Development of hepatopulmonary syndrome during combination therapy for portopulmonary hypertension

To the Editor:

Portopulmonary hypertension (PoPH) and hepatopulmonary syndrome (HPS) are rare pulmonary vascular complications of portal hypertension [1]. In PoPH, pulmonary vascular resistance (PVR) is elevated, resulting in heightened right ventricular workload which may lead to right-sided heart failure. HPS is characterised by progressive hypoxaemia due to diffusion–perfusion mismatching caused by regional, mostly basilar, intrapulmonary vascular dilatations of capillary and pre-capillary vessels. The exact pathogenesis of both conditions is unclear, as is the underlying predisposition causing a small proportion of patients with liver disease to develop PoPH or HPS.

Although few cases of simultaneous occurrence of PoPH and HPS have been reported [2, 3], most patients present with distinct syndromes, *i.e.* either PoPH or HPS. Of note, there are several case reports demonstrating resolution of HPS with the development of PoPH [4–6], suggesting that the development of an obliterating pulmonary vasculopathy may result in redistribution of pulmonary blood flow away from areas where intrapulmonary vascular dilatations are abundant. To the best of our knowledge, there are no reports on the development of HPS in patients undergoing medical treatment of PoPH. We here report on the clinical course of a patient initially presenting with severe PoPH who had resolution of pulmonary hypertension with combined pulmonary vasodilator therapy, but developed HPS at the same time.

This 56-year-old woman with a history of cirrhosis (Child–Pugh class B) and portal hypertension due to autoimmune hepatitis was admitted to our hospital because of progressive dyspnoea on exertion and right-sided heart failure with extensive fluid retention. On admission, she presented in World Health Organization functional class (FC) IV and was unable to walk. Echocardiography showed severely impaired right heart function. She was mildly hypoxaemic but contrast-enhanced echocardiography with agitated saline showed no appearance of microbubbles in the left heart, thus excluding the presence of HPS at that time. Right heart catheterisation revealed severe pulmonary hypertension (table 1). Other causes of pre-capillary pulmonary hypertension were ruled out and a diagnosis of PoPH was made. Combination therapy with the phosphodiesterase-5 inhibitor tadalafil and the endothelin-receptor antagonist macitentan was initiated.

Over the following weeks, the patient's clinical condition improved substantially (table 1). After 2 months, she presented in FC II with a 6-min walk distance of more than 400 m. After 6 months, N-terminal pro-B-type natriuretic peptide (NT-proBNP) dropped to near normal levels and echocardiography showed ameliorated right ventricle function. After 1 year, however, exertional dyspnoea started to increase again. At this time, hypoxaemia worsened, and the patient developed orthodeoxia with an adequate increase in arterial oxygen tension while breathing 100% oxygen (table 1). Pulmonary function testing showed normal lung volumes and the diffusion capacity for carbon monoxide was 73% of the predicted value. Computed tomography of the chest showed no signs of parenchymal lung disease or pleural effusions, but revealed dilated pulmonary vessels in the basilar lung zones. NT-proBNP remained low and echocardiography showed normalised right heart function. On right heart catheterisation, pulmonary artery pressures were near normal with a high cardiac output and a normal PVR (table 1). Now, contrast-enhanced

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Cite this article as: Olsson KM, Meyer K, Berliner D, *et al*. Development of hepatopulmonary syndrome during combination therapy for portopulmonary hypertension. *Eur Respir J* 2019; 53: 1801880 [https://doi.org/10.1183/13993003.01880-2018].

TABLE 1 Patient characteristics

	Baseline 06/2017	Follow up 09/2017	Follow up 01/2018	Follow up 07/2018	Follow up 08/2018
Functional class	IV	II	II	III	III
6-min walk distance m		412	473		363
PAH therapy		Tadalafil/macitentan	Tadalafil/macitentan	Tadalafil/macitentan	Tadalafil
NT-proBNP ng·L^{-1}	7086		198	171	131
Right atrial pressure mmHg	15			7	
Mean pulmonary artery pressure mmHg	48			23	
Pulmonary artery wedge pressure mmHg	10			11	
Cardiac output L·min^{-1}	4.3			9.4	
Cardiac index L·min^{-1}·m^{-2}	2.3			5.3	
PVR dyn·s·cm^{-5}	706			102	
Mixed venous oxygen saturation %	55			77	
P_{aO_2} mmHg (upright/supine/100% oxygen)	74/-/-	64/-/-	57/-/-	55/62/546	60/-/-
P_{aCO_2} mmHg	29	31	31	29	33

PAH: pulmonary arterial hypertension; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PVR: pulmonary vascular resistance; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension.

echocardiography disclosed severe intrapulmonary shunting (>100 microbubbles appearing in the left atrium and the left ventricle after four cardiac cycles), confirming the diagnosis of HPS [7, 8].

We interpreted these findings as complete resolution of PoPH complicated by development of HPS, both associated with the combined use of pulmonary vasodilator therapy. Therefore, macitentan was stopped and tadalafil was continued as monotherapy. 6 weeks later, the patient was still in FC III with slight improvement of her blood gases, while NT-proBNP remained low and echocardiography continued to show normal right ventricle function. At present, the patient is being evaluated for liver transplantation.

In summary, our case illustrates that HPS can develop as a consequence of the use of pulmonary vasodilators in patients with PoPH. We cannot exclude the possibility that drug-mediated pulmonary vasodilation was the direct cause of HPS, although we believe that it is more likely that pre-existing HPS was masked by the presence of severe pulmonary hypertension and unmasked by its successful treatment. It is important that physicians are aware that HPS may develop during medical treatment of PoPH and monitor their patients accordingly. In addition, it is possible that the risk of developing HPS is particularly high in patients with PoPH who receive combination therapy with pulmonary vasodilators, but this hypothesis needs to be addressed in future clinical trials.

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Received: Oct 03 2018 | Accepted after revision: Nov 14 2018

Conflict of interest: K.M. Olsson reports personal fees for speaking/consultations from Actelion. K. Meyer has nothing to disclose. D. Berliner has nothing to disclose. M.M. Hoeper reports personal fees for speaking/consultations from Actelion, Bayer, GSK and Merck.

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