CASE REPORT

Late-onset pulmonary arterial hypertension after successful early arterial switch surgery for simple transposition of the great arteries

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ABSTRACT

Pulmonary arterial hypertension rarely develops in patients with simple transposition of the great arteries who undergo neonatal surgical correction. We describe a young male patient who was diagnosed with severe pulmonary arterial hypertension 14 years after neonatal arterial switch surgery. The relevant literature is briefly reviewed. Clinicians should be aware of this rare, late, and potentially life-threatening condition. Continued long-term follow up of these patients should be provided. Early diagnosis and treatment with combination therapy may improve outcomes. SAHeart 2016;13:28-32

INTRODUCTION

Pulmonary hypertension, which is associated with significant morbidity and mortality, is rarely diagnosed in newborns, infants and children. Based on registries in The Netherlands and the United Kingdom, the estimated annual incidence of idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension associated with congenital heart disease are approximately 0.7 and 2.2 cases per million respectively. The point prevalence rate of pulmonary arterial hypertension associated with congenital heart disease is 15.6 cases per million.[1] Late-onset pulmonary arterial hypertension after a successful neonatal atrial or arterial switch procedure for simple transposition of the great arteries is a recognised, but rare, entity. The recent Panama consensus classification on paediatric pulmonary hypertensive vascular disease recognised it as a distinctive condition.[2] It is defined as new onset pulmonary arterial hypertension several years after successful early surgical repair of transposition of the great arteries and its associated defects. This complication has been reported in approximately 7% of patients after atrial switch surgery who survive to adulthood. Pre-operative systemic to pulmonary artery shunts, delayed reconstructive Mustard or Senning procedures, with mildly elevated base-line pulmonary pressures at early post-operative catheterisation, increase the risk of developing pulmonary arterial hypertension.[3-8] Reversible conditions like pulmonary venous baffle obstruction, and branch pulmonary artery stenosis, must be addressed.[7-9] Late-onset pulmonary arterial hypertension after neonatal arterial switch surgery for simple d-transposition without remaining defects is however extremely rare. To the best of our knowledge 4 such cases have been published.[3,9-20]

CASE-REPORT

We diagnosed a 14-year-old caucasian male with pulmonary hypertension (invasive pulmonary arterial pressures 110/50mmHg, pulmonary vascular resistance 18 Woods Units), after he previously underwent arterial switch surgery for simple d-transposition at the age of 32 hours. Additional congenital abnormalities included a right-sided aortic arch, anomalous origin of the left anterior descending coronary artery, coursing from the right coronary artery, mild thoracic scoliosis and cervical hemi-vertebrae for which he had had surgical intervention. Regular non-invasive follow up assessment by his private paediatric cardiologists until age 8, when he was lost to follow up, had been reported as normal. The family had relocated from Pretoria to Cape Town at the age of 10 years. His clinical condition had gradually deteriorated over the 6 months before presentation, with World Health Organisation functional class IV at presentation. At physical examination his blood pressure was 116/81mmHg, the pulse rate regular at 110/minute, with all pulses palpable. His central venous pressure was markedly elevated, and there was no perpheral pitting edema or central cyanosis at rest. P2 was prominent, with a soft murmur of tricuspid regurgitation, and mild hepatomegaly present. Laboratory assessment revealed mild polycythaemia (haematocrit 52.6%), and excluded liver disease, chronic arterial hypoxemia or connective tissue diseases. The resting 12-lead electrocardiography demonstrated resting sinus tachycardia, right atrial dilation and right ventricular hypertrophy with extreme right axis deviation (Figure 1). Non-invasive evaluation with Doppler echocardiography, contrasted multi-slice com-

puted tomography, cardiovascular magnetic resonance as well as the invasive right-sided heart study excluded intra- or extra-cardiac shunts, valvular disease, left ventricular dysfunction, underlying lung disease, pulmonary emboli and pulmonary artery branch stenosis. Continuous wave Doppler assessment over the tricuspid valve estimated peak systolic pulmonary pressures at 75mmHg plus right atrial pressure of 10 - 15mmHg.

MMode assessment of the tricuspid annular plane systolic excusion (TAPSE) estimated the right ventricular ejection fraction to be approximately 30%. Cardiovascular magnetic resonance confirmed right atrial and right ventricular dilation (RVEDV 315ml), right ventricular hypertrophy (120 gram, wall thicknesses up to 8mm) with impaired systolic right ventricular function (RVEF 26%) (Figure 2a). Non-invasive estima-tion

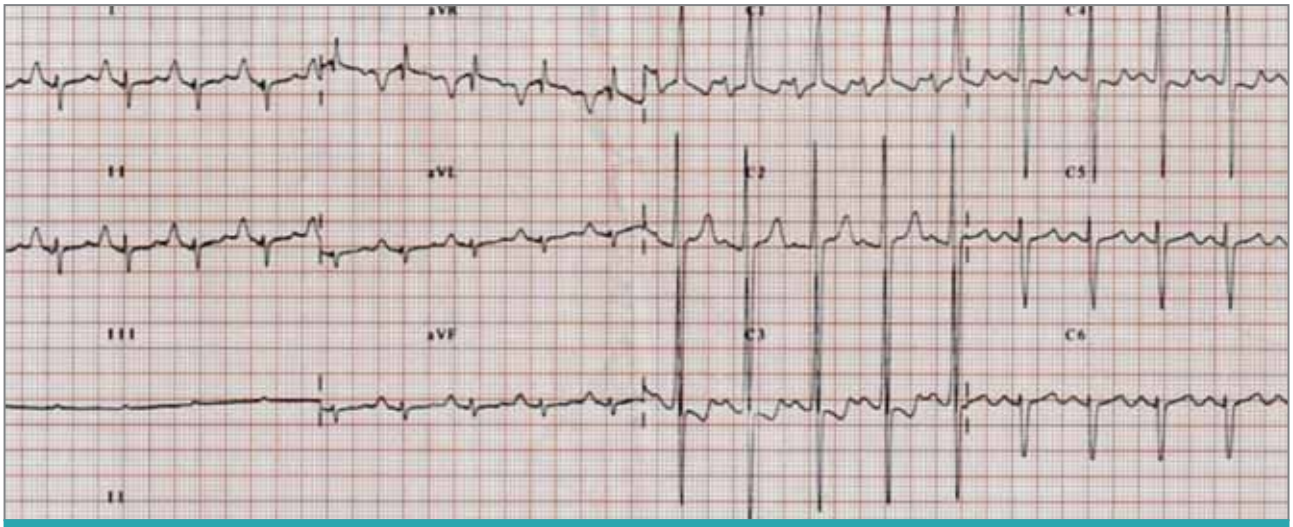

FIGURE 1: Resting 12-lead electrocardiogram.

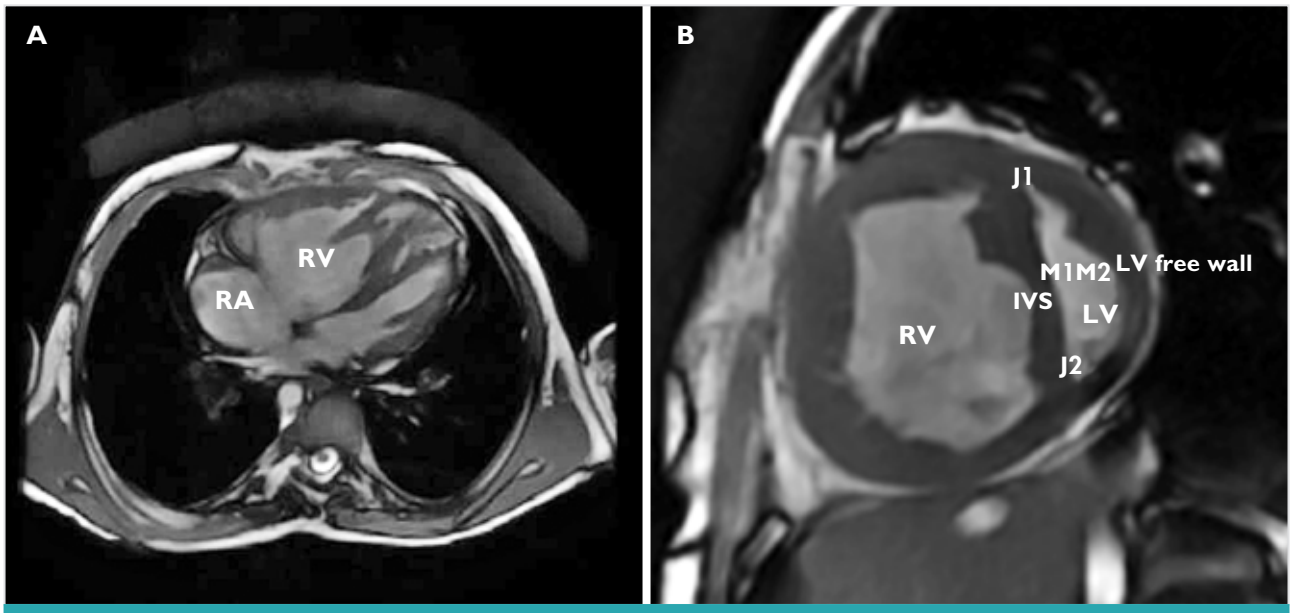

FIGURE 2:
A: Cardiovascular Magnetic Imaging demonstrates marked right atrial (RA) and ventricular (RV) dilation with right ventricular hypertrophy (end-diastolic frame, horizontal long axis view, Steady State Free Precession, 8mm slice).
B: Cardiovascular Magnetic Imaging demonstrates marked right ventricular (RV) dilation with right ventricular hypertrophy, the inter-ventricular septum (IVS) is shifted into the left ventricle (LV) signifying markedly increased right ventricular pressures (early diastolic frame, short axis view, Steady State Free Precession, 8mm slice). Non-invasive estimation of peak right ventricular systolic pressures using left ventricular septal-to-free wall curvature ratio according to Dellegrottaglie, et al. estimated the pressure to be 108mmHg.[21] (J1 and J2 anterior and inferior junctions between septum and free wall, M1 and M2 middle of septum and free wall).

of right ventricular systolic pressures with magnetic resonance using the left ventricular septal-to-free wall curvature ratio according to Dellegrottaglie, et al. estimated this to be 108mmHg (Figure 2b).[21] Sildenafil was the only effective agent available in South Africa to treat this condition. There was a delay in providing this drug to our patient due to difficulties in medical scheme funding. After a month of treatment with sildenafil 20mg 3 times daily (tds) the peak systolic pulmonary pressures had decreased by approximately 25mmHg. The non-invasive readings remained unchanged after increasing the dosage to 40mg tds over the following months. His functional class improved to World Health Organisation class I. After the initial favourable response to sildenafil, his condition gradually deteriorated. Warfarin, furosemide and spironolactone were pre-scribed. Fourteen months later he died of progressive right ventricular failure. Concomittant systemic conditions, such as infection, had been excluded. We were unable to obtain endothelin antagonists or prostacycline analogues. Post-mortem assessment was not performed.

DISCUSSION

An estimated 11 000 children are born annually in South Africa with congenital heart disease (0.6 - 0.8/1 000 live born children). Unfortunately, only 26% of the approximately 114 children with simple transposition of the great arteries born annually are diagnosed and receive life-saving corrective surgery.[22,23] The arterial switch operation for neonatal correction of transposition of the great arteries was introduced in South Africa in 1988. We estimate that approximately 1 100 children have undergone this procedure in our country. To the best of our knowledge our patient is the first reported South African with late-onset pulmonary arterial hypertension after neonatal arterial switch operation for simple transposition.

The pathophysiology of this condition is incompletely understood. The foetal circulation in transposition patients is different from normal. Antenatal constriction of the ductus arteriosus will result in a greater volume of blood with higher partial oxygen pressure flowing through the immature pulmonary vasculature at higher pressures. This can explain the early onset of pulmonary vascular disease in some infants with transposition of the great arteries. Antenatal ductal constriction is known to be associated with persistent pulmonary hypertension in neonates.[12,24]

In infants with transposition of the great arteries and intact ventricular septum as young as one week considerable intimal proliferation with luminal occlusion has been reported.[12,25] With persistence of extensive bronchial-pulmonary shunts resulting in increased blood flow, and inherent structural defects of the muscular pulmonary arteries secondary to chromosomal abnormalities, arteriolar spasm and a gradual increase in pulmonary vascular resistance follows.[2,3,12,14]

Transthoracic Doppler echocardiography is the recommended screening technique for pulmonary arterial hypertension. However, because of inaccuracies of right atrial pressure estimation, and technical challenges in determining the peak tricuspid regurgitation velocity, the degree of pulmonary hypertension can be over- or underestimated.[26,27]

Branch pulmonary artery stenosis must be aggressively sought when evidence of a high right sided pressure is found. As a result of the Le Compte maneuver during the arterial switch operation, pulmonary artery branches lie anteriorly and are very difficult to see on a standard ultrasound assessment, even in young children.[9] (Figure 3)

Cardiovascular magnetic resonance has the potential to overcome the anatomical limitations of imaging windows with transthoracic echocardiography in obese patients, or those with respiratory disease or chest wall deformities.[21,27]

The extent of the left ventricular end-systolic geometric distortion is related to the increase in end-systolic right ventricular pressure, which results in a left-sided shift of the inter-ventricular septum. The degree of distortion can be expressed as the ratio of the end-systolic inter-ventricular septal and end-systolic left ventricular free wall curvature at basal left ventricular level.[21] Both can be determined with either ultrasound or cardiovascular magnetic resonance. Figure 2b demonstrates how the end-systolic radius of both the end-systolic inter-ventricular septum and free wall can be determined by marking the anterior and inferior junctions between septum and free wall, and middle of septum and free wall.

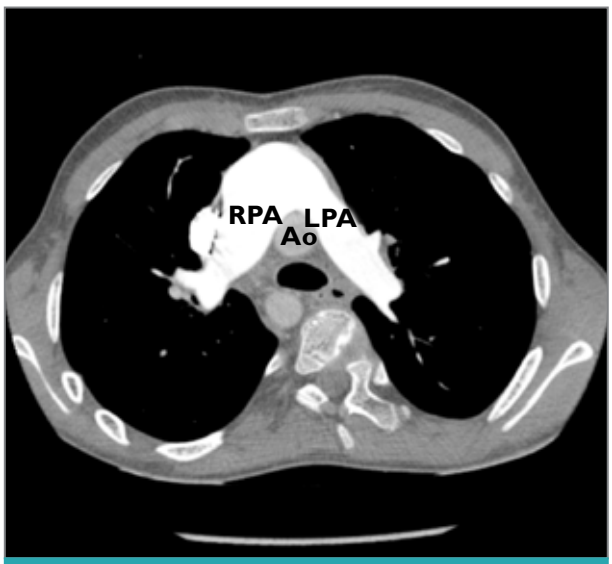

FIGURE 3: Computed Tomography Angiography demonstrated dilated proximal pulmonary arteries and excluded pulmonary artery branch stenosis or pulmonary emboli. RPA=right main pulmonary artery, LPA=left main pulmonary artery, Ao=ascending aorta.

By downloading the appropriate frame on an off-line work station the radius of the circles, which include these points in the septum and free wall, can be determined. The septal and free wall curvature can be calculated as 1 divided by the radius of the respective circles including these points in septum and free wall. The curvature ratio in a healthy individual is approximately 1, a lower curvature ratio signifies a higher right-sided end-systolic pressures. Dellegrottaglie, et al. demonstrated the left ventricular septal-to-free wall curvature ratio to be accurate and reproducible in 46 patients with pulmonary arterial hypertension (87% sensitivity, 100% specificity, mean difference -1.1mm Hg ±15.9).[21] Future studies employing ultrasound and magnetic resonance will determine the clinical relevance of this method.

Management of these patients is not different from the general approach in paediatric pulmonary arterial hypertension. Single agent therapy is initiated with bosentan (2 - 4mg/kg bd) or sildenafil (weight ≤20kg 10mg tds, weight >20kg 20mg tds), and in the case of insufficient response combination therapy seems to improve outcomes.[3,9,11,28] Recently the STARTS-2 study reported increased risk of death in children with idiopathic or inherited forms of pulmonary arterial hypertension when dosages higher than 20mg tds were prescribed in children over 20kg of weight with greater baseline disease severity.[29] These findings were unexpected because the higher dosages (40 - 80mg tds) were associated with improved exercise capacity, functional class and haemodynamic parameters, whilst lower dosages were ineffective. Future research will unravel the uncertainties concerning optimal individual dosing of sildenafil in paediatric pulmonary hypertension. Prostacycline analogues remain reserved for those in whom combination treatment with bosentan and sildenafil remains unsatisfactory.

A goal-oriented treatment strategy in children with pulmonary arterial hypertension, based on World Health Organisation functional class, pro-brain natriuretic peptide levels, and right ventricular function determined by tricuspid annular plane systolic excursion, has been shown to be feasible and successful. Improved survival was achieved with improvement of these parameters on targeted therapy.[30] Lung transplantation remains limited to a few highly selected individuals, and is severely limited by the scarcity of donor organs.

Long term outcome after arterial switch surgery is excellent with 96.7% ±1.8% and 96.6 ±0.1% overall and arrhythmia-free survival rates in peri-operative survivors at 25 years.[31] Patients with repaired congenital heart disease and pulmonary vascular disease remain at increased risk of adverse outcome.[1] The prognosis of pulmonary arterial hypertension in corrected transposition patients seems no different from the paediatric pulmonary arterial hypertension population at large. The prognosis is generally poor, unless adequately managed with the mentioned agents without delay in initiation. Prior to the availability of targeted therapies, a single-center cohort study showed that the estimated median survival of children and adults with idiopathic pulmonary arterial hypertension were similar (4.12 versus 3.12 years, respectively).[31] Current 5-year survival of idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension associated with congenital heart disease on targeted pulmonary vasodilators are reported to be 71 - 75%.[1] Torres, et al. and Cordina, et al. reported favourable responses up to a year after initiating a combination of bosentan and sildenafil in a 9-year and 16-year-old male respectively, both with severe late onset pulmonary arterial hypertension similar to our patient.[3,10] Carroll WD, et al. reported a favourable response to monotherapy with sildenafil in a 7 year-old boy lasting up to at least 9 months.[11] However, Chan, et al. reported little, to no, response to combination therapy of sildenafil and bosentan in a 16-year-old male with systemic pulmonary pressures.[9]

CONCLUSION

Late onset pulmonary arterial hypertension after neonatal arterial switch surgery for simple transposition is rare and has a poor prognosis. Treatment with combination therapy may improve functional status and outcomes, but clinical experience is currently limited to case-reports. Current research efforts are directed at gaining more insight into the demographics, pathophysiology and optimal management of this condition. Long-term follow up of patients after surgical correction of transposition should include routine non-invasive evaluation for pulmonary vascular disease. Non-invasive estimation of peak right ventricular systolic pressures, using left ventricular septal-to-free wall curvature ratio, may be a valuable alternative to continuous wave Doppler assessment of tricuspid regurgitation velocity. Invasive pressure measurements should be performed in patients with suspected pulmonary hypertension or in cases of diagnostic uncertainty.

Conflict of interest: none declared.

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