Pulmonary Arterial Hypertension Associated with Congenital Portosystemic Shunts Treated with Transcatheter Embolization and Pulmonary Vasodilators

Haruka Sato[1], Masanobu Miura[1], Nobuhiro Yaoita[1], Saori Yamamoto[1], Shunsuke Tatebe[1], Tatsuo Aoki[1], Kimio Satoh[1], Hideki Ota[2], Kei Takase[2], Koichiro Sugimura[1] and Hiroaki Shimokawa[1]

Abstract

Cardiopulmonary abnormalities are often present in patients with liver diseases. We herein report a case of congenital portosystemic shunts complicated by hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PoPH). A 57-year-old woman complained of dyspnea and was subsequently diagnosed with HPS and PoPH caused by congenital portosystemic shunts. Although shunt closure by transcatheter embolization was successfully performed, her dyspnea worsened and pulmonary artery pressure and pulmonary vascular resistance elevated. Conventional vasodilator therapy was started, resulting in an improvement of pulmonary hypertension (PH). In some patients with congenital portosystemic shunts, shunt closure could exacerbate PH, and vasodilator therapy may be effective.

Key words: congenital portosystemic shunts, portopulmonary hypertension, hepatopulmonary syndrome, shunt closure

Introduction

Pulmonary vascular disorders associated with liver diseases include portopulmonary hypertension (PoPH) and hepatopulmonary syndrome (HPS) (1-4). Shunt closure for congenital portosystemic shunts (CPSS) with PoPH or HPS is considered to be effective (5-8). We herein report a case of CPSS complicated by both HPS and PoPH treated with shunt closure treatment.
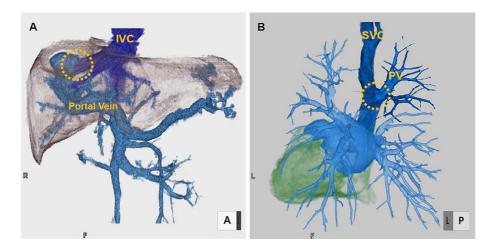
Case Report

A 57-year-old woman with no past history or family history was admitted to a hospital for dyspnea. The tricuspid regurgitation pressure gradient (TRPG) by echocardiography was elevated (59 mmHg), suggesting the presence of pulmo-

nary hypertension (PH). She was subsequently transferred to our hospital with WHO functional class (WHO-FC) II. The serum level of brain natriuretic peptide (BNP) (26.1 ng/dL) was slightly elevated and serum levels of NH_3 (75 μg/dL) and total bile acid (TBA) (93.9 μmol/L) were also elevated with normal liver functions and appearance and normal serum levels of aspartate aminotransferase/alanine aminotransferase (29 and 24 U/L, respectively). She had hypoxia with PaO_2 of 63.0 mmHg, SaO_2 of 92.8%, and alveolar-arterial oxygen difference of 46.2 mmHg. Echocardiography showed normal left ventricular contraction, markedly dilated right ventricle and leftward shift of the interventricular septum with a TRPG of 49 mmHg. Computed tomography showed portal-hepatic vein shunts in the right lobe of the liver with no sign of pulmonary embolism (Fig. 1A) and partial anomalous pulmonary venous return (PAPVR) from the right pulmonary vein to the superior vena cava (Fig. 1B).
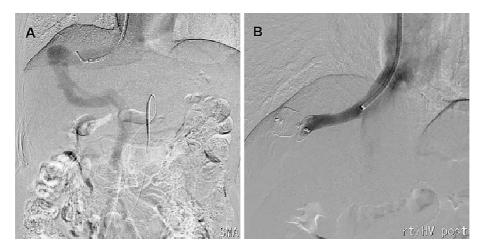
Figure 1. (A) Portosystemic shunt from the right portal vein to the right hepatic vein in the right lobe of the liver and (B) 3DCT imaging of PAPVR from the right pulmonary vein to the superior vena cava (posterior view). IVC: inferior vena cava, PAPVR: partial anomalous pulmonary venous return, PV: pulmonary vein, SVC: superior vena cava, 3DCT: 3-dimensional computed tomography
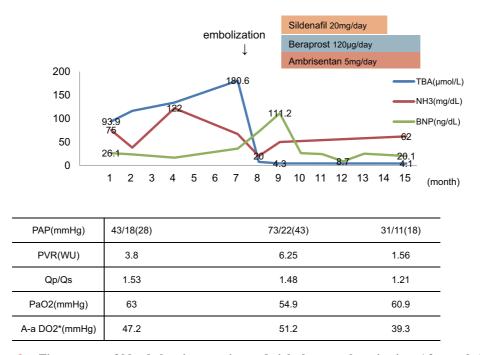

Figure 2. Angiography before (A) and after (B) embolization. (A) Portosystemic shunt from the right portal vein to the right hepatic vein. (B) After embolization using an Amplatzer Vascular Plug II (20×16 mm), no flow was observed from the portal vein to the hepatic vein.

Right heart catheterization (RHC) showed that she had pulmonary arterial hypertension (PAH) with a mean pulmonary arterial pressure (mPAP) of 29 mmHg, pulmonary vascular resistance (PVR) of 3.8 Wood units (WU) and pulmonary capillary wedge pressure of 8 mmHg. Perfusion and ventilation lung scans and pulmonary angiography showed no typical images of chronic thromboembolic pulmonary hypertension. With the presence of PAPVR, the Qp/Qs ratio was 1.53. A microbubble test from the right inferior pulmonary artery suggested the presence of an intrapulmonary shunt. However, the hepatic vein wedge pressure was not elevated (10 mmHg).

According to these findings, the patient was diagnosed as having HPS and PAH associated with a high flow with PAPVR or CPSS. After the diagnosis, because her hypoxia was severe and indications for surgical repair with a Qp/Qs ratio of 1.5 or more have remained controversial (9), transcatheter embolization for CPSS was first performed using a 20-mm AMPLATZER Vascular Plug II (St. Jude Medical,

St. Paul, USA) (Fig. 2). Three months later, the serum levels of NH_3 and TBA decreased to 20 μg/dL and 4.3 μmol/L, respectively, however, her symptoms, including dyspnea, worsened to WHO-FC III and the serum level of BNP increased to 111.2 ng/dL. RHC showed further elevation of mPAP (43 mmHg) and PVR (6.3 WU), indicating that transcatheter embolization had exacerbated her PAH. A microbubble test from the left pulmonary artery remained positive at the follow-up study, which might have been associated with hypoxia (Fig. 3). Therefore, conventional vasodilator therapy with ambrisentan (5 mg/day), sildenafil (20 mg/day) and beraprost (120 μg/day) was started. Six months later, hypoxia still remained, however, her symptoms improved to WHO-FC II, with a marked improvement in BNP (20.1 ng/dL), mPAP (18 mmHg) and PVR (1.5 WU) without worsening of the shunt ratio (Qp/Qs: 1.53 to 1.21) (Fig. 3).

PAP(mmHg)	43/18(28)	73/22(43)	31/11(18)
PVR(WU)	3.8	6.25	1.56
Qp/Qs	1.53	1.48	1.21
PaO2(mmHg)	63	54.9	60.9
A-a DO2*(mmHg)	47.2	51.2	39.3

Figure 3. Time course of blood chemistry testing and right heart catheterization. After emboliza-tion, the serum levels of TBA and NH3 decreased, whereas those of BNP and mPAP increased.Vaso-dilator therapy was subsequently started, which resulted in an improvement in BNP, mPAP and PVR. PaO$_2$ and A-aDO$_2$ were measured in room air. *A-aDO$_2$: alveolar-arterial oxygen difference, BNP: brain natriuretic peptide, TBA: total bile acid, mPAP: mean pulmonary artery pressure, NH3: ammonia, PVR: pulmonary vascular resistance

Discussion

The present case had coexisting HPS and PAH caused by CPSS. Pulmonary vascular disorders with liver diseases range from HPS to PoPH (1-4), and these two disorders dif-fer from one another according to a pathophysiological point of view. HPS is caused by vasodilation of the pulmonary ar-teries with normal PVR (1-4), whereas PoPH is caused by vasoconstriction of the muscular artery or high-flow circula-tion with elevated PVR (1, 2, 4). Although there are some reports of coexisting HPS and PoPH (10-12), it remains un-clear whether they actually coexist. In a previous autopsy case of HPS and PoPH, hypertensive pulmonary arteriopathy and pulmonary precapillary dilations were noted (10). In an-other report, HPS developed into PoPH in a patient with liver cirrhosis (12). In the present case, we consider that HPS and PoPH coexisted and only PAH worsened after em-bolization of the shunts.

CPSS also causes liver disease and pulmonary complica-tions (10). It was previously reported that 10-18% of pa-tients with CPSS were accompanied by HPS or PoPH and that shunt closure either by surgery or transcatheter emboli-zation was effective (5-8). HPS and PoPH are considered to be caused by a high-flow circulation and increased vasoac-tive mediators that are usually metabolized in the liver (1). To treat hypoxia caused by HPS in the present case, we suc-cessfully performed transcatheter embolization. However, the patient's PAH was exacerbated. Indeed, Franchi-Abella et al. reported that shunt closure was not effective in three pediat-ric patients with both PoPH and PAH caused by CPSS (5). Because embolization itself was successful, reversible fac-tor(s) other than the flow volume may be involved in the worsening of PAH. Moreover, hypoxia remained after em-bolization, which could have been due to the intrapulmonary shunt and/or vasodilator treatment for PAH.

Recent studies found that the exhaled nitric oxide (NO) concentration is elevated in patients with HPS associated with liver cirrhosis or portal hypertension (4, 13), and the endothelial expression of type B endothelin receptor is upregulated in HPS (14). In PAH patients, endothelin causes vasoconstriction through activation of endothelial type A and type B endothelin receptors (15). In HPS patients, only type B endothelin receptors are upregulated in the endothelium, leading to increased levels of NO (4, 14). In addition, Gram-negative bacteria and endotoxin, both of which origi-nate from the bowel, are usually trapped in the liver, causing NO production and vasodilation (4). This vasodilation is considered to cause intrapulmonary shunting (4). Thus, the same mechanism for HPS in portal hypertension may also exist in CPSS. In the present case, shunt closure isolated the pulmonary arteries from these vasodilators. Finally, conven-tional vasodilators, including endothelin antagonist, were ef-fective after shunt closure in the present case. It is possible that NO, endothelin and endothelin receptors are involved in the mechanism of the coexistence of HPS and PAH. How-

ever, further studies are needed to confirm this notion.

The patient had PAPVR, which could also cause PAH. After shunt closure, PVR or the mean PAP elevated, while the Qp/Qs ratio remained unchanged and hypoxia worsened. PAH was considered to be affected by the portopulmonary circulation, therefore, we started vasodilation therapy for PAH. Because the patient's pulmonary hemodynamics in the right heart catheterization test and symptoms improved, we continued vasodilation therapy. We closely monitored her hemodynamics and discussed whether to continue vasodilation therapy and indications for surgical repair of PAPVR.

In conclusion, we reported a case of PH associated with CPSS complicated by coexisting HPS and PoPH. Shunt closure exacerbated PAH, however, conventional vasodilator therapy was effective. Some substances that are usually cleared in the liver may be involved in the mechanism of coexisting HPS and PoPH.

The authors state that they have no Conflict of Interest (COI).

References

1. Hervé P, Lebrec D, Brenot F, et al. Pulmonary vascular disorders in portal hypertension. Eur Respir J **11**: 1153-1166, 1998.
2. Porres-Aguilar M, Gallegos-Orozco JF, Garcia H, Aguirre J, Macias-Rodriguez RU, Torre-Delgadillo A. Pulmonary vascular complications in portal hypertension and liver disease: a concise review. Rev Gastroenterol Mex **78**: 35-44, 2013.
3. Grace JA, Angus PW. Hepatopulmonary syndrome: update on recent advances in pathophysiology, investigation, and treatment. J Gastroenterol Hepatol **28**: 213-219, 2013.
4. Hoeper MM, Krowka MJ, Strassburg CP. Portopulmonary hypertension and hepatopulmonary syndrome. Lancet **363**: 1461-1468, 2004.
5. Franchi-Abella S, Branchereau S, Lambert V, et al. Complications of congenital portosystemic shunts in children: therapeutic options and outcomes. J Pediatr Gastroenterol Nutr **51**: 322-330, 2010.
6. Ohno T, Muneuchi J, Ihara K, et al. Pulmonary hypertension in patients with congenital portosystemic venous shunt: a previously unrecognized association. Pediatrics **121**: e892-e899, 2008.
7. Sokollik C, Bandsma RH, Gana JC, van den Heuvel M, Ling SC. Congenital portosystemic shunt: characterization of a multisystem disease. J Pediatr Gastroenterol Nutr **56**: 675-681, 2013.
8. Grimaldi C, Monti L, Falappa P, d'Ambrosio G, Manca A, de Ville de Goyet J. Congenital intrahepatic portohepatic shunt managed by interventional radiologic occlusion: a case report and literature review. J Pediatr Surg **47**: e27-e31, 2012.
9. Sears EH, Aliotta JM, Klinger JR. Partial anomalous pulmonary venous return presenting with adult-onset pulmonary hypertension. Pulm Circ **2**: 250-255, 2012.
10. Tasaka S, Kanazawa M, Nakamura H, et al. An autopsied case of primary pulmonary hypertension complicated by hepatopulmonary syndrome. Nihon Kyobu Shikkan Gakkai Zasshi **33**: 90-94, 1995 (in Japanese, Abstract in English).
11. Pham DM, Subramanian R, Parekh S. Coexisting hepatopulmonary syndrome and portopulmonary hypertension: implications for liver transplantation. J Clin Gastroenterol **44**: e136-e140, 2010.
12. Mal H, Burgière O, Durand F, Fartoukh M, Cohen-Solal A, Fournier M. Pulmonary hypertension following hepatopulmonary syndrome in a patient with cirrhosis. J Hepatol **31**: 360-364, 1999.
13. Nunes H, Lebrec D, Mazmanian M, et al. Role of nitric oxide in hepatopulmonary syndrome in cirrhotic rats. Am J Respir Crit Care Med **164**: 879-885, 2001.
14. Luo B, Liu L, Tang L, et al. Increased pulmonary vascular endothelin B receptor expression and responsiveness to endothelin-1 in cirrhotic and portal hypertensive rats: a potential mechanism in experimental hepatopulmonary syndrome. J Hepatol **38**: 556-563, 2003.
15. Davie N, Haleen SJ, Upton PD, et al. ET_A and ET_B receptors modulate the proliferation of human pulmonary artery smooth muscle cells. Am J Respir Crit Care Med **165**: 398-405, 2002.