

Clinical implications of partial anomalous pulmonary venous connection: a rare cause of severe pulmonary arterial hypertension

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Abstract

Isolated partial anomalous pulmonary venous connection (PAPVC) is an uncommon congenital heart anomaly that is sporadically associated with pulmonary arterial hypertension in the adult population. The diagnosis and therapy for this condition are challenging. We report on three cases of patients with unexpected severe precapillary pulmonary hypertension in single PAPVC treated with an upfront pulmonary arterial hypertension-specific combination therapy. Our cases indicate that the combination of PAPVC and pulmonary comorbidities may trigger the development of severe pulmonary arterial hypertension. The initiation of pulmonary arterial hypertension-targeted combination therapy revealed to be a safe and efficacious strategy for patients with PAPVC-associated severe pulmonary arterial hypertension.

Keyword

partial anomalous pulmonary venous connection, pulmonary arterial hypertension, chronic obstructive pulmonary disease, congenital heart disease, therapy

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Introduction

Partial anomalous pulmonary venous connection (PAPVC) defines a specific group of congenital cardiovascular anomalies caused by the abnormal return of at least one, but not all of the pulmonary veins directly to the right atrium or indirectly through a variety of venous connections from the anomalous pulmonary vein. We present three cases of PAPVC associated with severe precapillary pulmonary hypertension (PH) and discuss therapeutic options by reviewing the current literature.

Clinical case studies

Ethics

The ethics committee of the Medical University of Innsbruck waived the need for ethics approval for the collection,

analysis and publication of the retrospectively obtained and anonymized data for this clinical case series. Written informed consent was obtained for the publication of this non-research case series. Informed consent was provided by the subjects or their legally authorized representative.

Case 1

In January 2017, a 71-year-old male patient visited a primary care hospital because of a syncope and an

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exacerbation of an underlying chronic obstructive pulmonary disease (COPD; classified as GOLD 4D). Due to severe oxygen desaturation ($\text{PaO}_2 = 38 \text{ mmHg}$) despite oxygen supplementation at a flow rate of 15 L/min, the patient was transferred to the intensive care unit. Laboratory parameters revealed significantly elevated cardiac markers (N-terminal pro-B-type natriuretic peptide (NT-proBNP) 9762 ng/L), while inflammatory markers such as C-reactive protein (CRP) were only moderately elevated. Echocardiographic examination revealed signs of right heart failure, tricuspid regurgitation grade 3 and a calculated systolic pulmonary arterial pressure of 95 mmHg. The patient was subjected to a CT scan of the chest which presented no signs of pulmonary embolism, but revealed an anomalous pulmonary venous connection of the left upper vein to the brachiocephalic vein (Fig. 1). Right heart catheterization (RHC) was performed and revealed a severe pre-capillary PH with a mean pulmonary arterial pressure (mPAP) of 73 mmHg (Table 1). We therefore considered the use of pulmonary arterial hypertension (PAH) – specific drugs and initiated an upfront combination therapy with tadalafil 20 mg per day and ambrisentan 5 mg per day,

followed by an up-titration scheme. The PAH treatment was well tolerated and later intensified with the addition of the oral prostacyclin receptor agonist selexipag, resulting in an improvement in patients' symptoms, NT-proBNP, RHC hemodynamic measures and echocardiographic findings (Table 1).

Case 2

In August 2017, a 42-year-old male patient with an already established diagnosis of PAPVC (left upper vein to the brachiocephalic vein) who suffered from severe PH, was referred to our department. The diagnosis of PAPVC was established in 2010 at the age of 36 years because of progressive dyspnea on exertion. At that time, a CT scan of the chest revealed the anomalous pulmonary venous return (Fig. 1), and an echocardiographic examination indicated right heart dysfunction, while an interatrial septal defect with a left-right shunt was excluded (Fig. 2). RHC revealed a severe pre-capillary PH (Table 1), and the patient was evaluated for a combined heart–lung transplantation. However, this therapeutic option was rejected following

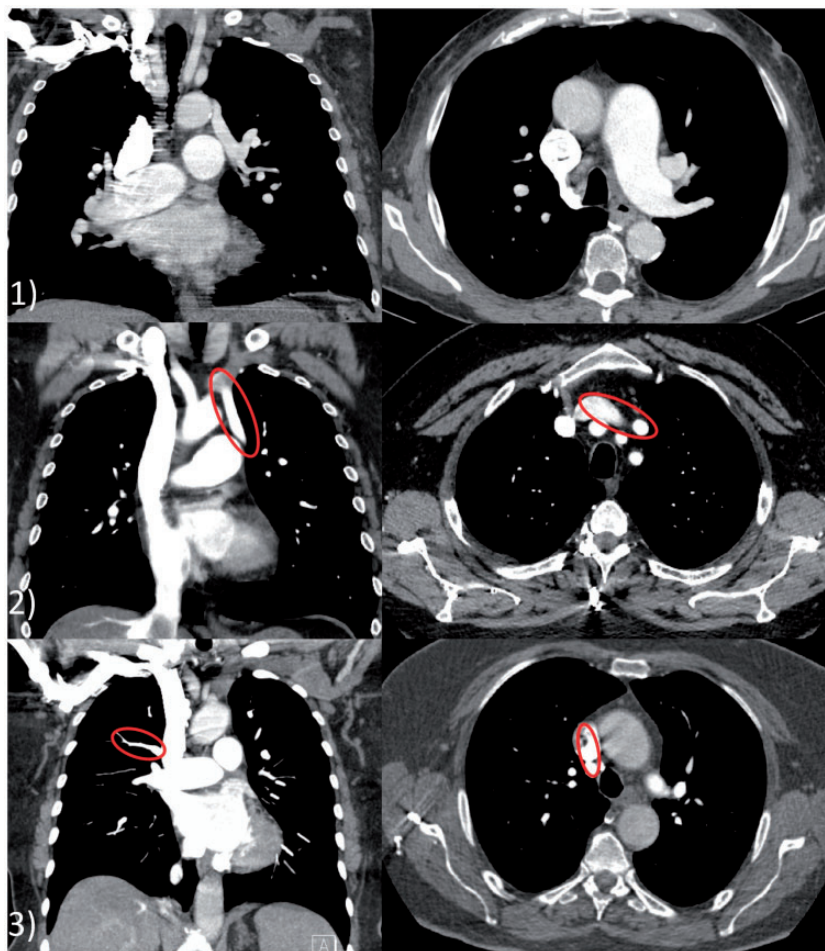


Fig. 1. CT scans of the thorax (patient from cases 1–3). Red circles indicate the partial anomalous pulmonary venous connection: (1) patient 1: left upper vein to the brachiocephalic vein; (2) patient 2: left upper vein to the brachiocephalic vein; (3) patient 3: right upper vein to superior v. cava.

Table 1. Characteristics of patients before and after initiation of PAH-targeted therapy.

	Case 1		Case 2		Case 3	
Age at diagnosis	71		36		76	
Follow-up in months	12		94		8	
Gender	M		M		F	
PAPVC details	Left upper vein to the brachiocephalic vein		Left upper vein to the brachiocephalic vein		Right upper vein to superior v. cava; patent foramen ovale	
Relevant pulmonary comorbidity	emphysema (A1AT genotype MZ), COPD grade 3, group D		obstructive sleep apnea (Apnea-Hypopnea Index = 25.7)			
PH-related parameters	Diagnosis	Follow-up	Diagnosis	Follow-up	Diagnosis	Follow-up
Functional class	III	II	III	III	III	II
TAPSE (mm)	26	30	–	28	15	22
RAA (cm ²)	40.5	35	27	46	31	22
mPAP (mmHg)	74	43	51	49	50	52
mRAP (mmHg)	10	11	9	12	12	14
mPAWP (mmHg)	10	13	6	9	11	12
DPG (mmHg)	40	25	29	18	22	19
PVR (WU)	11.23	3.33	11	8.04	16.73	13.65
CI (L/min/m ²)	3.94	4.62	2.78	4.81	1.27	1.72
Systemic flow (L/min)	7.60	12.49	6.00	10.33	2.06	3.35
Pulmonary flow (L/min)	5.69	10.41	4.09	4.97	2.32	3.14
SaO ₂	71.9	85.8	98.8	86.1	92	91.4
SMWD (m)	<100 m	248	540	–	<100 m	345 m
DLCOc (%)	16.6	18.0	85	54.5	75.9	68
Reveal score	12	10	7	9	10	7
PAH-specific therapy	Triple combination (tadalafil, ambrisentan, selexipag)		Triple combination (macitentan, riociguat, inhaled iloprost)		Double combination (sildenafil, macitentan)	
Laboratory findings						
NT-proBNP (ng/L)	4788	680	844	1192	3375	1208
Hemoglobin (g/dL)	16.3	16.0	16.5	14.9	15.9	13.7
CRP (mg/dL)	0.06	0.06	0.61	0.74	0.54	0.35
paO ₂ (mmHg)	49 (3 L/min O ₂)	44.6 (3 L/min O ₂)	58	55.9 (4 L/min O ₂)	64	66.8
AaDO ₂ (mmHg)	49 (3 L/min O ₂)	48 (3 L/min O ₂)	55.1	57.6 (4 L/min O ₂)	44.6	39

TAPSE: tricuspid annular plane systolic excursion; RAA: right atrium area; mPAP: mean pulmonary arterial pressure; mRAP: mean pulmonary arterial pressure; mPAWP: mean pulmonary arterial wedge pressure; DPG: diastolic pulmonary gradient; PVR: pulmonary vascular resistance; CI: cardiac index; SaO₂: arterial saturation of O₂; SMWD: six-minute walking distance; DLCOc: hemoglobin-adjusted diffusing capacity for carbon monoxide; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

the patients' will and because of recurrent alcoholism. Thus, PH was treated with a combination therapy with sildenafil, bosentan and inhalative iloprost. The pharmacological therapy was later modified to macitentan and the progression of clinical symptoms led to a switch from sildenafil to riociguat (2.5 mg 3 × /d), which was well tolerated and improved patients' symptoms and cardiopulmonary parameters.

Case 3

A 76-year-old female patient with a newly diagnosed PH presented at our department for further evaluation in February 2018. PAPVC and a patent foramen ovale (PFO) were detected by CT scan (Fig. 1), while an

interatrial septal defect with left-right shunt was excluded by transesophageal echocardiography (Fig. 2). RHC revealed severe precapillary PH with a mPAP of 50 mmHg (Table 1). The patient suffered from severe dyspnea on exertion and the initial six-minute walking distance (SMWD) was below 100 m. There was no evidence for other pulmonary comorbidities or diseases. We decided to initiate a specific PAH treatment strategy and started an upfront combination therapy with sildenafil and macitentan, which leads to a significant increase in the SMWD, a decrease in NT-proBNP, as well as a clear improvement of dyspnea and WHO functional class after 32 weeks of follow-up. In line with the clinical improvement, the follow-up RHC showed improved hemodynamic parameters (Table 1).

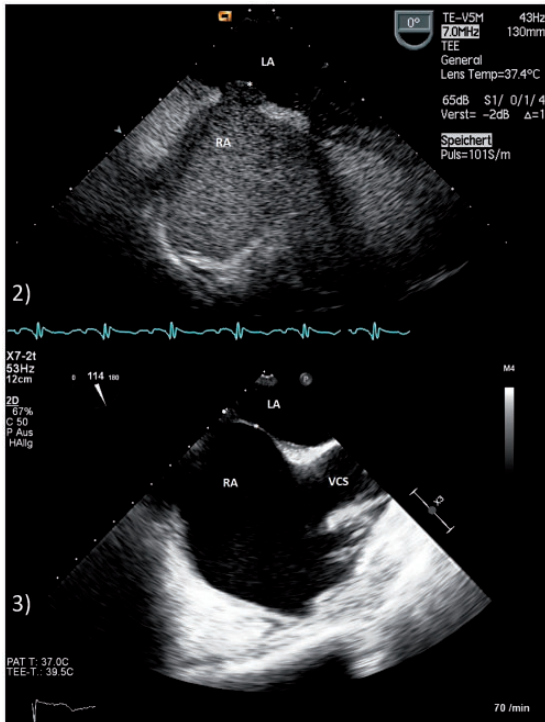


Fig. 2. An interatrial septal defect with a left–right shunt was excluded by transesophageal echocardiography (TEE) in two patients. The pictures above show standard TEE views at mid-esophageal level; (2) patient 2, (3) patient 3. RA: right atrium; LA: left atrium; AV: aortic valve; *interatrial septum.

Discussion

PAPVC is an uncommon congenital heart disease (CHD) with a reported prevalence of 0.4–0.7% in the general population according to autopsy studies.¹ The increasing number of case reports on incidental PAPVC suggests a higher incidence than so far estimated, owing to the fact that the clinical presentation of PAPVC is often asymptomatic.^{2–5} Right-sided PAPVCs draining into the superior vena cava have been reported to be more common (90% right vs. 17% left); however, recent data suggest a difference in anatomic distributions between pediatric and adult patients.^{6–9} CHD associated with PH is included in the group 1 of the WHO classification of pulmonary hypertension (PAH).¹⁰ Only scarce data are provided on the development of PAH in PAPVC patients. The initial predominant left-to-right shunting associated with this anomaly may go undetected for years with gradual development of right-sided volume overload that leads to PAH via pulmonary vascular remodeling and consecutive right heart failure.^{11,12} The European Society of Cardiology (ESC) statement on ASD associated with PAPVC from 2010 notes that pulmonary arterial pressure can be normal in affected patients, but on average increases with age.¹³ Severe pulmonary vascular disease is described to be rare (<5%) and its development presumably requires additional factors, including genetic predisposition, with similar genetic variations as seen in

idiopathic PAH. A retrospective study by Sahay et al. described PH in 14 patients with PAPVC (isolated or associated with other CHD).¹¹ PH was described in 42.8% of the patients; the overall mPAP was found to be 29.5 ± 13.8 mmHg, indicating predominate mild PH. Interestingly, elevation of mPAP was only observed if at least two pulmonary veins with anomalous drainage, additional CHD or an additional comorbidity (e.g. sickle cell disease) existed.

Interestingly, in each of the herein presented cases, we found an anomalous drainage of solely one pulmonary vein. All invasively assessed mPAP measurements were by definition of the ESC/ERS guidelines¹⁰ precapillary and distinctly higher as compared to those described in the available literature on PAPVC.

Regarding the presence of three patients with PAPVC in our local PH registry including 120 patients (=2.5%), we suggest that this congenital heart condition may be missed if not routinely investigated. In this context, a review of the literature reveals cases where PAPVC was missed especially in patients who underwent transcatheter closure of ASD.^{14,15} Furthermore, retrospective CT scan studies confirm a potential risk of misinterpretation, as 50% of RHC detected PAPVC were prior undetected by CT scan.¹⁶ According to the ESC guidelines,¹⁰ and taking into account age, comorbidities, as well as the severity of PH, a surgical correction of the PAPVC was not recommended in our cases. Notably, reparative surgery may be even contraindicated in some PAPVC patients, as it is unlikely to alter the disease course if extensive pulmonary vascular remodeling is present. A possible transplant option was discussed with the patient described in case 2, but later rejected because of the patient's will and his relapsing alcoholism.

The broad range of clinical manifestations of isolated and single PAPVC in adults stimulates the hypothesis on additional disease modifiers. Referring to our cases, underlying pulmonary diseases may influence vascular remodeling and severity of PAH presentation. Initially, the patient presented as case 1 was diagnosed to have PH according to WHO group 3 with severe COPD and emphysema. The available literature suggests an association between GOLD stage and mPAP measurements.¹⁷ However, severe PH is rare in patients with COPD, and mPAP > 35 to 40 mmHg is seen in less than 5%.^{17,18} Moreover, autopsy studies in patients with severe PH due to COPD showed that the morphologic lesions are similar to those characteristic of idiopathic PAH.¹⁹ The patient presented in case 1 may thus have developed severe PH due to the combination of PAPVC, COPD and emphysema, rather than to a single underlying disease. Therefore, it is important to raise awareness for concomitant conditions or diseases in the setting of a disproportional PH.

In all cases, a therapeutic approach with an upfront PAH-specific oral combination therapy and/or oral or inhaled prostanoid was initiated and revealed highly effective during follow-up. In general, most studies related to

PAH-specific therapy included only small numbers of patients with either corrected or not corrected CHD and specific data on subtypes are mostly missing. Subgroups at particular risk of PAH include predominantly unoperated aorto-pulmonary windows, atrioventricular septal defects, ventricular and atrial septal defects.^{20,21} All classes of PAH-targeted therapies such as endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, soluble guanylate cyclase stimulators and prostanoids have been employed in patients with PAH and CHD, especially in patients with Eisenmenger syndrome. Data on the successful use of PAH-specific drugs in patients with complex CHDs may underline its safety and efficacy in patients with PAPVC. However, the hemodynamic situation in patients with corrected PAPVC and non-corrected PAPVC significantly differs, thus resulting in variable treatment response.

Conclusion

PAPVC has been implicated as a cause of PAH, but this condition is often overlooked in the diagnostic workup of patients with PH. Awareness of this anomaly is important, as early detection helps to assess surgical therapy as a viable option before the development of severe PH and in case of inoperability carefully selected patients might positively respond to specific PAH treatment.

Conflict of interest

The author(s) declare that there is no conflict of interest.

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