

## Case Report

# Pulmonary arterial hypertension after splenectomy for hereditary spherocytosis

JP SMEDEMA, VJ LOUW

### Summary

**Hereditary spherocytosis consists of a group of haemolytic anaemias caused by defects in the proteins involved in the vertical interactions between the membrane skeleton and the lipid bilayer of the red blood cell. Inheritance is most commonly autosomal dominant with variable expression. Splenectomy may be indicated because of anaemia or for the prevention of gall-stones. We describe a patient who presented with symptoms of pulmonary hypertension 32 years after splenectomy. Idiopathic pulmonary arterial hypertension (IPAH) and chronic thromboembolic pulmonary hypertension (CTEPH) have been associated with splenectomy, while chronic haemolysis may result in haemolysis-associated pulmonary hypertension. We briefly discuss the current views on the pathophysiology, diagnosis and management of this rare condition.**

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Hereditary spherocytosis consists of a group of haemolytic anaemias caused by defects in the proteins involved in the vertical interactions between the membrane skeleton and the lipid bilayer of the red blood cell.<sup>1</sup> Inheritance is most commonly autosomal dominant with variable expression. Splenectomy may be indicated because of anaemia or for the prevention of gall-stones. We describe a patient who presented with symptoms of pulmonary hypertension 32 years after splenectomy. Idiopathic pulmonary arterial hypertension

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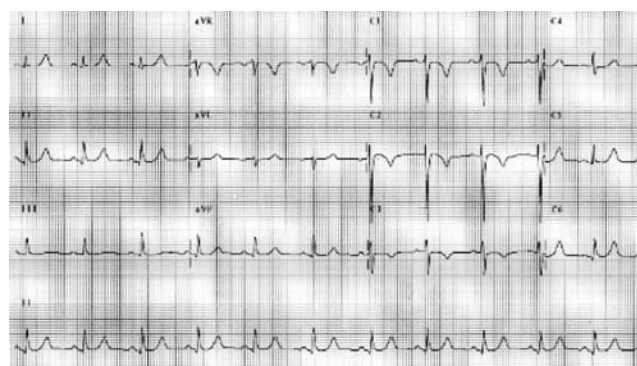
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(IPAH) and chronic thromboembolic pulmonary hypertension (CTEPH) have been associated with splenectomy, while chronic haemolysis may result in haemolysis-associated pulmonary hypertension.<sup>2-5</sup> We briefly discuss the current views on the pathophysiology, diagnosis and management of this rare condition.

### Case-report

A 47-year-old Caucasian man presented with sudden-onset retrosternal and left-sided chest pain at rest, with accompanying symptoms of dyspnoea, light-headedness and paresthesias in the left arm. He had been treated for left-sided pleuritis several years ago, and had undergone splenectomy at the age of 15 for haemolytic anaemia due to hereditary spherocytosis, and cholecystectomy at the age of 22 years. Apart from a family history of premature atherosclerosis and an inactive lifestyle, he had no cardiovascular risk factors.

At physical examination he did not appear acutely or chronically ill, was normotensive, with a normal, regular pulse rate, and normal central venous pressure, temperature and oxygen saturation. Apart from a prominent, fixed split, second heart sound, no other abnormalities were present. The resting 12-lead electrocardiogram showed sinus rhythm with signs of right ventricular pressure overload (Fig. 1).



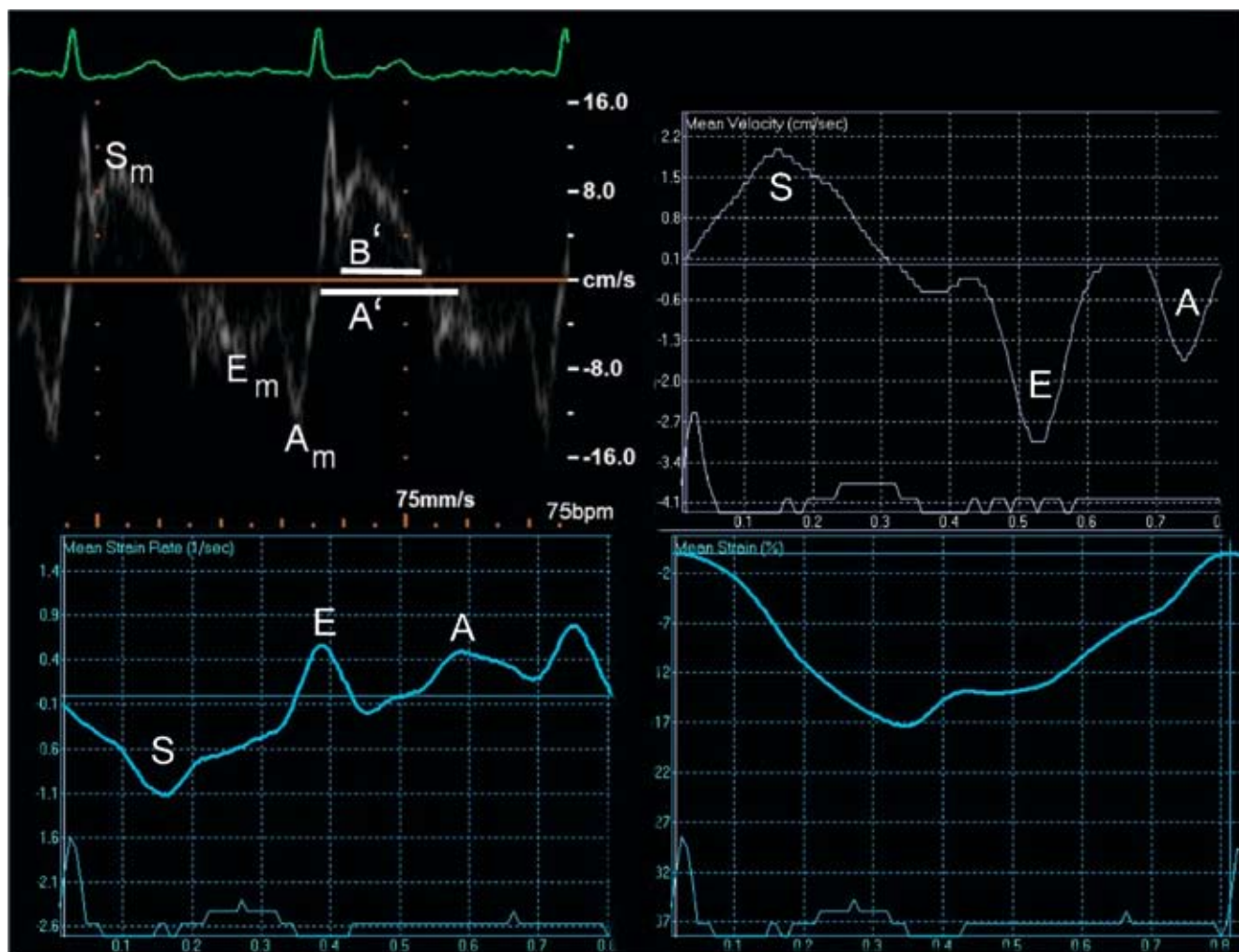
**Fig. 1.** The 12-lead electrocardiogram at presentation shows down-slope negative T waves in leads C1, C2 and C3, suggestive of right ventricular pressure overload.



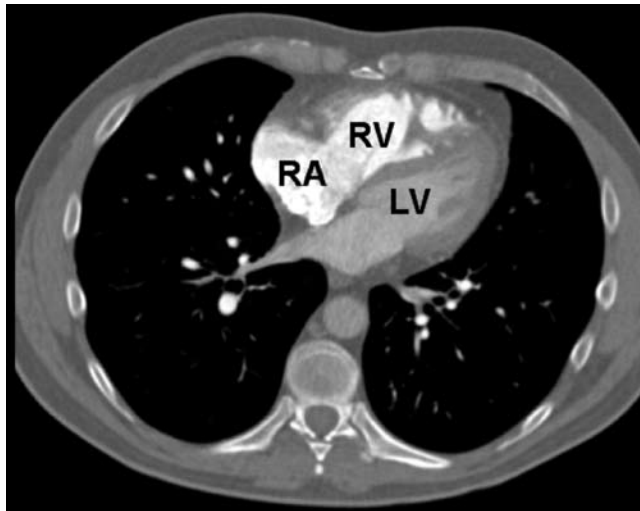
**Fig. 2. Two-dimensional echocardiography (four-chamber view) demonstrates mild right ventricular dilation and tricuspid regurgitation (arrow, velocities  $\geq 3.25$  m/sec).**

Laboratory tests, including full blood count, liver functions, cardiac enzymes, arterial blood gas and anti-nuclear factor were all normal, apart from mildly elevated D-dimers (0.68 mg/l) and decreased haptoglobin (0.08 g/l). Bedside echocardiography confirmed moderate right ventricular dilation, hypertrophy and elevated right-sided pressures of approximately 45 mmHg, without evidence for an intra-cardiac shunt (Fig. 2). Tissue Doppler evaluation of the right ventricle demonstrated impaired systolic right ventricular function (Fig. 3). He was treated with therapeutic dosages of low-molecular weight heparin, and contrast-enhanced multidetector computed tomography (MDCT) was planned to confirm the diagnosis of pulmonary embolism.

MDCT revealed prominent proximal pulmonary arteries, but excluded the presence of thrombi in the right heart and the proximal and peripheral pulmonary arteries, and showed normal pulmonary venous drainage (Fig. 4). Underlying structural pulmonary disease and coronary artery disease



**Fig. 3. Pulsed-wave Doppler of the tricuspid annulus (left upper panel) shows impaired systolic velocity (11 cm/sec, normal  $> 12$  cm/sec), with an abnormal right ventricular myocardial performance index (Tei index =  $A'-B'/B'$ ) of 0.63 (normal  $0.28 \pm 0.04$ ). Two-dimensional tissue Doppler echocardiography of the right ventricular free wall demonstrates decreased longitudinal tissue velocities (right upper panel – 2 cm/sec, normal  $5.19 \pm 2.51$  cm/sec), strain rate (left lower panel – 1.1, normal  $1.72 \pm 0.27$ ) and strain (right lower panel – 17%, normal  $27 \pm 6\%$ ), diagnostic of impaired systolic right ventricular function. The tricuspid annular plane systolic excursion was 16 mm (= RVEF  $\pm 40\%$ , not shown). The E/A ratio of 2 (right upper panel) suggests restrictive filling, secondary to the right ventricular hypertrophy.**



**Fig. 4. Sixty-four-slice multi-detector computed tomography (transverse view) shows moderate right atrial and ventricular dilation with prominent apical trabecularisation of the hypertrophied right ventricle.**

were excluded. A Swan Ganz study showed partly reversible pulmonary hypertension with normal oxygen saturations in the vena cava, atrium, ventricle and pulmonary artery (Fig. 5A, B).

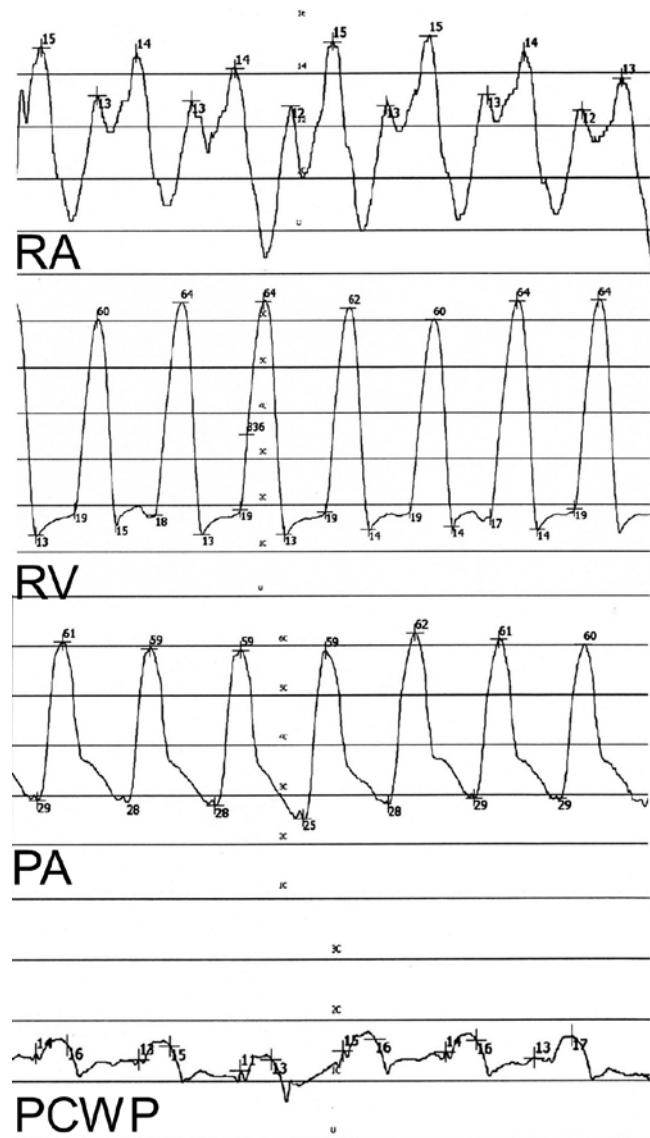
Cardiac magnetic resonance (CMR) determined the right and left ventricular output to be normal (4.82 and 5.03 l/min, respectively), with impaired systolic right ventricular function without evidence of focal septal or right ventricular fibrosis (Figs 6, 7). According to the revised clinical classification of pulmonary hypertension (Venice 2003) he was diagnosed with pulmonary arterial hypertension (PAH, class 1.3.6), most likely related to previous splenectomy, and low-grade haemolysis due to spherocytosis, and started on life-long oral anticoagulation (warfarin), antiplatelet therapy (aspirin) and sildenafil.<sup>6</sup>

## Discussion

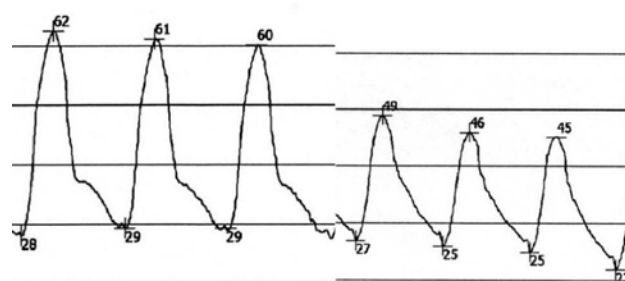
In a variety of conditions, splenectomy has been associated with an increased risk of developing PAH. In a prospective case-control study, multi-variate analysis found splenectomy to be an independent risk factor for CTEPH (odds ratio 13; 95% CI 2.7–127.0).<sup>3</sup> In a retrospective analysis of patients with CTEPH, 8.6% had previous splenectomy compared to 2.5% of patients with IPAH and 0.56% in patients with other chronic pulmonary diseases.<sup>4</sup>

PAH has been reported in patients who had had splenectomy for haemolytic anaemias such as hereditary spherocytosis, stomatocytosis, thalassemia, sickle-cell disease, paroxysmal nocturnal haemoglobinuria and fructokinase deficiency, as well as severe non-neuropathic type 1 Gauchers disease, and in those in whom the spleen was removed after blunt abdominal trauma.<sup>7-14</sup> In patients with haemolytic anaemias, the interval between splenectomy and diagnosis of PAH ranged from four to 32 years.<sup>2-4</sup>

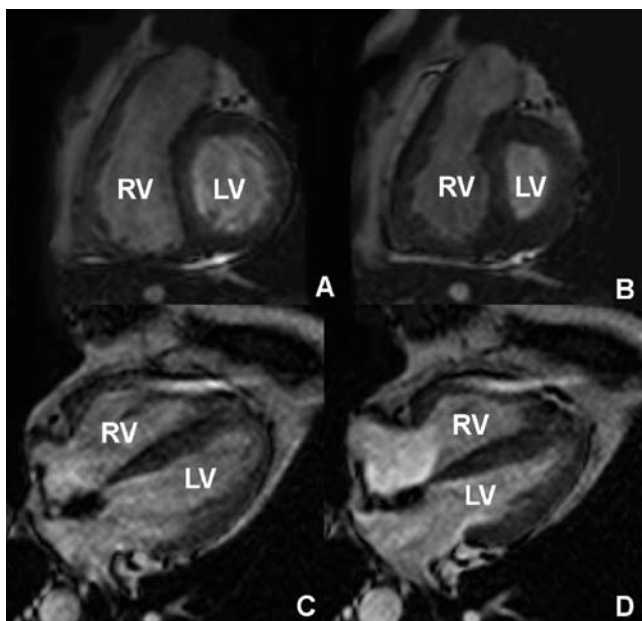
The structure of the red pulp of the spleen enables it to remove abnormal and older erythrocytes, as well as cellular debris and erythrocyte products.<sup>15</sup> The pathophysiology of



**Fig. 5A. Swann Ganz study at baseline, and 90 min after the oral administration of 100 mg/kg L-arginine the pulmonary arterial pressures remained 60/28/40 mmHg, with the cardiac output at 6.33 l/min, and the pulmonary and systemic peripheral vascular resistance indices respectively 624 (80–240) and 2 018 (1 200–2 500) dynessec/cm<sup>5</sup>.**



**Fig. 5B. After the intracardiac administration of 200 µg nitroglycerine the cardiac output remained unchanged, while the pulmonary and systemic peripheral vascular resistances decreased to respectively 540 and 1 840 dynessec/cm<sup>5</sup>. The pulmonary arterial pressures decreased from 60/29 (left) to 45/25 mmHg (right).**



**Fig. 6. Cardiac magnetic resonance imaging (steady-state free precession) delineates the hypertrophied, moderately dilated, poorly contracting right ventricle (A – short-axis and C – four-chamber end-diastolic frames, B – short-axis and D – four-chamber end-systolic frames) with a clear left-sided shift of the interventricular septum during systole (B and D), signifying elevated right ventricular pressures. The right ventricular mass was  $34 \text{ g/m}^2$  (normal  $23.3 \pm 1.4 \text{ g/m}^2$ ), end-diastolic and end-systolic volumes respectively 143 and 115 ml (normal respectively  $157 \pm 35$  and  $63 \pm 20$  ml), with an ejection fraction of 22% (normal  $60 \pm 7\%$ ).**

sickle-cell disease followed by autosplenectomy or surgical splenectomy gives some insight into the mechanism of pulmonary hypertension in patients with red cell membrane defects.<sup>16</sup> Surgical or autosplenectomy results in the persistent circulation of dysmorphic erythrocytes, unfiltered red cell membrane products, free haemoglobin and arginase.

The combination of hereditary haemolytic anaemias resulting in circulating dysmorphic erythrocytes, free haemoglobin and arginase, and the absence of splenic filtration may be particularly harmful for the pulmonary circulation. It

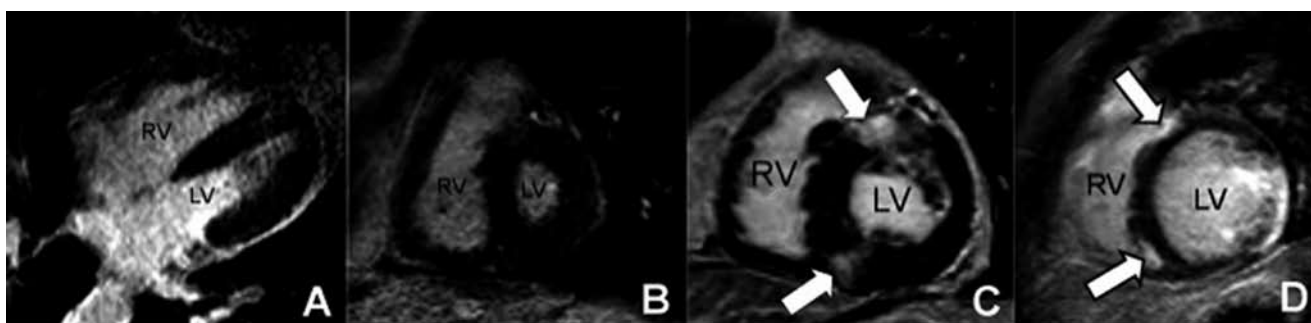
has been suggested that the unfiltered red cell membrane products may cause activation of platelets that then become trapped in the pulmonary circulation, leading to CTEPH. This mechanism may also predispose to the development of deep-vein thrombosis.

In haemolytic conditions such as congenital spherocytosis, release of free haemoglobin and red cell arginase results in a reduction of the nitric oxide synthetase substrate, L-arginine and reduced production of nitric oxide, causing endothelial dysfunction and PAH (Fig. 8).<sup>17,18</sup> During haemolysis, plasma arginine is scavenged by superoxide, produced by xanthine oxidase and cell-free haemoglobin. Reduced bioavailability of nitric oxide amplifies cell signaling pathways involving endothelial cell adhesion molecules, which orchestrate the recruitment and binding of inflammatory cells to the vascular endothelium (Fig. 8).<sup>19</sup> Free haemoglobin itself also functions as a very potent nitric oxide scavenger. Increased thrombin activity, thrombomodulin-tissue factor imbalance, prothrombotic activity of abnormal erythrocytes, interaction between the abnormal erythrocyte membrane and pulmonary vascular endothelium, and abnormal platelet activation may result in *in-situ* thrombosis (Fig. 8).<sup>20</sup>

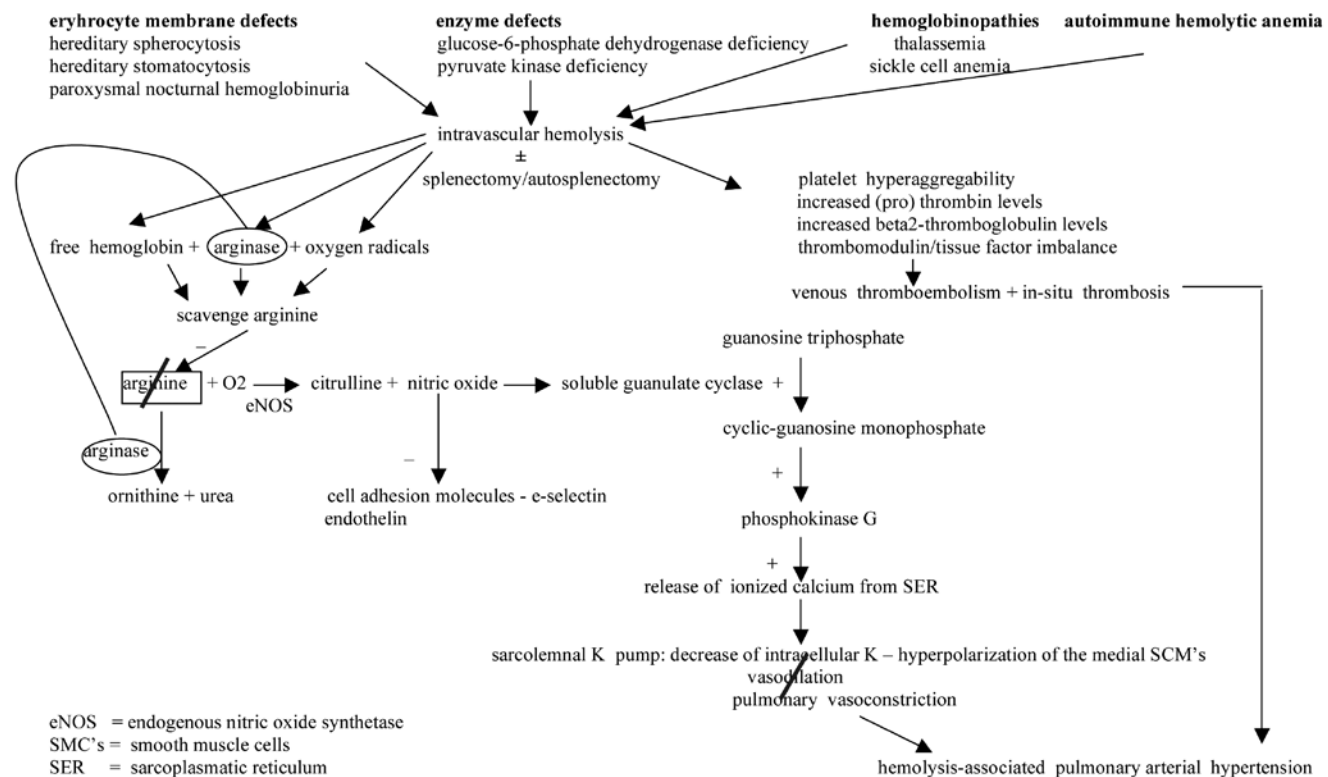
In patients with beta-thalassemia and previous splenectomy, platelet hyperaggregability and significantly higher levels of beta-2-thromboglobulin and thrombin-antithrombin III complexes were present when compared to those without splenectomy, and healthy controls.<sup>21,22</sup> Increased expression of soluble endothelial cell adhesion molecules have been found in patients with sickle-cell disease and PAH, and were independently associated with the risk of death.<sup>23</sup>

Open-lung biopsy, evaluation of explanted lungs and post-mortem assessment in patients with haemolytic anaemia and pulmonary hypertension revealed abundant thrombotic lesions, predominantly affecting the small pulmonary arteries (micro-thromboembolism), intimal thickening, medial hypertrophy and plexiform arteriopathy, abnormalities which are seen in both CTEPH and IPAH.<sup>2,5,6</sup> Smaller muscular pulmonary arteries are not visualised by MDCT, and it is here that endothelial dysfunction, with exaggerated vasoconstriction and intimal and luminal obstruction play an important role in IPAH.

In a number of reported patients with PAH after splenec-



**Fig. 7. Cardiac magnetic resonance imaging (inversion-recovery gradient echo sequence, A – four-chamber and B – short-axis views) demonstrates absence of focal right ventricular and septal fibrosis in our patient; C – fibrosis at the right ventricular insertion points (arrows) in a patient with hypertrophic cardiomyopathy; D – fibrosis at the right ventricular insertion points (arrows) in a patient with pulmonary sarcoidosis and pulmonary hypertension.**



**Fig. 8. Schematic representation of the pathophysiology of haemolysis-associated pulmonary hypertension.**

tomy, pulmonary embolism has been reported.<sup>2,10</sup> The division between CTEPH and IPAH has however been questioned, and both are currently considered to be part of the same disease spectrum.<sup>5</sup>

Ventilation/perfusion scintigraphy has been largely superseded by MDCT angiography, which is able to delineate the pulmonary vascular tree up to subsegmental level. Computed tomography angiography (CTA) shows luminal thrombi, organised mural thrombi, occlusions and webs, just as conventional angiography, while being non-invasive and considerably cheaper. In addition, MDCT provides information on pulmonary venous drainage, cardiac anatomy, ventricular volumes and systolic function, and pulmonary interstitium.<sup>24</sup>

Pulmonary magnetic resonance angiography (MRA) also correlates well with CTA, but beyond the segmental level, the higher spatial resolution makes CTA superior. Pulmonary MRA has similar accuracy to ventilation/perfusion scintigraphy in distinguishing between CTEPH and IPAH, and has replaced conventional angiography in the surgical management of patients with CTEPH.<sup>24</sup>

Cardiac magnetic resonance imaging (CMR) is performed to determine right and left ventricular mass, volumes, systolic function and output, as well as the presence of right ventricular and septal fibrosis.<sup>25,26</sup> CMR can be used to determine the size of intracardiac shunting. Blyth *et al.* reported delayed gadolinium enhancement at the right ventricular insertion points and interventricular septum in 23 of 25 patients diagnosed with pulmonary hypertension.<sup>27</sup> The extent of contrast enhancement, ie myocardial fibrosis, correlated positively with right ventricular function and pulmonary haemody-

namics. Enhancement was associated with abnormal early diastolic septal motion.

Management is similar to that of IPAH and CTEPH, and consists of life-long oral anti-coagulation, anti-platelet therapy, with vasodilators (calcium blockers, prostacyclin, bosentan, sildenafil) in patients with reactive pulmonary vasculature.<sup>28</sup> Endarterectomy may be considered in patients with predominantly proximal chronic pulmonary thrombosis.<sup>28</sup>

Therapies that maximise arginine and nitric oxide bioavailability, such as L-arginine supplementation, and increase soluble guanylate cyclase activity may benefit patients with underlying haemolytic disease.<sup>28</sup> Arginine supplementation (0.1 g/kg three times daily) in 10 patients with sickle-cell disease and PAH resulted in a 15.2% reduction ( $63.9 \pm 13$  to  $54.2 \pm 12$  mmHg,  $p = 0.002$ ) in estimated pulmonary artery systolic pressure after five days of treatment.<sup>29</sup>

Recently, treatment with hydroxy urea in sickle-cell disease patients was found to modulate erythrocyte arginase activity, with a concomitant induction of eNOS activity and/or increased arginine bioavailability through improved cellular transport activity.<sup>30</sup> This drug remains to be investigated in other haemolytic anaemias. Both L-arginine and hydroxy urea are relatively safe, inexpensive and clinically available oral pharmaceuticals.<sup>29,30</sup>

## Conclusion

We believe our patient suffered from haemolysis-associated pulmonary hypertension, a condition not previously reported in South Africa. Considering the limited sensitivity of physical examination and 12-lead electrocardiography, we

encourage screening of patients with haemolytic anaemias and those after previous splenectomy, regardless of indication, with Doppler-echocardiography for PAH.<sup>31</sup> Considering the significant morbidity and poor prognosis of PAH, early detection and adequate treatment may alter the outcome of this condition.<sup>32</sup>

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