Review Article

Portopulmonary hypertension*

EDUARDO GARCIA[TE SBPT], JOSÉ SILVA MOREIRA, AJÁCIO BANDEIRA DE MELO BRANDÃO, ALESSANDRA ISABEL ZILLE, JULIANA CARDOZO FERNANDES

Portal hypertension and cirrhosis can result in complex changes in the pulmonary vascular bed, the most important among them being the hepatopulmonary syndrome and portopulmonary hypertension. When pulmonary hypertension accompanies cirrhosis and portal hypertension, it is seldom diagnosed. Its prevalence is estimated to range from 1% to 2% in patients with portal hypertension or cirrhosis, regardless of gender, and the condition is predominantly seen in patients in their 40s. Etiologic factors have not been sufficiently well defined to explain the increase in pulmonary artery pressure and pulmonary vascular resistance. Most patients are asymptomatic until developing dyspnea on exertion, which generally occurs when the mean pulmonary artery pressure exceeds 40 mmHg. Concomitant hepatic disease with progressive hypoxemia or right ventricular failure increase mortality rates. Further studies are needed in order to determine the benefits of using oral, inhaled or intravenous vasodilators, as well as to evaluate the outcomes of liver transplant, which may be the sole definitive therapeutic option.

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* Study carried out at the Universidade do Rio Grande do Sul (UFRGS), Porto Alegre, RS
Correspondence to: Eduardo Garcia - Rua Vasco da Gama, 51/304 - Porto Alegre - RS - CEP 90420111
Tel: 55 51 3211 2766 - E- mail: eduardosgarcia@terra.com.br
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INTRODUCTION

The broad spectrum of the remodeling of the pulmonary vasculature in chronic liver disease and portal hypertension presents extensive variation – from hepatopulmonary syndrome (characterized by intrapulmonary vascular dilations) to portopulmonary hypertension (in which pulmonary vascular resistance is elevated). Their clinical presentations are quite different, including alterations in gas exchanges (such as those seen in hepatopulmonary syndrome) and even hemodynamic failure (such as that occurring in portopulmonary hypertension)[1].

Pulmonary hypertension is defined as mean pulmonary artery pressure greater than 25 mmHg at rest and greater than 30 mmHg upon exertion, in the absence of any identified secondary causes[2]. Its prevalence ranges from 0.13% to 0.73% in the general population[2] and up to 2%[2-4] in patients with liver cirrhosis. It is a complex clinical entity that may result from congenital heart disease, human immunodeficiency virus infection, use of anorexigens, pulmonary thromboembolism, collagen diseases or sarcoidosis, among others[1,5].

Pulmonary hypertension accompanied by cirrhosis and portal hypertension was first described in 1981 and was considered a subtype of primary pulmonary hypertension[4,6], and only became recognized as secondary in 1993, being thereafter denominated portopulmonary hypertension (portoPH)[7,8]. Its diagnosis involves the exclusion of other causes of secondary pulmonary hypertension. It is defined as mean pulmonary pressure greater than 25 mmHg and pulmonary vascular resistance greater than 120 dynes/sec/cm^2, accompanied by severe liver disease and portal hypertension[9,10].

The prevalence of portoPH ranges from 1% to 2% (3.1%) in patients with portal hypertension or cirrhosis, regardless of gender, occurring more frequently in patients in their 40s[3,4]. The first retrospective studies of necropsies showed a prevalence of pulmonary hypertension ranging from 0.25% to 0.73% in the population of patients with portal hypertension or cirrhosis, in contrast with a prevalence of 0.13% in noncirrhotic individuals[3,4]. A transversal study previously carried out by the authors of the present study involved a review of cases of cirrhotic patients submitted to liver transplant at the *Complexo Hospitalar da Santa Casa de Porto Alegre* (Porto Alegre Santa Casa Hospital Complex) from January 1999 to July 2002 (43 months) and showed a portoPH prevalence of 14.6%[11]. In that study, there was a predominance of virus-related cirrhosis (80 cases; 61.5%), followed by alcohol-related cirrhosis (20 cases; 15.4%), cryptogenic cirrhosis (15 cases; 11.5%), alcohol/virus-related cirrhosis (5 cases; 3.8%), autoimmune cirrhosis (3 cases; 2.3%), primary biliary cirrhosis (1 case; 0.8%), hemochromatosis (1 case; 0.8%) and miscellaneous (5 cases; 3.8%)[11].

PHYSIOPATHOLOGY

The physiopathology of this disease remains unclear, although it has been proposed that certain mechanisms, such as hyperdynamic circulation, secondary to an imbalance between vasoconstrictor and vasodilator factors, which are influenced by liver dysfunction secondary to liver cirrhosis, are involved[1,12]. These alterations would be similar to those causing portoPH (hypertrophy of the middle layer and fibrosis of the inner layer of the pulmonary artery muscles with a concentric laminar configuration). Plexiform lesions are seen in the small arteries, and the large muscular pulmonary arteries present dilatation[9,13,14].

All of the vascular abnormalities combined contribute to the increase in pulmonary vascular resistance. Such abnormalities include vasoconstriction, arterial wall remodeling and *in situ* microthrombosis, among other less well-established angiogenic factors, such as genetic susceptibility, increased levels of vasoactive mediators (cytokines, growth factors and serotonin) and increased interleukin production[10,13].

Patients with portal hypertension would be at increased risk for developing portoPH because endogenous components derived from the splanchnic circulation, which are normally metabolized in the liver, would reach the pulmonary circulation through portosystemic collateral pathways. In genetically susceptible patients, these substances may induce alterations in the pulmonary vessels through endothelial lesion and metabolic dysfunction, leading to pulmonary arteriopathy and development of pulmonary hypertension[12].

Among these mediators, serotonin and interleukin 1 have been identified as relevant. Serotonin causes pulmonary vasoconstriction and proliferation of the smooth muscles of the pulmonary artery; it is produced by the enterochromaffin cells of the

intestine and stored in the platelets. Under normal conditions, the pulmonary vascular bed is not exposed to elevated levels of serotonin. However, in patients with portoPH, plasma concentration of serotonin is high, whereas its concentration in platelets is low. Levels of interleukin 1 are also elevated in patients with cirrhosis, which suggests that this cytokine is involved in portoPH development. Hepatocyte and vascular endothelial growth factors may influence the development of pulmonary hypertension in susceptible patients with portal hypertension[3,12].

Pulmonary vascular endothelial cells play an important role in the development of the disease. Alterations in the cellular function may be triggering factors, whereas the vasoconstriction caused by the contraction of the smooth muscle could only be an expression of the endothelial lesion. Vasodilators produced by the endothelium, such as prostacyclin and nitric oxide, inhibit the platelet endothelial adhesion, having an antimitogenic effect on smooth muscle cells and decreasing vascular muscle tone[12,15].

Vasoconstrictors such as endothelin and thromboxanes promote replication of the smooth muscles and coagulation. Patients with portoPH present elevated levels of thromboxane-A2, low levels of prostacyclins and normal levels of endothelin[5,13]. The nitric oxide, a vasodilator derived from the endothelium, has received special attention regarding the physiopathological involvement in several diseases, including portoPH. In animal models, a higher pulmonary concentration of endotoxin has been identified, inhibiting nitric oxide synthase, with consequent activation of guanylyl-cyclase in animals with portal hypertension, which suggests that low concentrations of nitric oxide may contribute to pulmonary hypertension secondary to portal hypertension[15,18].

Several factors have been considered as triggers or promoters of portoPH, such as hypoxemia, autoimmune toxins and increased sympathetic tone. Cellular remodeling in response to injury represents the final common pathway for the development of pulmonary hypertension[4].

The identification of a gene responsible for familial pulmonary hypertension will enable significant reconsiderations of the current concepts and mechanisms which induce portoPH[19,20].

CLINICAL MANIFESTATIONS

The symptomatology related to the disease generally results from right ventricular failure or low cardiac index. The most common symptoms are dyspnea (upon exertion), fatigue and chest pain. Lesser common symptoms are syncope, palpitations and peripheral edema. These generally appear when the mean pulmonary artery pressure exceeds 40 mmHg[21]. The findings upon physical examination are also related to right ventricular failure[1,13,21].

DIAGNOSIS

A diagnosis of portoPH is based on the presence of pulmonary hypertension of unknown cause in a patient with severe liver disease. The most common alterations found in each diagnostic test are described herein.

Electrocardiograms show classic characteristics of right heart overload: right bundle branch block, right axis deviation and right ventricular hypertrophy with secondary T-wave alterations. Abnormalities in the echocardiogram are found in 80% of cases[3].

Chest X-rays present enlarged right ventricle, prominent main pulmonary artery, obliteration of the peripheral vasculature and angled superior diversion of the pulmonary vessels[3]. In the great majority of the cases, chest X-rays appear normal, as documented in the present study (Table 1).

The pulmonary function tests show mild restrictive ventilatory defect, secondary to liver cirrhosis complications (ascites, pleural effusion, hepatomegaly, basal atelectasis) and decreased carbon monoxide diffusion capacity caused by interstitial pulmonary edema and hepatopulmonary syndrome.

Blood gas analysis shows mild hypoxemia and compensatory respiratory alkalosis. These findings are not exclusive to portoPH, also occurring in isolated portal hypertension.

The Doppler echocardiogram, in addition to ruling out other causes of secondary hypertension, is also used to identify alterations in the dimensions of the right heart chambers, valve function and integrity, as well as to estimate pulmonary artery pressure in a noninvasive way. The objective assessment of pulmonary artery pressure is performed using the Doppler technique. The most commonly used process is estimation of systolic pulmonary artery pressure by analysis of tricuspid regurgitation, commonly detectable in pulmonary hypertension treatment regimens, even under normal conditions[23].

The gold standard for diagnosis is mean pulmonary artery pressure greater than 25 mmHg at rest, with pulmonary capillary pressure below 15 mmHg and pulmonary vascular resistance greater than 120 dynes/sec/cm^2, as measured through

TABLE 1

Distribution of radiographic findings in 130 patients diagnosed with portopulmonary hypertension

Radiographic findings	Frequency	
Normal	91	(70%)
Criteria for COPD	12	(9.2%)
Hydrothorax	8	(6.2%)
Sequelae of granulomatous disease	7	(5.4%)
Small laminar atelectasis	6	(4.6%)
Cardiomegaly	2	(1.5%)
Pulmonary nodule	2	(1.5%)
Criteria for pulmonary hypertension	2	(1.5%)
Total cases	130	(100%)

COPD: chronic obstructive pulmonary disease

catheterization of the pulmonary artery[24]. This procedure involves transcutaneous puncture or venous surgical dissection as an approach to directly access the pulmonary artery circulation so as to enable the sequential and rapid registration and direct measurement of the pressures throughout all right heart chambers, as well as of the proximal segments of the systemic and pulmonary circulation. In special situations, as previously described in heart, lung and liver transplants, or in pulmonary hypertension status resulting from hypoventilation or apnea, the length of time that the catheter used for continuous monitoring of pulmonary artery pressure is left in place has been considered valuable not only for diagnosis but also for assessing the treatment used[24-26]. To confirm the diagnosis and estimate the severity of the disease, cardiac catheterization is fundamental in all patients with pulmonary hypertension. A recent prospective study compared transthoracic echocardiogram to right cardiac catheterization and demonstrated that transthoracic echocardiogram presented 80% sensitivity, 96% specificity, 60% positive predictive value, 98% negative predictive value and 96% accuracy in diagnosing portoPH, using a cutoff value of 40 mmHg of pulmonary artery pressure[21]. Another similar study, using the same cutoff point, demonstrated 100% sensitivity, 88% specificity and 30% positive predictive value[27]. Both studies suggest that the transthoracic echocardiogram is a good method of tracking portoPH. However, since there are high numbers of false-positive results, positive cases should be re-evaluated using cardiac catheterization[21,27].

The confirmation of cirrhosis through liver biopsy, clinical findings or images showing portal hypertension combined with increased pulmonary artery pressure, reinforces the portoPH diagnosis[3,28,29].

TREATMENT

The treatment for portoPH has not been completely established. Among the more recently studied options is oral vasodilator (calcium channel blocker) therapy, which promotes remission of right ventricular hypertrophy, although the long-term benefits have yet to be well established. Increased survival is observed only in patients presenting acute ventricular response[30]. Patients are considered responsive to vasodilators if there is a more than 20% decrease in pulmonary vascular resistance and mean pulmonary artery pressure[4]. Inhaled nitric oxide, a selective pulmonary vasodilator, has not provided clear results. It has been suggested that it might be useful in preoperative management of patients who are liver transplant candidates[9]. Recent reports indicate some new drugs as treatment options preceding liver transplant[30,31,32]. Among these is intravenous prostacyclin, which reduces mean pulmonary artery pressure and has shown potential for improving exercise tolerance and hemodynamic parameters. Among the prostaglandin analogs, epoprostenol and beraprost are the most studied drugs[31,32]. Other treatment options, such as other prostaglandin inhibitors (treprostinil, iloprost) and endothelin receptor antagonists (bosentan, sitaxsentan), are being studied. However, these drugs have been evaluated as therapy in pulmonary hypertension of primary or secondary etiology to other causes (collagen diseases, congenital heart disease, acquired immune deficiency syndrome). No studies on the use of these drugs in portoPH have been published. Surgical interventions such as atrial septostomy are only indicated in cases of pulmonary hypertension secondary to congenital heart disease in children[30].

Retrospective studies involving liver transplant postoperative stated portoPH was an absolute contraindication for transplant due to the high intraoperative mortality. It is currently known that the improved preoperative evaluations and better anesthetic conditions available provide new treatment possibilities. Therefore, liver transplant may become a more common treatment for portoPH. There have been few studies of portoPH treatment through liver

transplant. Among those, some have reported negative results, and others have shown positive results such as decreased postoperative pulmonary artery pressure[10,33]. In transplant patients, preoperative factors, such as hemodynamic response to epoprostenol observed through serial cardiac catheterization, arterial oxygen tension greater than 50 mmHg, pulmonary hypertension classified as mild to moderate, and proper right heart function are indicators of better prognosis. Other preoperative factors, such as pulmonary artery pressure greater than 35 mmHg, vascular resistance greater than 300 dynes/sec/cm^2 and arterial oxygen tension less than 50 mmHg, have been shown to increase postoperative mortality considerably in such patients[23,34].

In addition to the lack of answers to questions concerning the real benefits of liver transplant in portoPH, there have been no definitive studies showing either isolated liver transplant or multi-organ transplant to be the best option[35,36]. Recently, heart-lung-liver transplants were reportedly performed in two cases of severe portoPH that were refractory to clinical treatment[36]. Only one of the procedures was successful, reflecting the uncertainty concerning multiple organ transplant.

CONCLUSION

A diagnosis of portoPH should be considered as a differential diagnosis when pulmonary diseases that appear together with dyspnea and cyanosis, mainly in cases associated to chronic liver disease, are evaluated. Even though it is considered uncommon and of indefinite prognosis, there is no justification for not offering patients with portoPH some of the available treatment modalities, in an attempt to revert or decrease its symptoms. Among these modalities are new drugs, such as nitric oxide, prostacyclin and epoprostenol, as well as the, as yet unproven, option of liver transplant.

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