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Progressive pulmonary hypertension in cyanotic congenital heart disease with severe pulmonary stenosis

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Abstract We report the progressive development of pulmonary hypertension despite the presence of severe pulmonary stenosis in three patients with cyanotic congenital heart disease. The associated intracardiac lesions were complete transposition with a ventricular septal defect, double outlet right ventricle, and a heart with univentricular atrioventricular connection, respectively. Serial measurements on hemodynamics and histological findings documented the progression of pulmonary hypertension and pulmonary vascular diseases. The underlying etiology remains speculative. In view of the possibility of development of pulmonary hypertension despite a 'protected' pulmonary vasculature, corrective surgery should be contemplated as soon as technically feasible.

Key words: Pulmonary hypertension; pulmonary stenosis; cyanotic heart disease

THE DEVELOPMENT OF PULMONARY HYPERTENSION and pulmonary vascular disease is an important factor in the prognosis and management of patients with congenital heart disease. Children with excessively large pulmonary blood flow, especially those with complete transposition, are known to be at risk for early onset and development of severe pulmonary vascular disease.[1-3] On the other hand, the presence of pulmonary stenosis tends to protect the pulmonary vasculature.[2,4] This is, however, not invariably the case, as obstructive pulmonary vascular disease has been found in patients with complete transposition and ventricular septal defect despite associated pulmonary stenosis.[2,5-9] Serial longitudinal hemodynamic data documenting such changes is scarce. Besides, the development of pulmonary hypertension in other complex cyanotic cardiac lesions with obstruction of the pulmonary outflow tract has not, to the best of our knowledge, been reported in the literature. We report three such cases with documentation of the progressive changes of the pulmonary arterial pressure.

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Case 1

An 18-year-old boy first presented to us with moderate cyanosis at the age of seven years. His hemoglobin then measured 18 g/dl and his chest x-ray showed pulmonary oligemia. Cardiac catheterization revealed the diagnosis of double outlet right ventricle, subpulmonary ventricular septal defect and severe infundibular pulmonary stenosis. The pulmonary arterial pressure measured 25/11 (mean 16) mm Hg. He was regularly followed up and had limited exercise tolerance. Repeated catheterization for preoperative evaluation at nine years of age showed essentially similar findings. The parents, however, were reluctant to sanction an operation and the patient was managed conservatively. The patient defaulted until the age of 17, when progressive decrease in exercise tolerance was noted. There was clinical evidence of pulmonary hypertension with a loud pulmonary component of the second heart sound. Pruning of pulmonary vessels was evident in the chest x-ray. There was severe polycythemia with a hemoglobin of 25 g/dl. Severe pulmonary hypertension (62/25 mm Hg, mean 40 mm Hg) was revealed on catheterization. One year later, the patient presented to the hospital with repeated episodes of hemoptysis. Screening for tuberculosis, bronchiectasis and other infections were all

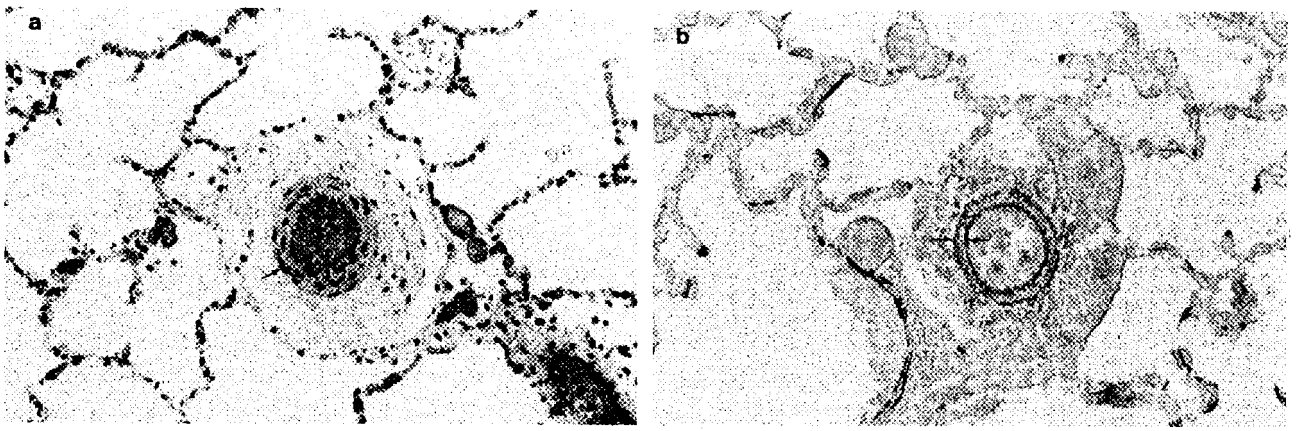

Figure 1. *Lung sections showing medial hypertrophy (arrows) in small muscular arteries. (a) Percentages of medial thickness is 30% (H&E stain, 660x). (b) Percentages of medial thickness is 20% (Victoria Blue elastic stain, 660x).*

negative. The hemoptysis was attributed to the underlying severe pulmonary vascular disease.

Case 2

A three-year-old girl presented at birth with severe cyanosis and the echocardiographic diagnosis was complete transposition, ventricular septal defect and severe subvalvar pulmonary stenosis. At 18 months of age, cardiac catheterization confirmed the intracardiac anatomy and documented a low pulmonary arterial pressure (26/15 mm Hg, mean 20 mm Hg), the pulmonary gradient measuring 25 mm Hg. Preoperative investigation showed a hemoglobin of 19.2 g/dl and relatively normal pulmonary vasculature on her chest X-ray.

A Rastelli operation was only performed at the age of three years because of a long waiting list. Repeated echocardiographic assessment prior to operation revealed a gradient of 36 mm Hg and an estimated pulmonary arterial pressure of 40 mm Hg. This degree of pulmonary hypertension was accepted, with the assumption that postoperatively the right ventricle could support the pulmonary circulation. Postoperatively, however, she developed low cardiac output with increasing cyanosis. A transesophageal echocardiogram performed in the intensive care unit revealed severe dilation of the right atrium and ventricle. There was no residual ventricular septal defect, nor evidence of obstruction in the conduit. Doppler assessment of the tricuspid regurgitation estimated the right ventricular systolic pressure at 70 mm Hg. The child died on the second postoperative day. Post-mortem examination confirmed the absence of residual shunting and a patent conduit. The lungs showed grade III (Heath and Edwards classification) hypertensive vascular changes in small arteries with diameters of 80-180 microns. The distribution of the lesions was diffuse and was most striking in the intraacinar arteries (diameters of <150 microns). There was muscularization of the small peripheral arteries, medial hypertrophy and intimal thickening with

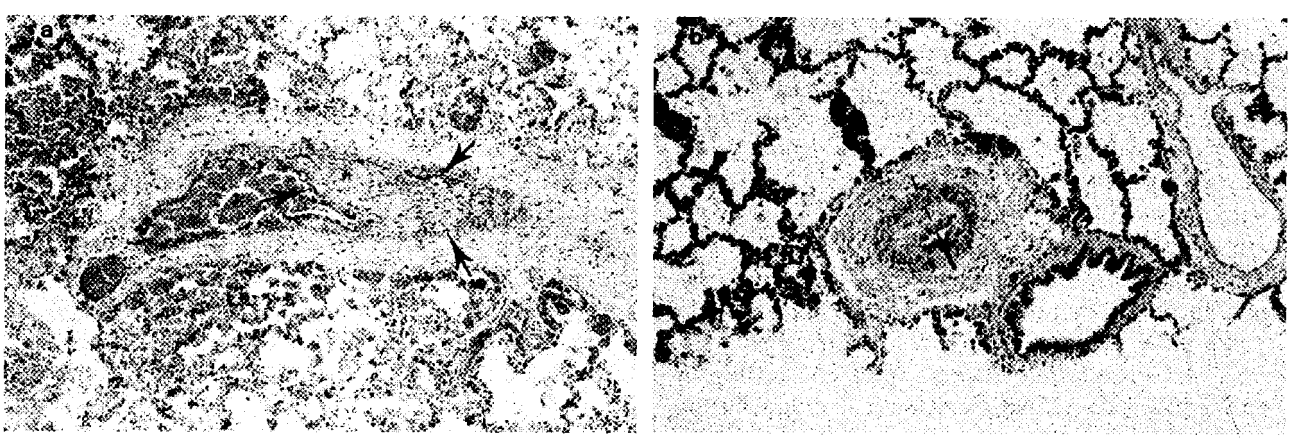

Figure 2. *(a) Longitudinal section of the preacinar artery showing irregular fibrous tissue proliferation in the intima (arrows) producing eccentric and irregularly shaped residual lumina (H&E stain, 330x). (b) Transverse section of the preacinar artery showing medial thickening (thin arrows) and luminal occlusion (bold arrow) amounting to over 90% (H&E, 330x).*

Table. Serial hemodynamic data.

Age (yrs)	Oxygen saturation (%) Ao	PA	PV	SVC	Pressure (mm Hg) RA	RV	MPA	LA	LV	Ao	Blood gas (Room air) Site	pO_2	pCO_2	Hgb (g/dl)
Case 1														
7	84	91	100	68	6/2 (4)	105/5	25/11 (16)	10/5 (7)	100/5	100/65	Ao	44	21	18
9	84	95	100	60	8/4 (6)	110/4	22/12 (17)	9/5.5 (6.5)	105/6	100/60	Ao	49	35	20
17	86	–	97	70	4/1 (2.5)	77/4	65/25 (40)	5.5/1.5 (2.7)	77/5	77/55	LA	93	24	25
Case 2														
1.5	75	87	100	65	9/7 (8.5)	85/0	26/15 (20)	9.5/5.5 (7.5)	90/0	90/57	Ao	41	45	16
3					30[a]	70[b]								19
Case 3														
4	70	70	98	50	12/8 (9)	90/8	24/16 (20)			110/80	Ao	40	50	19
7	74	79	100	53	5/3 (4)	95/12	50/35 (42)			98/70	Ao	44	43	20

a: By central venous line at the inferior caval vein-right atrial junction; b: by continuous wave Doppler measurement; Ao: aorta; Hgb: hemoglobin; LA: left atrium; LV: left ventricle; MPA: pulmonary trunk; PA: pulmonary artery; PV: pulmonary vein; RA: right atrium; RV: right ventricle; SVC: superior caval vein.

luminal occlusion. In 33 arteries measured (80-180 microns), medial thickness ranged from 7-50% of the external vascular diameter (normal: 3-7%) (Figure 1). The intimal thickening was irregular, and produced crescentic peripheral and central stellate lumen (Figure 2a). Intimal thickening was observed in approximately half the arteries and the degree of luminal occlusion ranged from 24-97% of the internal vascular diameter (average 85.5%) (Figure 2b). In the majority of arteries with intimal thickening, the proliferating tissue consisted of myxomatous fibroblastic tissue. Arteries with concentric laminar intimal fibrosis were also seen.

Case 3

An eight-year-old boy had a neonatal echocardiographic diagnosis of right isomerism, double inlet right ventricle via a common atrioventricular valve, and double outlet from the dominant right ventricle with severe valvar pulmonary stenosis. The pulmonary veins returned into an effectively common atrium and there was no evidence of pulmonary venous obstruction. A palliative Pott's shunt was performed at three months of age. Postoperatively, the child remained cyanotic without evidence of pulmonary plethora on chest X-ray. Deterioration in exercise tolerance with progressive cyanosis was noticed when he was four years old. Cardiac catheterization revealed almost complete blockage of the Pott's shunt with relatively small pulmonary arteries. The pulmonary arterial pressure then measured 24/16 mm Hg, with a mean of 20 mm Hg. A modified Blalock-Taussig shunt was constructed using a 5 mm Gore-tex tube, aiming to promote the growth of the pulmonary arteries. Repeated preoperative cardiac catheterization at seven years of age revealed pulmonary hypertension with a pressure of 50/35 mm Hg, mean 42 mm Hg. There was mild atrioventricular regurgitation and the mean pressure in the common atrium remained low at 4 mm Hg. In view of the pulmonary hypertension, a Fontan operation was precluded.

Discussion

The presence of pulmonary stenosis does not guarantee complete protection in patients with complete transposition.[2,5-9] Under such circumstances, pulmonary vascular disease has mostly been described in older children. Rarely, grade II pulmonary vascular changes have been reported in a four-month-old baby but the arteriolar pathology was probably related to failure of regression of the fetal pulmonary vasculature.[2] Thus, for our Case 2, who developed obstructive pulmonary vascular disease at the early age of three years, the progressive development of pulmonary arterial changes under a pressure of 26/15 mmHg documented at 1.5 years old has strong surgical implications. The occurrence of grade III pulmonary vascular disease contributed significantly to the postoperative low cardiac output and death. Despite the presence of histologically documented pulmonary vascular disease, significant pulmonary hypertension was not detected preoperatively. The falsely low estimated pulmonary arterial pressure was probably a consequence of the low pulmonary blood flow. The Rastelli operation should, therefore, be performed as early as it is technically feasible. Waiting until the optimal age of 3-4 years may allow the insidious development of the pulmonary vascular changes despite protected lung fields.

In the setting of complex intracardiac anatomy, serial hemodynamic data and clinical manifestations in our first and third cases demonstrated clearly the progressive development of pulmonary hypertension over the

years, despite the presence of severe pulmonary stenosis. Concomitant pulmonary venous obstruction, excessive pulmonary blood flow after a shunt procedure, or severe atrioventricular valvar regurgitation might contribute to the proliferation of the pulmonary vascular pathology, but none of these factors was judged to be the causative factors in our patients. While the Pott's procedure has been associated with a relatively high incidence of severe pulmonary vascular disease, ranging from 10 to 50%,[10,11] the shunt in Case 3 was almost completely blocked and could not have contributed to the complication. Moreover, his chest X-ray never showed plethora, and his arterial saturation was never above 75%. Again, the relatively mild atrioventricular valvar regurgitation with a low common atrial pressure could not have significantly affected the pulmonary venous and arterial walls.

The etiology for the development of pulmonary vascular disease in our patients with 'protected' lung fields remains speculative. It has previously been described that cyanotic congenital heart disease predisposes to widespread thrombosis of the pulmonary vasculature, because of the reduced pulmonary blood flow and the increased blood viscosity secondary to polycythemia.[12] Thrombosis was thought to be the cause for intimal proliferation, especially the eccentric crescentic changes. In all of our three patients, increases in blood viscosity relating to a high hemoglobin concentration of 19 to 20 g/dl had been measured during the course of follow-up (Table). Predisposition to spontaneous thrombosis of the pulmonary vasculature might be a real possibility.

While the etiology of proliferation of the pulmonary vascular pathology in these patients remains speculative, the important question concerns the optimal timing for surgery in these children. In view of possibility of progressive pulmonary hypertension despite the presence of pulmonary stenosis, corrective surgery should be contemplated as soon as it is technically feasible, even in the presence of an apparently protected pulmonary vasculature.

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