The role of the second heart field in pulmonary vein development : new insights in the origin of clinical abnormalities

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Unilateral Pulmonary Vein Stenosis with a Contralateral Pulmonary Varix

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Case Presentation

A 41-year-old woman was admitted by the pulmonologist in July 2004 because of progressive complaints of dyspnea on exertion. There was no remarkable medical history except for mild dyspnea existing from about 1996. Physical examination revealed no dyspnea at rest, with normal breath sounds. There were no signs of cyanosis. Laboratory data demonstrated a normal hematologic profile and there was no serologic evidence for a systemic disease. The chest film showed bilateral interstitial abnormalities and a blurred left hemidiaphragm (Fig.1).

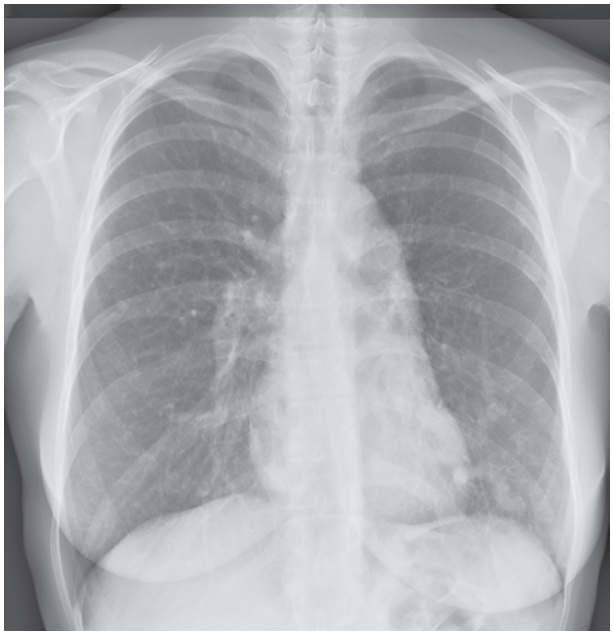

Figure 1. Chest film showing bilateral interstitial abnormalities and a left-sided blurry vascular structure above the diaphragm.

Bronchoscopic findings were within normal limits. Pulmonary function tests showed mild bronchial obstruction with normal static volumes (Table 1). Ventilation and perfusion lung scintigraphy revealed nearly symmetrical ventilation (R 58%, L 42%) but very asymmetrical perfusion to the detriment of the left lung (R 83%, L 17%) (Fig.2a,b).

Table 1. Preoperative and postoperative pulmonary function

	Pre Op	Post Op	Predicted
FEV_1 (L)	3.0	3.0	3.0
VC (L)	4.1	3.8	3.6
FEV_1/VC	74	78	81
TLCO/VA, % pred.	68	72	100

Forced expiratory volume in 1 second (**FEV1**) in liters (**L**); diffusion capacity corrected for alveolar volume (**TLCO/VA**); vital capacity (**VC**).

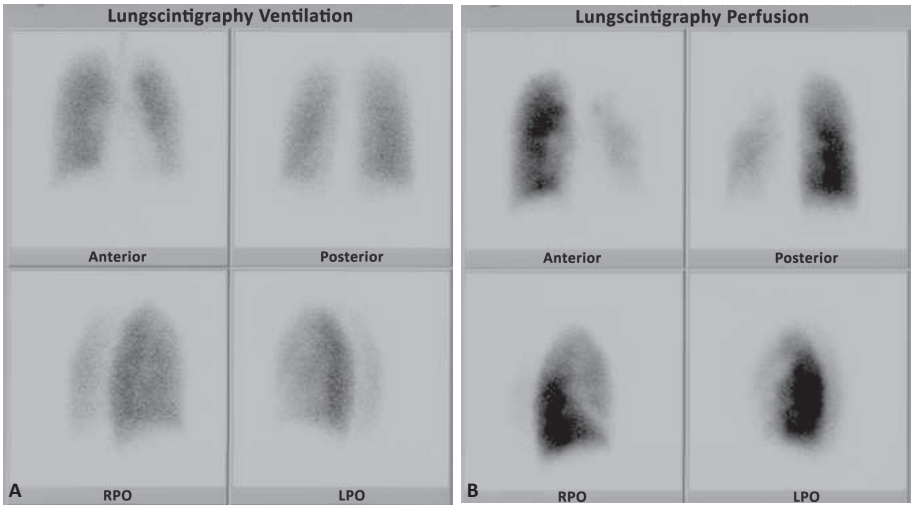

Figure 2. Ventilation (a**)** and perfusion (b) lung scintiscans showing symmetrical ventilation (right 58% , left 42%) but asymmetrical perfusion to the detriment of the left lung (right 83%, left 17%). Right posterior oblique (**RPO**), left posterior oblique (**LPO**).

Cardiac auscultation was completely normal. The electrocardiogram showed signs of right ventricular overload and transesophageal echocardiography showed turbulent flow at the level of the right pulmonary veins (PVs), together with mild mitral valve regurgitation. Cardiac catheterisation showed a pulmonary arterial hypertension (40/15-28 mm Hg), discrepant high left pulmonary artery wedge pressure (30 mmHg) compared to the left ventricular end-diastolic pressure (LVEDP, 14 mmHg) together with a high pulmonary vascular resistance (PVR): 9,5 Woodunits (left); 5 Woodunits (right)). There were no signs of coronary artery sclerosis.

Cardiac triggered multidetector computed tomography during intravenous contrast administration demonstrated bilateral pulmonary arteriovenous malformations most pronounced on the left side (Fig.3a,b). Magnetic resonance (MR) angiography was performed to clarify flow directions in the arteriovenous malformations, but it left the origin of the tortuous PVs unclear. Stenosis of the PVs at the level of the entrance in the left atrium (LA) was most pronounced on the right side. A digital substraction angiogram of the pulmonary vessels confirmed a much smaller caliber of the left pulmonary artery compared to the right, together with a corresponding difference in lung perfusion. The left PVs seemed to be aberrant and varicous but not stenotic.

Based on these findings, surgical resection of the stenotic parts of the right PVs was suggested without intervention on the left side because of its underdeveloped pulmonary vasculature and its aberrant but uninterrupted inflow of the PVs into the LA. Besides that, inspection and possible repair of the mitral valve was indicated.

By means of a median sternotomy, both lungs could be inspected. They had an abnormally pale appearance with multiple small vessel injections, more pronounced on the left side, so that a lingular as well as a middle lobe biopsy was done. Intrapericardially, the right superior and inferior PVs were macroscopically stenotic at the entrance to the LA. On the left side, a small vein resembling a left superior caval vein was seen together with a vein to the lower lobe. The origin and course of these veins were not visible. By inspection inside the right atrium, the possibility of a left superior caval vein could be rejected. After atrial septotomy, the entrance of the left-sided veins in the LA could be passed and appeared not to be stenotic. However, on the right side the diameters of the superior and inferior PVs at their entrance into the LA were only 4 and 7 mm, respectively. The mitral valve was sufficient and structurally normal. Both right PVs were incised longitudinally into the LA. The circumscript stenotic parts were resected, which resulted in an increase in diameter to 12 and 13 mm, respectively. A so-called sutureless pulmonary venoplasty[1,2] was performed by suturing the LA wall to the pericardium posteriorly and using an autologous pericardial patch anteriorly. The postoperative course was uncomplicated.

The lung biopsies were sent for pathologic analysis in Groningen and the resected stenotic parts of the right-sided PVs were analyzed in the Department of Anatomy and Embryology of Leiden.

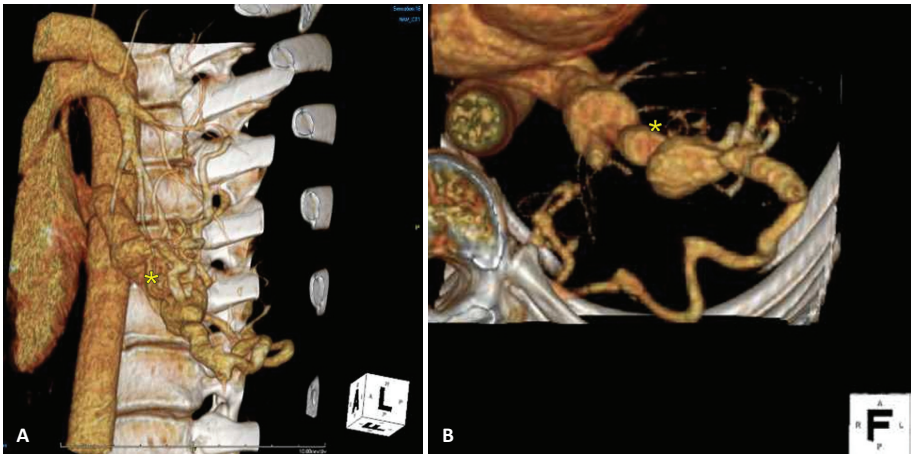

Figure 3. Multidetector computed tomography. a. Left lateral view and b. Caudal view. A varicous pulmonary vein (asterisk) connects to the original pulmonary vein ostium.

Histological examination of the pulmonary biopsies revealed serious vascular pathology with asymmetric and eccentric obliteration of venous as well as arterial branches, most pronounced on the left side, to be interpreted as post-thrombotic vasculopathy. Thereby, extensive hemosiderosis was seen on the right side.

Staining of the stenotic rim revealed a large mass of collagen (Fig.4a,b).

Two weeks after the operation the patient was discharged from the hospital. On echocardiography, no turbulence was seen in the right PVs.

After one year's follow-up, the ventilation-perfusion mismatch between the right and left lungs was exactly the same as preoperatively. Exercise capacity, assessed by cycle-ergometry, had not improved. Maximal oxygen uptake was 71% predicted at a maximal workload of 90 Watts (78% of predicted). Large disturbances in gas exchange were shown during the test compatible with large ventilation-perfusion mismatch. Also, these findings were comparable with the preoperative situation (Table 1). It was decided to be expectative about probable future effects of dead space ventilation on the left side.

High-resolution CT demonstrated non-stenotic veno-atrial transitions on the right side (Fig.5). In relation to the right inferior PV, the right superior PV had a smaller caliber and a more tortuous course.

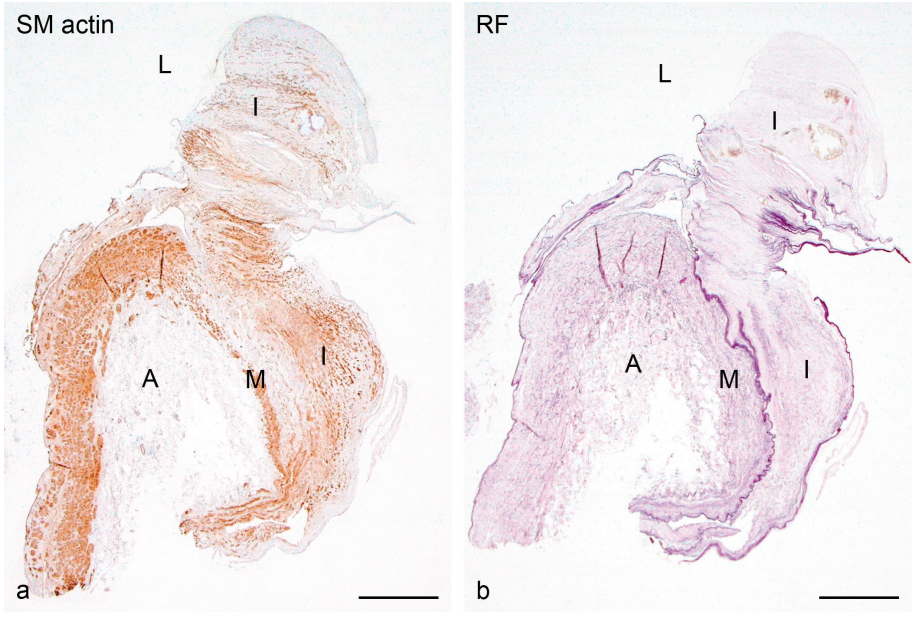

Figure 4. Sections of the excised circumferential stenosis of the right superior pulmonary vein stained for α-smooth muscle (**SM**) actin (a), and Resorcin-Fuchsin (**RF**) (b)**,** showing severe intimal proliferation (**I**) by means of a stenotic rim of collagen without elastic fibers. Lumen (**L**), media (**M**), adventitia (**A**). Scale bars are 600μm.

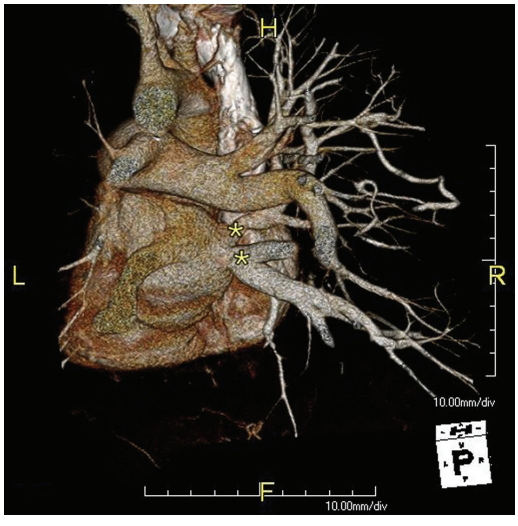

Figure 5. Multidetector computed tomography. Posterior view. The repaired right pulmonary veins (asterisks) are nonstenotic. Compared to the right inferior pulmonary vein, the right superior pulmonary vein is relatively small and tortuous**.**

Discussion

PV stenosis is part of the spectrum of abnormal PV drainage. Usually congenital in origin, the site of the stenosis depends on the embryologic stage at which it develops[3,4]. The stenosis can also be acquired, called pulmonary veno-occlusive disease (PVOD), a condition for which various agents can be responsible[5,6]. Especially in adults, it can be very difficult to determine whether the origin of the anomaly in a particular patient is congenital, acquired, or a combination of both[7]. Extremely rare is a PV varix[8], which can be associated with a diseased mitral valve[9].

When PV stenosis is congenital, two different types can be distinguished[10]. In the first, the so-called hypoplasia of the PVs, narrowing involves the intrapulmonary and extrapulmonary part of the PVs for a variable distance. The second type is characterized by narrowing at the veno-atrial junction, commonly called localized PV stenosis.

In normal development, the embryonic heart is connected to the mediastinum by means of the dorsal mesocardium. The major part of this structure regresses, after which, at the end of the fifth embryonal week, the lumen of the common PV develops in the remaining part of the dorsal mesocardium, and the common PV connects with the peripheral PV system[11-13]. By this point, the lung buds, which drained via the splanchnic plexus into the cardinal and umbilical veins, drain directly via the common PV into the LA. The connections with the splanchnic plexus and the umbilical and cardinal venous system become of less importance and regress. The common PV is then incorporated into the posterior LA wall, finally resulting in four individual PVs entering the LA. On the left side, also two PVs forming one common PV ostium that enters the LA are seen[14,15].

If atresia of the common PV occurs very early in development, total anomalous PV drainage develops and the embryonic systemic venous connections do not regress but establish a supra- or infracardiac drainage unless the PVs drain into the right atrium. If stenosis of the common PV occurs later, incorporation is disturbed which may result in cor triatriatum[3,4]. Atresia or stenosis of the left or right common PV leads to partial anomalous PV drainage so that the ipsilateral systemic venous drainage persists. If stenosis occurs very late, after PV incorporation has been completed, stenosis or atresia of individual PVs is the result. During fetal life, the hemodynamic effect of

partial obstruction of one or more PVs may not be enough to preserve embryologic (systemic) venous drainage[16,17]. After delivery, an increasing amount of blood volume reaches the lungs by which the hemodynamic effect of individual PV stenosis can be more pronounced.

If necessary, therapeutic options are percutaneous transluminal balloon angioplasty, stenting or surgical resection.

Acquired PV stenosis or PVOD is characterized by extensive and diffuse occlusion of PVs by fibrous tissue. Usually the (eccentric) intimal thickening involves venules and small veins but, occasionally, also larger veins and, in later stages, arterioles. The media of the veins may become arterialized with an increase in elastic fibers. The most consistent early parenchymal change is interstitial edema, which may progress to deposition of collagen fibers in the lobular septa and alveolar walls, as often observed when histologic features are obtained[18]. Lymphatic vessels are dilated. A more obvious finding, in particular in later stages, is hemosiderosis, found commonly in alveolar macrophages or less commonly also in the interstitium.

Clinically, cases present with pulmonary arterial hypertension without elevation of the pulmonary arterial wedge pressure[7,18]. Many agents may be responsible for the etiology of PVOD. Infectious, genetic, and toxic factors have been described as well as a thrombotic diathesis and autoimmune disorders[18]. Because PVOD is a rare condition, no randomized therapeutic trials have been undertaken to compare the effect of current treatment modalities, that is, vasodilators, immunosuppressives, anticoagulants and oxygen, on outcome. Because the prognosis is usually bad within 2 years after diagnosis, lung transplantation seems the only option for significantly prolonging life expectancy.

A PV varix is also a very uncommon anomaly that can be congenital or acquired. The congenital form usually is asymptomatic. The acquired form develops as a result of obstructed PV drainage and presents with symptoms of the underlying disease causing PV hypertension, for instance mitral valve disease or PV stenosis. Treatment consists of observation. If size increases, or in case of hemoptysis, surgical treatment is indicated[8].

In our patient, the etiology of the right-sided focal PV stenosis at the veno-atrial junction is likely to be congenital in origin in view of the combination with a diseased (nonfunctional) left lung. Acquired central PV stenosis in combination with a nonfunctional left lung would be very unlikely because in hemodynamically comparable situations of normal PVs in patients who have had pneumonectomy, subsequent development of contralateral pinpoint central PV stenosis is very uncommon. However, an additional acquired component in this region must have been responsible for the progression of the dyspnea; the function of the left lung decreased and flow to the right lung subsequently increased, thereby inducing intimal proliferation at the right veno-atrial junction to a critical point by means of altered flow profiles as turbulence[19]. Nonetheless, the significant ipsilateral hemosiderosis with moderate obliteration of small veins and arteries in the biopsy specimen, together with a normal right-sided pulmonary arterial wedge pressure, suggests a possible superposed PVOD. On the left side, the small caliber pulmonary artery, the elevated pulmonary artery wedge pressure, and the decreased perfusion of the left lung because of a very high PVR in combination with histologic fibrotic changes mimicking micro-infarction suggests left-sided PV atresia. Considering the two apparently normal left PV ostia entering the LA and the nonhypoplastic left lung, this atresia must have been developed during the late fetal period. After this, and under pressure, the varicous vein must have developed and connected with both left PVs, after which left-sided PV drainage was delayed but uninterrupted. If we deal in this case with some degree of PVOD in the right lung, careful follow-up is necessary because of its aggressive behaviour. Now the venous flow of the right lung to the LA is unobstructed, theoretically, dead space ventilation on the left side will increase. So long as this patient is doing well, an expectant policy is warranted. Thus for ethical reasons, we have not yet performed a postoperative recatheterization. If her situation deteriorates, cardiac recatheterization should be performed. In case of increased dead space ventilation on the left side, combined with acceptable PA pressures and PVRs on the right, a left pneumonectomy would be an option. In case of an irreversible increased right-sided PVR and a very bad clinical condition, this patient should be screened for lung transplantation.

In conclusion, differentiation between congenital or acquired stenosis of PVs or a combination of both can be very difficult. However, cardiac catheterization and a lung biopsy can bring more clarity. This is necessary inasmuch as the acquired form behaves more aggressively than the congenital version and needs a closer follow-up because of its tendency to relapse and its worse prognosis on the long term.

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