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Brief Report

Management of a child with pulmonary arterial hypertension presenting with systemic hypertension

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Abstract We describe the course and management of a 12-year-old girl with severe pulmonary arterial hypertension who initially presented with severe systemic hypertension. Successful therapy included pulmonary vasodilators and an atrial septostomy, while ensuring adequate maintenance of her systemic vascular resistance to maintain cardiac output. Clear understanding of the physiology and judicious medical management in patients with severe pulmonary arterial hypertension using extreme compensatory mechanisms is vitally important.

Keywords: Pulmonary arterial hypertension; systemic hypertension; paediatrics

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Case report

Children with idiopathic pulmonary arterial hypertension usually present with syncope, dyspnoea on exertion, or fatigue,[1] and less frequently present with wheezing, chest pain, and oedema.[2] Although systemic vascular resistance is often elevated because of the activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system and increased release of arginine vasopressin, severe systemic hypertension has not been previously described as a presentation of pulmonary arterial hypertension.[3] We describe a case of severe pulmonary arterial hypertension in a child who initially presented with severe systemic hypertension. She required a phenylephrine infusion to maintain systemic vascular resistance for the prevention of myocardial ischaemia while escalating pulmonary vasodilator therapy.

A 12-year-old girl presented with severe systemic hypertension during routine paediatric evaluation. Her history was significant for meconium aspiration and multiple small muscular ventricular septal defects, which resolved by 3 months of age. At 6 years of age, she had a syncopal episode ascribed to dehydration. Subsequently, she had a gradual decline in exercise tolerance and a decreasing appetite with intermittent emesis. Her family history was unremarkable.

Physical examination demonstrated a heart rate of 90 beats/minute, blood pressure of 192/139 mmHg with no upper-to-lower extremity gradient, and an oxygen saturation of 100%. She had an active praecordium and a left parasternal lift. The second heart sound was prominent with wide, fixed splitting. A grade I/VI systolic regurgitant murmur and a grade II/IV high-pitched diastolic murmur were heard at the left lower and upper sternal borders, respectively. The chest was clear. There was no hepatic or splenic enlargement. Chest radiography demonstrated cardiomegaly and main pulmonary arterial dilation. Electrocardiography revealed sinus rhythm, right atrial enlargement, right ventricular hypertrophy, and T-wave inversion in inferior leads. Echocardiography revealed normal segmental anatomy, normal left ventricular systolic function, severely depressed right ventricular systolic function, bi-ventricular hypertrophy, and systolic bowing of the ventricular septum into the left ventricle (Fig 1a and c). The tricuspid regurgitant velocity was 6.8 m/s, and the end-diastolic pulmonary regurgitant velocity was 3.4 m/s (Fig 1a). There was no atrial or ventricular level shunting. The aortic valve was bi-comissural without stenosis or insufficiency.

Diagnostic cardiac catheterisation revealed pulmonary artery pressures of 148/94 mmHg (mean 114 mmHg),

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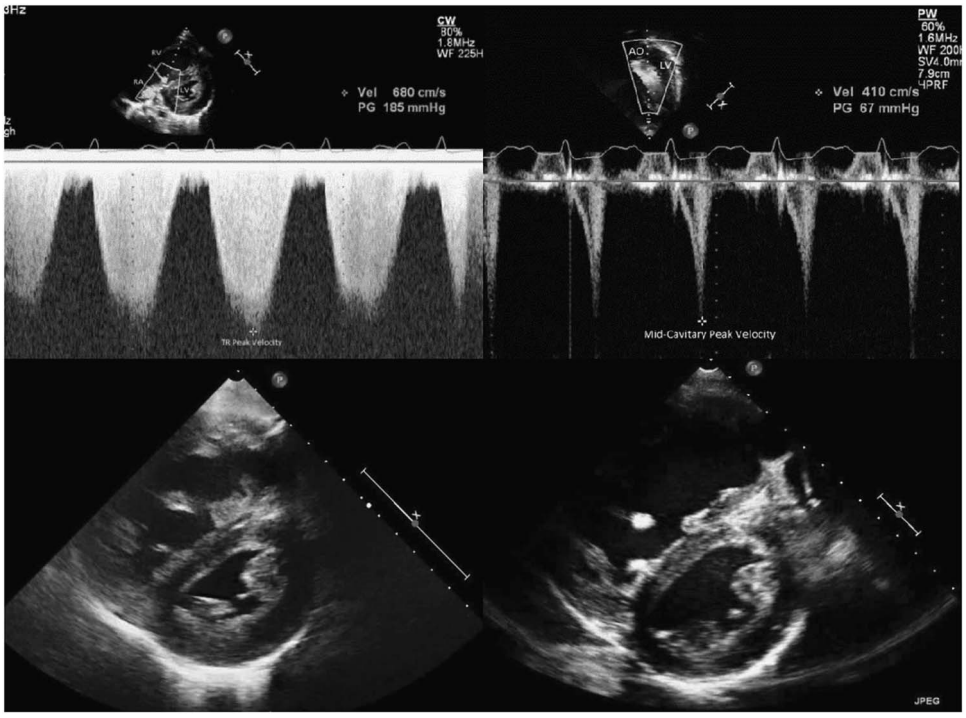

Figure 1.
*Echocardiogram images. (**a**) Parasternal short-axis view with elevated tricuspid regurgitation jet velocity at presentation. (b) Apical four-chamber view demonstrating a high left ventricular intra-cavitary gradient during a hypotensive episode. (c) Parasternal short-axis view at presentation. (**d**) Parasternal short-axis view at follow-up.*

systemic blood pressure of 148/104 mmHg, cardiac index by thermo-dilution of 3 L/minute/m^2, and pulmonary vascular resistance and systemic vascular resistance of 33 and 51 Wood units × m^2, respectively. Mean right atrial and wedge pressures were 3 and 10 mmHg, respectively; IV epoprostenol and nitric oxide decreased the cardiac index to 2 L/minute/m^2 with no change in the pulmonary vascular resistance.

Nitric oxide was continued as sildenafil and enalapril were introduced and, along with epoprostenol, slowly increased. On day 8, 1 hour after receiving enalapril, her blood pressure dropped suddenly from 170/100 to 60/35 mmHg with tachycardia and vomiting. Electrocardiography – ventricular ectopy, ST segment, and T wave changes – and cardiac biomarkers – troponin I 18.2 ng/ml and CK-MB 60.4 ng/ml – suggested myocardial injury. Echocardiography demonstrated hyperdynamic left ventricular systolic function and near-obliteration of the left ventricular cavity with an intra-cavitary gradient of 67 mmHg (Fig 1b). Vasopressin, norepinephrine, and phenylephrine infusions resolved hypotension and ischaemic changes. Vasopressin and norepinephrine were weaned off after 24 hours, but she remained on phenylephrine. Cardiac catheterisation performed to create an atrial septal defect demonstrated pulmonary and systemic vascular resistances of 24 and 37 Wood units × m^2, respectively, pulmonary artery pressure of 103/76 mmHg (mean 88 mmHg), and systemic blood pressure of 195/110 mmHg.

Thereafter, therapy concentrated on escalating prostanoid dosage while tolerating systemic hypertension. Attempts to wean phenylephrine were associated with left ventricular compression and ischaemic electrocardiography changes. Her systemic blood pressure declined slowly with escalating prostanoid dosage, and phenylephrine was successfully withdrawn after 3 weeks. At discharge, her systemic blood pressure was 155/90 mmHg, the tricuspid regurgitant velocity was 5.4 m/s, right ventricular systolic function was improved, and there was no intra-cavitary left ventricular gradient. Her discharge medications included sildenafil, bosentan, and treprostinil.

During her admission, tests to exclude secondary causes of systemic and pulmonary hypertension were all negative, including computed tomography of the chest and abdomen, renal artery ultrasounds, and a comprehensive metabolic evaluation. The most recent cardiac catheterisation – that is, 8 months after discharge – demonstrated a mean pulmonary artery pressure of 100 mmHg, normal cardiac index, and identical systemic and pulmonary vascular resistances of 20 Wood units × m^2. She has returned to school full-time and is asymptomatic. She continues to have mild systemic hypertension (138/80 mmHg).

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Diagnosis of pulmonary arterial hypertension often comes late, which is associated with poor prognosis for survival, as early symptoms are subtle and slowly progressive.[5,6] We describe a case identified when severe systemic hypertension was detected during routine evaluation. Extensive investigations failed to reveal a secondary cause (Table 1), and the systemic hypertension improved without specific therapy, and thus we conclude that it was likely compensatory for severe, untreated pulmonary arterial hypertension. Although meconium aspiration syndrome and ventricular septal defects are possible aetiologies, echocardiography at 3 months of age was normal, and there was no family history; therefore, her pulmonary hypertension is likely "Idiopathic pulmonary arterial hypertension" (5th World Symposium on Pulmonary Hypertension Group 1.1).[4] On the other hand, given the unclear role of the systemic hypertension, it is also reasonable to classify the patient as "Pulmonary hypertension with unclear multifactorial mechanisms" (5th World Symposium on Pulmonary Hypertension Group 5).[4]

We postulate that systemic vasodilation was not tolerated because falling left ventricular afterload shifted the intra-ventricular septum leftwards in the face of severe right ventricular hypertension. In this way, decreased left ventricular filling impaired cardiac output. Dropping systemic vascular resistance reduced her diastolic pressure, decreasing her coronary perfusion pressure, and contributing to myocardial ischaemia. Furthermore, compensatory tachycardia decreased the intervals for left ventricular filling and coronary perfusion, which further impaired cardiac output. This pathologic cycle was only broken with the addition of systemic vasoconstrictors. This phenomenon was witnessed on multiple occasions while escalating pulmonary vasodilator therapy, during sedation, and during attempts at weaning the phenylephrine.

Severe systemic hypertension has not previously been reported as a presentation of pulmonary arterial hypertension in children, but the diagnosis should be considered by clinicians, given the importance of early diagnosis and treatment. This case demonstrates the dangers of rapid changes in systemic vascular resistance in patients with severe pulmonary arterial hypertension, and suggests both a pathophysiological mechanism for decompensation and also an appropriate pharmacological management strategy.

Table 1. Differential diagnosis for systemic hypertension.

System	Disease	Diagnostic studies	Patient values
Renal	Renal artery stenosis	Doppler U/S	Normal
	CKD	CT abdomen	Normal
	PCKD		
	Dysplastic kidney		
	Glomerulonephritis		
	Nephritic syndrome		
Endocrine	Hyperthyroidism	Free T4	1.5 (1–2.8 ng/dl)
	TRD	TSH	2.36 (0.53–4 mcIU/ml)
	CAH	Cortisol level	4.8 (1.2–14.8 mcg/dl)
	Hypercortisolism	Renin level	14.6 (0.5–33.3 ng/dl)
	RAAS abnormalities	Aldosterone level	1.6 (1–31 ng/dl)
	Cushing syndrome		
Cardiac	William syndrome	Echocardiogram	See text
	Noonan syndrome	Echocardiogram	See text
	Coarctation of the aorta	Echocardiogram	See text
Autoimmune	SLE	Anti-dsDNA autoantibodies	Negative
	Vasculitis	Anti-nuclear antibodies	Negative
	HUS		
Tumour	Pheochromocytoma	Plasma-free metanephrines	0.29 (0–0.49 nnmol/L)
	Carcinoid tumours	Plasma normetanephrine	0.57 (0–0.89 nmol/L)
	Paraganglioma	Urine metanephrine	149 (0–320 mcg/g)
	MEN	Urine normetanephrine	280 (0–450 mcg/g)
	PPNAD	PTH	54 (22–84 pg/ml)
	Carney complex	Calcitonin	2 (0–5.1 pg/ml)
		PET/CT	Normal

CAH = congenital adrenal hyperplasia; CKD = chronic kidney disease; CT = computed tomography; dsDNA = double-stranded DNA; HUS = haemolytic uraemic syndrome; MEN = multiple endocrine neoplasia; PCKD = polycystic kidney disease; PET = positron emission tomography; PPNAD = primary pigmented nodular adrenocortical disease; RAAS = Renin–angiotensin–aldosterone system; SLE = systemic lupus erythematous; TRD = thyroid receptor defects; TSH = thyroid stimulating hormone; U/S = ultrasound

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Conflicts of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board.

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