Aggravation of Hepatopulmonary Syndrome after Sildenafil Treatment in a Patient with Coexisting Portopulmonary Hypertension

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Hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPHTN) are complications of portal hypertension and cirrhosis. Their pathophysiological mechanisms clearly differ. HPS is characterized by a defect in arterial oxygenation induced by pulmonary vascular dilatation in the presence of liver disease.1,2 In contrast, PPHTN is predominantly due to excessive pulmonary vasoconstriction and vascular remodeling that eventually leads to right-heart failure, but is rarely associated with hypoxia. We report a case of a patient who had both HPS and PPHTN at the time of presentation. HPS was aggravated after sildenafil administration for the treatment of PPHTN. We demonstrated increased amount of intrapulmonary shunt after sildenafil challenge by using agitated saline contrast transthoracic echocardiography. (Korean Circ J 2015;45(1):77-80)

KEY WORDS: Hepatopulmonary syndrome; Pulmonary arterial hypertension; Sildenafil.

Introduction

Hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPHTN) are complications of portal hypertension and cirrhosis. HPS is characterized by a defect in arterial oxygenation induced by pulmonary vascular dilatation in the presence of liver disease.1,2 In contrast, PPHTN is predominantly due to excessive pulmonary vasoconstriction and vascular remodeling that eventually leads to right-heart failure, but is rarely associated with hypoxia. We reported a case in which a patient had both HPS and PPHTN at the time of presentation. HPS was aggravated after sildenafil administration for the treatment of PPHTN.
Liver cirrhosis was staged as Child-Pugh class B. N-terminal pro-B-type natriuretic peptide was 535.3 pg/mL. Arterial blood gas analysis (ABGA) obtained at room air in supine position revealed a resting PaO2 of 84.4 mm Hg and an alveolar-arterial (A-a) oxygen gradient of 22.9 mm Hg. Initial transthoracic echocardiography (TTE) demonstrated normal left-ventricular and right-ventricular function and mild tricuspid regurgitation (Fig. 1C), with an increased right ventricular systolic pressure of 53 mm Hg (Fig. 1D). Albumin macroaggregate lung perfusion scan showed normal perfusion without significant intrapulmonary shunt (IPS). A saline-contrast TTE (SC-TTE) showed delayed appearance of bubbles in the left atrium following five heart cycles, suggestive of IPS (Fig. 2A). Thirty minutes after a challenge dose of 50 mg sildenafil orally, SC-TTE showed IPS aggravation (Fig. 2B) with a PaO2 drop to 56.1 mm Hg. Four hours after the sildenafil challenge, SC-TTE showed IPS improvement with a PaO2 rise to 71.1 mm Hg (Fig. 3). On the next day, the symptoms and PaO2 did not improve after a challenge dose of 5 mcg iloprost inhalation (PaO2 values were obtained from two ABGAs, performed just before and 15 minutes after the start of iloprost inhalation: 89.8 mm Hg and 86.3 mm Hg, respectively). After administration of furosemide and permanent discontinuation of sildenafil, the patient had significant clinical improvement. The patient remained in WHO FC II without further hospitalization at the 7 months follow-up. Living donor liver transplantation was eventually performed due to advanced liver cirrhosis.

**Discussion**

The patient had longstanding liver cirrhosis and portal hypertension before he presented with exertional dyspnea. Additionally, a right-heart catheterization showed an elevated mean PAP at rest (35 mm Hg). There was no evidence of an alternative cause of the
such as collagen vascular disease, congenital heart disease, and pulmonary thromboembolism. Thus the patient was diagnosed as PPHTN. However, dyspnea worsened after sildenafil treatment. The lack of decompensating factors led to the consideration of IPS as the predominant cause of worsening dyspnea, after sildenafil administration. After admission to our hospital, ABGA revealed an oxygenation defect (alveolar-arterial oxygen gradient >15 mm Hg) and SC-TTE showed positive findings, i.e., microbubble opacification of the left heart chambers 5 cycles after right atrial passage. Therefore, coexisting HPS was diagnosed. Significant clinical improvement occurred on administration of diuretics and discontinuation of sildenafil. We recognized that our case had several limitations. Firstly, we do not know the exact reason for CMR at the other hospital, rather than pulmonary CT angiography, prior admission to our institution. We speculated that CMR was performed for assessment of structure and function of the right ventricle, via the measurement of right ventricular volumes and ejection fractions. We did not perform pulmonary CT angiography because pulmonary thromboembolism was excluded based on the CMR. Secondly, we did not perform any functional test.

Pathophysiologically, HPS is almost exactly the opposite of PPHTN. While abnormal intrapulmonary vascular dilatation is the hallmark of the HPS, PPHTN results from excessive pulmonary vasoconstriction and vascular remodeling. It was interesting that these two independent and opposite processes could occur in the same patient.

There have been 10 other documented cases of coexisting HPS and PPHTN in the same adult patient. Sequential development was suspected in 8 of the 10 cases, with HPS developing first, followed by PPHTN; and in the other 2 cases, HPS and PPHTN coexisted at the time of presentation. Our case was unique in that a patient with both HPS and PPHTN at the time of presentation developed aggravation of HPS on sildenafil therapy for the treatment of PPHTN. We demonstrated increased amount of IPS after sildenafil administration by SC-TTE.

Sildenafil is an oral phosphodiesterase-5 inhibitor with proven benefits to patients with PAH via enhanced nitric oxide (NO) availability in pulmonary vasculature. Patients with PPHTN showed sustained improvement in a 6 minutes walking distance and a decrease in B-type natriuretic peptide in response to sildenafil alone or in combination with prostanoid. Additionally, sildenafil effectively reduced PVR in patients prior to liver transplantation. However, in theory any vasodilator can exacerbate hypoxemia by reduction of PVR and aggravation of ventilation-perfusion mismatch. A high dose of sildenafil resulted in a dose-dependent fall in PVR associated with a marked increase in ventilation-perfusion heterogeneity in a porcine model. A patient with a history of PAH and treated with...
sildenafil, was reported with IPS and severe hypoxemia. Accurate diagnosis by SC-TTE and drug discontinuation allowed rapid symptomatic recovery and improvement of hypoxemia in the presented case.

Interestingly, inhaled iloprost neither improved nor aggravated the symptoms and hypoxemia. The mechanism by which sildenafil but not iloprost, aggravated IPS in this case, might be related to differential expression of the endothelin-1 (ET-1) receptor between HPS and PPHTN, as well as different mechanisms of the two drugs. ET-1 bound to receptor A leads to vasoconstriction and increased PVR. In contrast, as seen in rat models of HPS, binding of ET-1 to receptor B leads to upregulation of endogenous nitric oxide synthetase and increased nitric oxide production, resulting in pulmonary vasodilatation. This results in pulmonary vasodilatation, shunting, and hypoxemia characteristic of HPS. Sildenafil is an oral phosphodiesterase-5 inhibitor that enhances NO-mediated vasodilation, while iloprost is a synthetic analog of prostacyclin that causes cyclic adenosine monophosphate mediated smooth muscle relaxation and vasodilatation. Therefore, different mechanisms of the two drugs may have resulted in a different clinical course in this patient.

The diagnosis of HPS requires confirmation of pulmonary vascular dilatation and SC-TTE is considered the most practical method to do so. Under normal circumstances, only right heart chambers are opacified and the microbubbles are trapped in the pulmonary capillaries. The presence of microbubbles in the left chamber is suggestive of an arteriovenous connection. Late arrival of microbubbles in the left atrium after a time delay of 4–8 cardiac cycles is diagnostic of IPS. SC-TTE may be performed to exclude HPS before initiation of vasodilator therapy for the treatment of PPHTN.

In conclusion, HPS and PPHTN can occur in the same patient and sildenafil may be associated with aggravation of HPS in patients with coexisting HPS and PPHTN. In such cases, SC-TTE may be helpful to demonstrate IPS.

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