

Pulmonary arterial hypertension combined with a high cardiac output state: Three remarkable cases

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ABSTRACT

A congenital extrahepatic portosystemic venous shunt (CEPVS), also known as an Abernethy malformation, is a rare cause of pulmonary arterial hypertension (PAH). In this case series, we describe three male patients of 30, 23, and 27 years of age with PAH due to a CEPVS. In all three patients, a right heart catheterization revealed a high cardiac output. The aim of this case series is to make pulmonary hypertension physicians aware of the possibility of a CEPVS when PAH is accompanied with a high cardiac output state.

Key Words: abernethy malformation, congenital extrahepatic portosystemic venous shunt, congenital extrahepatic portosystemic shunt, pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is usually accompanied by a decreased cardiac output. A high cardiac output in a patient with PAH could point to the presence of anemia, chronic hypercapnia, hyperthyroidism, congenital heart disease, or portal hypertension.^[1,2] The aim of this case series is to make pulmonary hypertension physicians aware that, in absence of these disorders, a congenital extrahepatic portosystemic venous shunt (CEPVS) needs to be considered as a determinant of PAH in patients with a high cardiac output state.

CASE REPORTS

Case 1

When this patient was 21 years old, a routine examination showed right axis deviation on an electrocardiogram (ECG). A subsequent cardiac ultrasound showed a dilated pulmonary trunk and mild tricuspid regurgitation. Eight years later, the patient complained of chest pain and hemoptysis during a mountain hike. Evaluation by the cardiologist revealed a hypertrophic and dilated RV and a dilated RV outflow tract. He was referred to our

hospital for the evaluation of pulmonary hypertension. Prior to the episode of hemoptysis, the patient had been in perfect health with normal exercise tolerance. Physical examination was normal except for a systolic murmur loudest in the second intercostal space on the left side. A laboratory blood test showed elevated liver tests and an elevated ammonia (Table 1). A chest radiograph showed enlargement of the central pulmonary arteries, while evidence of right axis deviation and right atrial enlargement were seen on the ECG. Pulmonary function test showed a mild reversible obstructive pattern (Table 2). The patient completed a normal cardiopulmonary exercise test (Table 2). On a CT angiography, a dilated pulmonary trunk and right ventricle were visible, but no signs of pulmonary embolism. A high-resolution computed tomography (HRCT) showed normal lung parenchyma. A right heart catheterization (RHC) confirmed PH with a mean pulmonary artery pressure (mPAP) of 51 mmHg, pulmonary capillary wedge pressure (PCWP) of 3 mmHg, pulmonary vascular resistance (PVR) of 442 dyne.s.cm⁵,

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Access this article online

Quick Response Code:

Website: www.pulmonarycirculation.org

DOI: 10.4103/2045-8932.113185



How to cite this article: Spruijt OA, Bogaard H, Vonk-Noordegraaf A. Pulmonary arterial hypertension combined with a high cardiac output state: Three remarkable cases. *Pulm Circ* 2013;3:440-3.

right atrial pressure (RAP) 3 mmHg, and a cardiac output (CO) of 8.9 L/min (Table 3). Cardiac magnetic resonance imaging (cMRI) was performed showing signs of RV hypertrophy and dilatation. An increased RV end-diastolic volume (RVEDV) of 246 ml and an RV ejection fraction (RVEF) of 64% were measured indicating RV enlargement with a well-maintained right ventricular function (Table 4). The elevated liver tests and the elevated ammonia suggested a hepatic problem. Ultrasonography (US) of the liver was performed and showed signs of a CEPVS. Further evaluation through MR angiography of the abdomen revealed splenomegaly and drainage of the portal vein (PV) directly into the inferior vena cava (IVC). PAH due to a CEPVS (Abernethy malformation Type II) was diagnosed. The first patient was described in a previous case report in 2007.^[3] In that paper, the patient's medical history was described from a different perspective. Here, we highlight the presence of a high cardiac output in CEPVS, which we found in all subsequent CEPVS patients treated for PH in our clinic.

Case 2

At the age of 23, this man was admitted to the emergency department because of hemoptysis. The patient had no relevant medical history. Because a severely dilated pulmonary trunk on CT angiography (which was negative for pulmonary embolism) raised the suspicion of PH, the patient was referred to our hospital for further evaluation. At first presentation, the patient was asymptomatic with a normal exercise tolerance. Physical examination was normal except for a systolic murmur loudest in the second intercostal space on the left side. Blood biochemistry showed slightly elevated liver tests (Table 1). Pulmonary function tests and a cardiopulmonary exercise test were normal (Table 2). A lung perfusion SPECT showed irregular perfusion defects consistent with severe PH, but no clear signs of pulmonary embolism. An RHC confirmed PH with an mPAP of 42 mmHg, PCWP of 8 mmHg, PVR of 309 dyne.s.cm⁵, RAP of 4 mmHg, and a CO of 8.8 L/min (Table 3). A cMRI was performed showing signs of RV hypertrophy and dilatation, tricuspid regurgitation, and a strongly dilated pulmonary trunk. An increased RVEDV of 259 ml and an RVEF of 50% was measured indicating RV enlargement with almost preserved right ventricle function (Table 4). Because of the hyperdynamic circulation and elevated liver tests, Doppler US of the liver was performed. The US showed no flow in the portal vein and multiple regenerative nodular changes in the liver. For further evaluation, an MR angiography of the liver was performed, showing no portal vein and a widened hepatic artery and IVC. No CEPVS was visualized. A year later, a CT angiography of the liver was performed showing no portal vein, widened hepatic veins, splenic vein (SV), superior mesenteric vein (SMV), and drainage of the SV and SMV with a common trunk into the IVC. PAH due to a CEPVS (Abernethy malformation type I-B) was diagnosed.

Table 1: Baseline demographics, type of CEPVS, NYHA functional class and laboratory tests

	Cases		
	1	2	3
Age/sex	30/man	23/man	27/man
NYHA I/II/III/IV	I	I	I
Type of CEPVS	Type II	Type I-B	Type II
Laboratory tests (reference values)			
Bilirubine (<17 µmol/l)	37↑	27↑	8
Conjugated (<5 µmol/l)	10↑	8↑	-
AF (<86 U/l)	161↑	79	123↑
Y-GT (<55 U/l)	148↑	61↑	82↑
AST (<35 U/l)	43↑	47↑	56↑
ALT (<45 U/l)	37	37	46↑
Troponin (<0.05 µg/l)	<0.01	<0.01	<0.01
ProBNP (<86 ng/l)	47	215↑	74
Ammonia (10-45 µmol/l)	139↑	70↑	-

CEPVS: congenital extrahepatic portosystemic venous shunt; **NYHA:** New York Heart Association

Table 2: Cardiopulmonary exercise test and pulmonary function test

	Cases		
	1	2	3
VO ₂ max/Kg (ml/kg/min)	31.5	40.5	18
% from predicted	70	82	42
Work max (watt)	264	269	121
% from predicted	98	96	52
FEV1 (L)	4.3	4.1	3.4
% form predicted	92	85	79
Tiffenau (%)	69	70	76
DLCO (%)	72	-	67

FEV: Forced expiratory volume; **DLCO:** Diffusing Capacity of the Lung for Carbon Monoxide

Table 3: Right heart catheterization

RHC	Cases		
	1	2	3
mRAP (mmHg)	3	4	3
mPAP (mmHg)	51	42	37
PCWP (mmHg)	3	8	5
PVR (Dyne.s.cm ⁵)	442	309	298
CO (L/min)	8.9	8.8	8.6

mRAP: mean right atrial pressure; **mPAP:** mean pulmonary artery pressure; **PCWP:** pulmonary capillary wedge pressure; **PVR:** pulmonary vascular resistance; **CO:** cardiac output; **RHC:** right heart catheterization

Table 4: Cardiac magnetic resonance imaging

cMRI	Cases		
	1	2	3
(Reference values mean; SD)			
RV EDV (142 ml±31)	246	259	231
RV SV (88 ml±22)	158	130	100
RV EF (62%±10)	64	50	43

cMRI: cardiac magnetic resonance imaging; **EDV:** end-diastolic volume; **SV:** splenic vein; **EF:** ejection fraction; **RV:** reference value

Case 3

At the age of 25, this man was admitted to the hospital because of acute confusion. His medical history included mesangiocapillary glomerulonephritis and chronic

lymphedema. A hyperammonemia due to a persistent ductus venosus was found. Because of the known risk of developing PH in the presence of a ductus venosus, the patient was referred to the cardiologist. A cardiac ultrasound revealed a PAP of 52 mmHg. The patient, was referred to our hospital in 2008 for further evaluation. At presentation the patient was asymptomatic with a normal exercise tolerance. Physical examination showed no abnormalities except for bilateral lymphedema of the lower extremities. Laboratory blood tests revealed slightly elevated liver tests (Table 1). A chest radiograph showed no abnormalities. Pulmonary function tests were normal, but the peak oxygen uptake during cardiopulmonary exercise testing was decreased (Table 2). An HRCT showed normal lung parenchyma and a widened pulmonary trunk. A lung perfusion SPECT showed no perfusion defects. An RHC confirmed PH with an mPAP of 37 mmHg, PCWP of 5 mmHg, PVR of 298 dyne.s.cm⁵, RAP of 3 mmHg, and a CO of 8.6 L/min (Table 3). A cMRI was performed showing RV hypertrophy and tricuspid regurgitation. An increased RVEDV of 231 ml and an RVEF of 43% indicated RV enlargement and a slightly diminished right ventricular function (Table 4). Angiography of the superior mesenteric artery showed the PV and ductus venosus. A CEPVS from the PV into the right atrium was also visualized. PAH due to a combination of a persistent ductus venosus and a CEPVS (Abernethy malformation Type II) was diagnosed.

DISCUSSION

We described three patients with PAH due to an uncommon vascular anomaly, a CEPVS. PAH is normally accompanied by a low cardiac output. When PAH is combined with a high cardiac output and the most common causes of a high cardiac output state are excluded, a CEPVS should be considered.

Since 84% of PAH patients have severe symptoms and are in NYHA functional Class III/IV by the time of diagnosis,^[4] it is remarkable that the three described cases were asymptomatic at first presentation. Nevertheless, a literature search revealed that RV adaptation in CEPVS patients is not always as good as in our patients. Around 80 cases with a CEPVS have been described and in only a few of these cases, a combination with PAH was noted.

Ohno et al.^[5] described six patients with PAH due to a CEPVS. All patients were diagnosed under the age of 18. Three died of right heart failure at the age of 1, 16, and 22, respectively. Ersch et al.^[6] described a 20-month-old boy who died from right heart failure due to PAH caused by a CEPVS. Raghuram et al.^[7] described a one-year-old boy with a medical history of a corrected transposition of the great arteries and a moderate-sized ventricular septum defect. The patient presented with cyanosis and an RHC showed severe PAH which could not be explained by the intracardiac defect alone. Additional diagnostic tests revealed a CEPVS. Witters et al.^[8] described six patients with a CEPVS, of which there was one with PAH. This 17-year-old female presented with dyspnea and additional diagnostic tests revealed a CEPVS and a ventricular septum defect (VSD). Hori et al.^[9] and Lida et al.^[10] described the treatment of two young patients (3 and 7 years old) with PAH due to CEPVS with a living donor liver transplantation.

A CEPVS is a rare cause of PAH. A CEPVS was first described in 1793 by John Abernethy. In 1994, Morgan and Superina classified CEPVS into two groups, Abernethy type I and II based on hepatic portal perfusion.^[8,11] In Type I, hepatic portal branches are absent and there is no perfusion of the liver with portal blood. Abernethy Type I is subdivided into Type I-A and Type I-B. In Abernethy Type II, the hepatic portal system is intact, but some of the portal flow is diverted leading to partial perfusion of the liver with portal blood (Fig. 1; Adapted from ref.

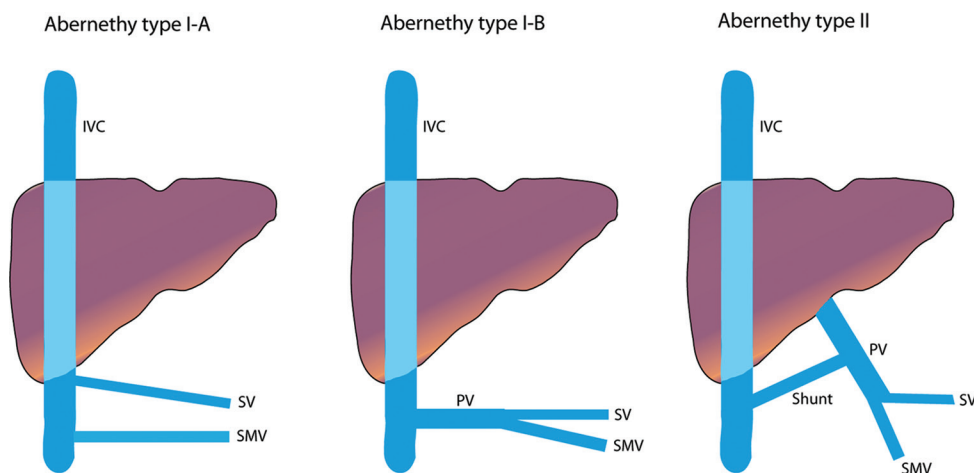


Figure 1: IVC: inferior vena cava; SV: splenic vein; SMV: superior mesenteric vein; PV: portal vein

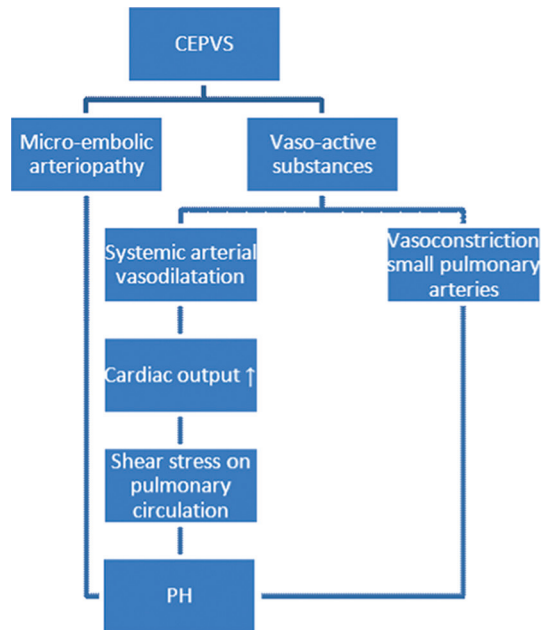


Figure 2: Pathophysiology CEPVS.

[12]). Drainage to the IVC is most common; however, drainage into the renal veins, iliac veins, azygos vein, or right atrium is also described.^[13,14]

It is thought that a CEPVS is the result of the complex embryonic development of the PV. Additional anomalies are often seen in patients with a CEPVS. A review of Murray et al.^[13] described 61 cases of CEPVS, both Abernethy Types I and II. Thirty-one percent of these cases had congenital heart disease. Hepatic lesions, such as nodular hyperplasia, hepatocellular carcinoma, and hepatoblastoma, are also frequently found in conjunction with CEPVS.

The pathophysiology of PH as a result of a CEPVS is still unclear. Witters et al.^[8] suggested that the mechanism of a hyperdynamic circulatory state in CEPVS patients could be partly similar to the mechanism in portal hypertension. Increased concentrations of vasoactive substances, normally metabolized in the liver, lead to systemic arterial vasodilatation and a compensatory increase in cardiac output.^[15] The high cardiac output induces shear stress in the pulmonary circulation which can lead to pulmonary vascular remodeling and an increase of PVR. Paradoxically, the low systemic vascular resistance may be accompanied by pulmonary vasoconstriction, caused by other unmetabolized vasoactive substances.^[2,8] Ohno et al.^[5] speculated about the possibility of the development of a microembolic

arteriopathy in the lung when absence of portal flow results in failure of hepatic clearance of microparticles coming from the mesenteric circulation (Fig. 2).

In conclusion, PAH combined with a high cardiac output state is a rare phenomenon. When other causes of a high cardiac output are excluded, a CEPVS as a determinant of PAH should be considered.

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Source of Support: Anton Vonk-Noordegraaf was financially supported by the NWO, Vidi Grant, project number 91.796.306, **Conflict of Interest:** None declared.