAH-specific therapies pre-LT in order to improve pulmonary haemodynamic measurements, so the procedure can then be performed with significantly lower risks.

Introduction and definitions

Pulmonary hypertension (PH) is a haemodynamic state defined by a resting mean pulmonary artery pressure (PAP) $\geq$ 25 mmHg as assessed by right heart catheterization (RHC) [1—3]. Since this is a haemodynamic definition (Table 1), PH can be found in a variety of clinical conditions, which have been grouped in 6 different clinical categories each of them with specific characteristics (Table 2) [2,4]. PH encompasses both pulmonary arterial hypertension (PAH) as well as pulmonary venous hypertension due to left heart disease, pulmonary hypertension due to lung disease and/or hypoxia, chronic thromboembolic PH and PH due to miscellaneous conditions [2,5].

PAH is a progressive condition characterised by elevated PAP, high pulmonary vascular resistance (PVR) leading to right heart failure, exercise limitation and premature death. PAH is a form of pre-capillary PH (i.e., with normal left ventricular filling pressures), and its diagnosis requires the exclusion of other forms of pre-capillary PH such as PH due to lung disease and/or hypoxia, chronic thromboembolic PH, and PH with unclear and/or multifactorial mechanisms [3,6]. The definition of PAH also requires the demonstration of a normal pulmonary artery occlusion pressure (PAOP) in order to exclude that the elevation in PAP is not simply due to elevated left ventricular filling pressures [5]. Histologically, PAH is characterized by pulmonary vascular cell proliferation, medial hypertrophy, plexiform lesions and *in situ* thrombosis [4,7]. Although most commonly idiopathic, PAH may also be associated with other conditions such as connective tissue diseases (as systemic sclerosis), congenital heart disease, HIV infection, and portal hypertension, the latter association termed porto-pulmonary hypertension (PoPH) [2,6,8—10].

A mild increase in PAP is commonly seen in patients with cirrhosis and/or portal hypertension, although this is generally due to the usual hyperdynamic state characteristic of liver disease and driven by splanchnic bed vasodilation [11] or due to elevated left ventricular filling pressures in the context of a volume overload state. In contrast, PoPH is a severe pulmonary vasculopathy, defined by the presence of PAH in the setting of portal hypertension with or without underlying advanced liver disease and in the absence of other causes of PAH [8]. It is now a well-recognised cause of PAH in the 2013 Updated classification of PH (Table 2) [12]. Accordingly, it is defined by resting mean PAP $\geq$ 25 mmHg, raised PVR ($\geq$ 3 Wood units [WU]) and a PAOP $\leq$ 15 mmHg, in a patient with a clinical diagnosis of portal hypertension [8,13].

The combination of portal hypertension with PAH was first described in 1951 by Mantz and Craige, who reported the case of a 53-year-old female patient with portal vein thrombosis with spontaneous portocaval shunt who exhibited an enlarged pulmonary artery and upon post-mortem examination revealed intimal thickening in medium and large pulmonary arteries as well as endothelial proliferation of terminal pulmonary arterioles [14]. After its initial description several advances have been made in the diagnosis and management of this condition. In more recent years the interest in PoPH has increased in view of it significant impact in the prognosis of patients listed for liver transplantation (LT). Here we review the latest epidemiological evidence, the developments in determining the diagnosis and clinical course of the condition, and the treatments available.

Epidemiology

PoPH is a relatively rare condition. Although most commonly observed in patients with end-stage liver disease, PoPH has also been identified in the context of non-cirrhotic portal hypertension, including nodular regenerative hyperplasia, portal vein thrombosis, Budd-Chiari syndrome, and schistosomiasis (itself a cause of PAH) [14—17]. This observation supports the notion that portal hypertension, rather than cirrhosis, is the key factor for the development of PoPH.

The actual incidence and prevalence of PoPH are unknown. Very few descriptive epidemiological studies are available and the majority of estimates are in patients with end-stage liver disease undergoing evaluation for LT. Moreover, since there are no standard criteria for its screening, published reports on the epidemiology of PoPH vary greatly according to the criteria used to define this condition as well as to the population studied (Table 3).

In 1979, Lebrec et al. reported the first case-series description of 9 patients with portal hypertension who had subsequently developed PH [16]; although there were no estimates on the incidence or prevalence of it, the authors argued that PH was a rare complication of portal hypertension, and that by then hepatologists were not aware of this condition. An autopsy study, conducted more than 30 years ago and including 17,901 unselected patients older than 1-year-old, showed histopathological findings suggestive of PAH in 0.73% of patients with cirrhosis compared to only 0.13% when all patients were considered [18]. In a clinical prospective study comprising over 500 hospitalised patients with portal hypertension, but without previously known PH, who were then submitted to RHC, Hadengue et al. found that 10 (2%) of them had PAH; of those 6 patients were clinically asymptomatic at the time of diagnosis [19].

The existence of PoPH in LT candidates has been retrospectively assessed by several studies, all reporting a