Prevalence of Spontaneous Portosystemic Shunts in Patients With Portopulmonary Hypertension and Effect on Treatment

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This article has an accompanying continuing medical education activity on page e13. Learning Objective: Upon completion of the CME activity, successful learners will be able to establish the relationship between spontaneous porto-systemic shunts and porto-pulmonary hypertension (POPH), and define the response to therapy of POPH in patients with such shunts.

BACKGROUND & AIMS: We documented the frequency of large spontaneous portosystemic shunts in patients with moderate or severe portopulmonary hypertension (POPH) and determined the association between large shunts and response to treatment. **METHODS:** We performed a retrospective case-control study of data from patients with mild (mean pulmonary artery pressure [MPAP], 25–35 mm Hg; n = 18), moderate (MPAP, 35–50 mm Hg; n = 45), and severe POPH (MPAP, >50 mm Hg; n = 16). Data were compared with those from controls (normal echocardiography with estimated right ventricular systolic pressure, <35 mm Hg; n = 122). Spontaneous portosystemic shunts greater than 10 mm in diameter, identified by computed tomography or magnetic resonance, were classified as large. Response to treatment at 6 months was defined by right ventricular systolic pressure or MPAP as significant (<35 mm Hg), partial (35–50 mm Hg), or no response (>50 mm Hg). **RESULTS:** The frequency of spontaneous shunts did not differ significantly between groups of subjects with severe (n = 14 of 16), moderate (n = 38 of 45), or mild POPH (n = 11 of 18) or normal echocardiograms (controls, n = 86 of 122) (P = .77). Large shunts were associated with severe (14 of 16) and moderate POPH (32 of 45), compared with mild POPH (6 of 18) or controls (30 of 122) ($P < .01$). In 13 patients with severe POPH, large shunts were associated with lack of response to treatment in 90% (8 of 9) or partial response in 50% (2 of 4). Among 27 patients with moderate POPH, large shunts were associated with no response to treatment in 13 of 19 (68%) and a partial response in 2 of 6 (33%). **CONCLUSIONS: Large spontaneous portosystemic shunts are associated significantly with moderate and severe POPH, and with lack of response to treatment.**

Keywords: Portal Hypertension; Cardiac Output; Hemodynamics; Vasodilators.

Portopulmonary hypertension (POPH) is a clinical syndrome characterized by the presence of portal hypertension (most commonly from cirrhosis) and hemodynamic criteria at right heart catheterization including the following: (1) a mean pulmonary artery pressure (MPAP) of 25 mm Hg or greater; (2) pulmonary vascular resistance (PVR) of 240 dynes/s/cm^{-5} or greater, and (3) pulmonary capillary wedge pressure (PCWP) less than 15 mm Hg.[1] Transthoracic Doppler echocardiography is an effective, noninvasive method of screening for POPH in patients with cirrhosis.[2,3] Further, transthoracic Doppler echocardiography can appropriately identify patients who require right heart catheterization to confirm and grade the severity of POPH.[4] Although selected patients with mild to moderate POPH can benefit from liver transplantation,[5] significant perioperative mortality has been observed in patients with moderate to severe POPH and, thus, liver transplantation is contraindicated in patients with MPAP greater than 50 mm Hg at the time of liver transplantation.[6,7] Despite the recent literature examining various medical therapies for POPH, there is yet to be a controlled clinical trial that identifies an effective treatment option.[8] The pathophysiology underlying POPH involves endothelial and smooth muscle proliferation and plexogenic arteriopathy in the pulmonary arterioles[9,10]; these findings are not specific for POPH given their occurrence with idiopathic pulmonary arterial hypertension.[10]

The link between portal hypertension and the development of POPH remains poorly understood. Only about 5%–10% of patients with portal hypertension develop POPH and, thus, factors other than portal hypertension must be involved in the pathogenesis of POPH. Liver dysfunction is also not a prerequisite for the development of POPH because the condition may develop in patients with portal vein thrombosis or idiopathic portal hypertension in whom liver function is excellent.[11,12] Existing literature has documented the association between con-

Abbreviations used in this paper: MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; POPH, portopulmonary hypertension; PVR, pulmonary vascular resistance; RVSP, right ventricular systolic pressure.

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CLINICAL LIVER

genital portosystemic shunts and POPH, and transjugular intrahepatic portosystemic shunts and the worsening of pulmonary hypertension.[13] The latter relationship may be temporary and related to increased pulmonary blood flow rather than increased pulmonary vascular resistance. Because the pulmonary circulation is downstream from the splanchnic vascular bed and portal circulation, putative vasoactive factors produced in the splanchnic circulation may escape metabolism in the liver in the presence of portosystemic shunts and mediate vasoconstriction in the pulmonary vascular bed. If portosystemic shunting of splanchnic blood is large, the pulmonary vascular bed may be presented with a larger concentration of vasoactive factors produced in the splanchnic bed. Large portosystemic shunts therefore may increase pulmonary arterial pressure both by increasing pulmonary flow and by increasing pulmonary vascular resistance as a result of vasoactive factor–mediated pulmonary vasoconstriction. Thus, the severity of POPH could be related to the degree of portosystemic shunting. Moreover, the response to treatment of POPH may be less favorable in patients with large portosystemic shunts. The aim of our study was to estimate the frequency of large spontaneous portosystemic shunts detected by cross-sectional imaging in patients with moderate to severe POPH. We also determined the association between lack of response to medical therapy and large spontaneous portosystemic shunts in patients with POPH.

Materials and Methods

Patients

Patients with POPH and at least 6 months of follow-up evaluation if treated, were identified from electronic medical records and a dedicated clinical database. Patients who had undergone either transjugular intrahepatic portosystemic shunts or surgical portosystemic shunt procedures were excluded. The prospective data collection and retrospective data analyses were reviewed and approved by the Mayo Institutional Review Board. Individuals with suspected POPH were identified from 2 sources: (1) a protocolized screening program for POPH among consecutive referrals for liver transplantation at the Mayo Clinic (Rochester, MN), and (2) clinical evaluation within the ambulatory pulmonary and hepatobiliary clinics. In these clinics, investigation for POPH was performed if clinically suspected on the basis of symptoms of fatigue, or cardiac findings of pulmonary hypertension. Each patient included underwent screening for POPH with 2-dimensional transthoracic color Doppler echocardiography. In addition to standard measurements, tricuspid regurgitant peak velocity was determined by the apical, parasternal, and subcostal views. The right ventricular systolic pressure (RVSP) was estimated using the modified Bernoulli equation where RVSP = 4 × (tricuspid regurgitant peak velocity)^2 + estimated right atrial pressure.[2] The right atrial pressure estimate was determined via echocardiographic assessment of the inferior vena cava size and the degree of collapse with respiration.

Individual patients with an estimated right RVSP greater than 50 mm Hg on echocardiography subsequently were referred for right heart catheterization to define hemodynamic parameters and document the diagnosis of POPH. Our previous studies had shown that patients with an estimated RVSP less than 50 mm Hg on echocardiography are unlikely to have MPAP greater than 35 mm Hg on right heart catheterization and, thus, do not require right heart catheterization.[2] Right heart cardiac catheterization was conducted using a triple-lumen, balloon-tipped thermodilution catheter. Percutaneous vascular assess was accomplished via the internal jugular vein when the international normalized ratio for prothrombin time was 1.5 or less. Cardiac outputs were determined via thermodilution using 10 mL of 5% dextrose solution (average, 3 assessments). Standard pressure measurements included determinations of mean right atrial pressure, pulmonary artery systolic pressure, MPAP, and PCWP, with the pressure transducer positioned at the midaxillary line. PCWP was measured at the end of expiration to provide an estimate of central blood volume and the left atrial pressure. PVR was calculated using the standard formula PVR (dynes.s.cm^{-5}) = (MPAP – PCWP)/cardiac output × 80.[14,15] The difference between MPAP and PCWP is referred to as the transpulmonary gradient.

As described earlier, patients with POPH were identified as those with MPAP of 25 mm Hg or greater,[1] PVR greater than 240 dynes × s × cm^{-5}, and PCWP less than 15 mm Hg.[1] Patients with moderate POPH were described by MPAP between 35 and 50 mm Hg, whereas severe POPH was defined by a MPAP 50 mm Hg or greater.[16] Two other groups also were identified to facilitate comparison with patients with moderate to severe POPH. The first group included patients with suspected POPH based on Doppler echocardiography, but right heart catheterization revealed evidence of only mild POPH (MPAP, 25–35 mm Hg) or a normal MPAP (≤25 mm Hg). The second control group consisted of consecutive patients with cirrhosis referred for liver transplantation in whom Doppler echocardiography revealed a normal structural and hemodynamic parameters including an estimated RVSP less than 35 mm Hg. Two patients with estimated RVSP less than 35 mm Hg were selected as controls for each patient with moderate or severe POPH.

Identification of Spontaneous Portosystemic Shunts

Patients with POPH were included in the study only if they had undergone cross-sectional imaging by multidetector computed tomography or magnetic resonance imaging within 12 months of diagnosis of POPH. Triple phase-contrast–enhanced imaging by computed tomography or gadolinium-enhanced magnetic resonance imaging was performed. Patients in the databases with POPH who did not undergo abdominal imaging by multidetector computed tomography or magnetic resonance imaging were excluded from the study (n = 114).

The detection of spontaneous portosystemic shunts (diameter, >5 mm) was performed by a clinician (P.S.K.) who was blinded to the clinical information. Luminal varices and retroperitoneal collaterals not obviously connecting to systemic veins were not considered portosystemic shunts. When required, the interpretation was confirmed by an independent radiologist (J.C.A.) who also was blinded to the clinical information. The classification of spontaneous portosystemic shunts was based on their anatomic orientation within the abdomen. Categories of shunts included the following: (1) splenorenal shunt involving the presence of a large venous collateral connecting the splenic vein to the left renal vein (Figure 1); (2) paraumbilical or umbilical vein shunt defined by the presence of a patent umbilical vein located along the anterior abdominal wall and connecting with a systemic vein, usually the inferior epigastric vein (Figure