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Pulmonary arterial hypertension after systemic-to-pulmonary shunt correction (RCD code: II-1A.4d)

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Abstract

Pulmonary arterial hypertension develops in a significant number of patients with congenital heart diseases. Congenital heart diseases predispose to pulmonary vascular remodeling as a result of increased pulmonary blood flow and increased pulmonary pressure. Pulmonary arterial hypertension associated with congenital heart diseases is a major determinant of functional capacity and survival in this group of patients. JRCD 2013; 1 (3): 118–121

Key words: congenital heart disease, pulmonary hypertension, Endothelin Receptor Antagonist

Case presentation

A 23 year-old woman after surgical closure of atrial and ventricular septal defect was admitted to the hospital due to worsening of dyspnoea. CHD was diagnosed at the age of 4 years. The main clinical symptoms at childhood were recurrent infections of the upper respiratory tract. On echocardiography, atrial septal defect (ostium secundum type) with left-to-right shunt and perimembranous ventricular septal defect with left-to-right shunt were diagnosed. Also a mild enlargement of the right atrium and right ventricle and mild tricuspid and pulmonary regurgitation were observed. On ECG, sinus rhythm of 90 beats/min and right-axis deviation were registered. In laboratory tests, no signs of polycythemia were observed (red blood cell, 5×10^3; hematocrit, 41.6%; hemoglobin, 14.1 g/dL). The patient underwent corrective cardiac surgery, atrial and ventricular defects were closed. On echocardiography, performed a couple of days after the surgery, no residual shunts through atrial or ventricular septum were observed. Moreover, no tricuspid regurgitation or elevated right ventricular systolic pressure were diagnosed. No right heart catheterization was performed at that time. After discharge, she was routinely monitored in an outpatient clinic at least once a year.

Ten years after the surgery, she started to complain of syncope during exercise. She was admitted to a pediatric cardiac department. On a physical examination, no signs of heart failure were observed, arterial oxygen saturation was between 96% and 100%, and blood pressure was 120/80 mm Hg. An ECG revealed right-axis deviation and right ventricular hypertrophy. A 24-hour ECG showed no abnormalities. On echocardiography, enlargement of the right atrium and right ventricle, elevated right ventricle systolic pressure (110 mm Hg), and elevated diastolic pulmonary artery pressure (70 mm Hg) were observed. On right heart catheterization pulmonary arterial hypertension was confirmed (mean pulmonary artery pressure, 85 mm Hg; pulmonary capillary wedge pressure, 14 mm Hg; cardiac output, 3.8 L/min; cardiac index, 2.2 L/min/m^2; pulmonary vascular resistance, 17.4 Wood units). According to the European Society of Cardiology guidelines, she was administered sildenafil at a standard dose of 20 mg three times a day and vitamin K antagonist (VKA).

After 3 months of therapy, the patient reported improvement in exercise capacity. On right heart catheterization, an increase in the cardiac index (2.65 L/min/m^2) and a decrease in pulmonary vascular resistance (8.8 Wood units) were observed. Sildenafil and VKA were continued.

In 2009, 5 years after the diagnosis of PAH had been established, she was admitted to the Centre for Rare Cardiovascular Diseases at the John Paul II Hospital because of dyspnea, low exercise tolerance, and dizziness. On admission, she was in class III of the World

Conflict of interest: none declared.

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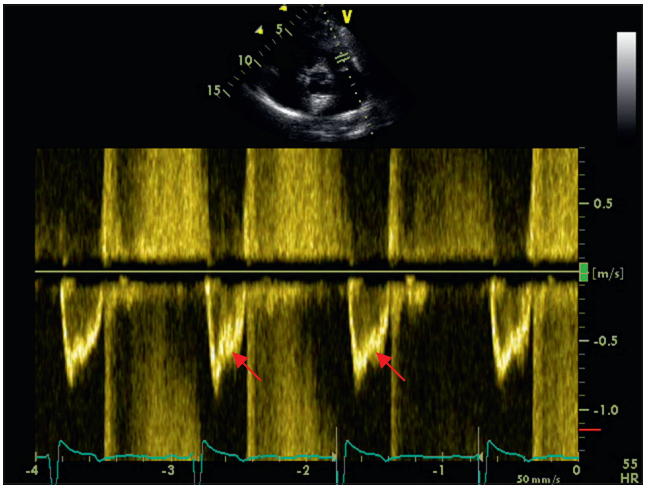

Figure 1. Transthoracic echocardiography. Parasternal short-axis view. Pulsed wave Doppler through the pulmonary valve. Shortening of the acceleration time to 53 ms, characteristic for pulmonary hypertension systolic notch (red arrows)

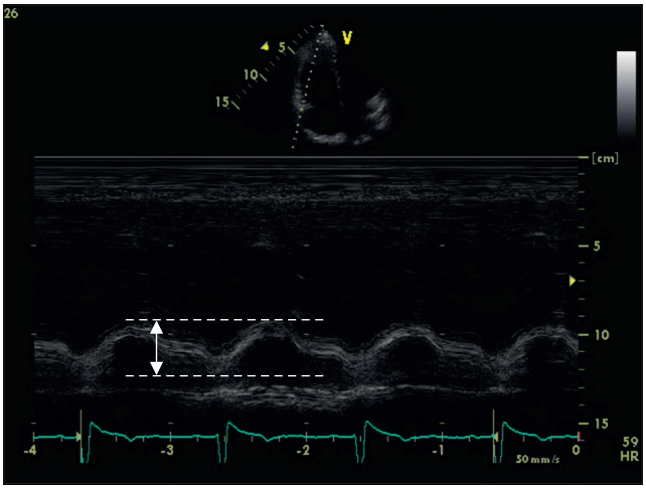

Figure 2. Transthoracic echocardiography. Four-chamber view. M-mode. Tricuspid annular plain systolic excursion (TAPSE) 16 mm (white arrow)

Health Organization functional classification. Brain natriuretic peptide levels was low – 17 pg/mL (normal range, 0–100 pg/mL). A distance in the 6-minute walk test was 411 meters. Echocardiography showed signs of severe pulmonary hypertension, including the enlargement of right heart chambers shortening of the acceleration time, systolic notch of pulmonary flow (fig. 1), severe tricuspid regurgitation with right ventricular systolic pressure of 80 mm Hg, and tricuspid annular plain systolic excursion of 16 mm (fig. 2). Right heart catheterization showed the following parameters: mean pulmonary artery pressure of 91 mm Hg, pulmonary capillary wedge pressure of 15 mm Hg, mixed venous blood saturation of 62%, cardiac index of 2.7 L/min/m^2, and pulmonary vascular resistance of 16.8 Wood units. Acute vasoreactivity test with inhaled nitric oxide was negative.

The patient was included in the Study with an Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve cliNical outcome (SERAPHIN), which was a randomized, placebo controlled study to assess the efficacy of a novel endothelin receptor antagonist, macitentan, in patients with PAH. After 3 months of a blinded phase, she was switched to an open-label phase of the trial from that time having been on dual PAH-specific therapy. A significant improvement was observed. Currently, she is in functional class II with the N-terminal pro-B-type natriuretic peptide level of 330 pg/mL (normal range, <125 pg/mL) and a 6-minute walk distance of 542 meters.

Discussion

Epidemiology of PAH-CHD

PAH leads to right ventricular failure, decreased functional capacity, and ultimately death.

The prevalence of CHD in adults is increasing, probably because more children survive to adulthood [4]. A significant proportion of the patients with CHD develop PAH, especially when left untreated. The prevalence of PAH associated with congenital systemic-to-pulmonary shunts in Europe and North America was estimated at 1.6 to 12.5 per million adults; 25% to 50% of this population had Eisenmenger's syndrome [1]. Among all adults with PAH, 11.3% have PAH-CHD [2]. In 2007, Duffels et al. [3] reported, based on the Dutch registry, that the overall prevalence of PAH among CHD patients was 4.2%. PAH was most frequently found in the aortopulmonary window (100%), atrioventricular septal defect (41%), double outlet right ventricle (17%), univentricular heart (11%), ventricular septal defect (11%), and atrial septal defect (7.6%). Eisenmenger's syndrome was observed in 58% of the patients with septal defect. It was shown that PAH developed in 3% of the patients with previously closed atrial or ventricular septal defect, which means that closure of the defect does not necessarily prevent the development of PAH.

In many cases, it is not clear whether irreversible pulmonary vascular lesions were already present before the surgical intervention or weather the pulmonary vascular disease has progressed despite successful correction [8].

Classification of PAH-CHD

PAH-CHD has been classified as belonging to the same broad group of PAH as idiopathic PAH. Classification of PAH-CHD from the Dana Point meeting is shown in Tables 1 and 2. This classification was designed to include clinical as well as anatomical and physiological changes to precisely define the different strategies used in the management and treatment in four PAH-CHD categories [5]. The final group in clinical classification are patients with high pulmonary vascular resistance and pulmonary artery pressure after corrective cardiac surgery, despite normalized heart anatomy.

Pathophysiology of PAH-CHD

Pathophysiological mechanisms leading to PAH-CHD are similar to those causing idiopathic PAH [6,7]. Left-to-right shunting

Table 1. Clinical classification of congenital systemic-to-pulmonary shunts associated with PAH [5]

A. Eisenmenger's syndrome
Eisenmenger's syndrome includes all systemic-to-pulmonary shunts due to large defects leading to a severe increase in PVR and resulting in a reversed (pulmonary-to-systemic) or bidirectional shunt. Cyanosis, erythrocytosis, and multiple organ involvement are present.

B. Pulmonary arterial hypertension associated with systemic-to-pulmonary shunts
In these patients with moderate-to-large defects, the increase in PVR is mild to moderate, systemic-to-pulmonary shunt is still largely present, and no cyanosis is present at rest.

C. Pulmonary arterial hypertension with small a defects
In cases with small defects (usually ventricular septal defects <1cm and atrial septal defects <2 cm of effective diameter assessed by echocardiography) the clinical picture is very similar to idiopathic PAH.

D. Pulmonary arterial hypertension after corrective cardiac surgery
In these cases, congenital heart disease has been corrected but PAH is either still present immediately after surgery or has recurred several months or years after surgery in the absence of significant postoperative residual congenital lesions or defects that originate as a sequela to previous surgery.

[a] The size applies to adult patients.
PAH – pulmonary arterial hypertension; PVR – pulmonary vascular resistance

Table 2. Anatomical-pathophysiological classification of congenital systemic-to-pulmonary shunts associated with PAH [5]

1. Type
  1.1 Simple pre-tricuspid shunts
    1.1.1 Atrial septal defect (ASD)
      1.1.1.1 Ostium secundum
      1.1.1.2 Sinus venosus
      1.1.1.3 Ostium primum
    1.1.2 Total or partial unobstructed anomalous pulmonary venous return
  1.2 Simple post-tricuspid shunts
    1.2.1 Ventricular septal defect (VSD)
    1.2.2 Patent ductus arteriosus
  1.3 Combined shunts
  1.4 Complex congenital heart disease
    1.4.1 Complete atrioventricular septal defect
    1.4.2 Truncus arteriosus
    1.4.3 Single ventricle physiology with unobstructed pulmonary blood flow
    1.4.4 Transposition of the great arteries with VSD (without pulmonary stenosis) and/or patent ductus arteriosus
    1.4.5 Other

2. Dimension
  2.1 Hemodynamic (specify Qp/Qs)[a]
    2.1.1 Restrictive (pressure gradient across the defect)
    2.1.2 Nonrestrictive
  2.2 Anatomic[b]
    2.2.1 Small to moderate (ASD ≤2.0 cm and VSD <1.0 cm)
    2.2.2 Large (ASD >2.0 cm and VSD >1.0 cm)

3. Direction of shunt
  3.1 Predominantly systemic-to-pulmonary
  3.2 Predominantly pulmonary-to-systemic
  3.3 Bidirectional

4. Associated cardiac and extracardiac abnormalities

5. Repair status
  5.1 Unoperated
  5.2 Palliated [specify type of operation(s), age at surgery]
  5.3 Repaired [specify type of operation(s), age at surgery]

[a] Ratio of pulmonary (Qp) to systemic (Qs) blood flow.
[b] The size applies to adult patients.
ASD – atrial septal defect, VSD – ventricular septal defect

causes increased pulmonary blood flow and increased pulmonary artery pressures, leading to the damage of the endothelial barrier. Endothelial dysfunction induces vasoconstriction, smooth muscle hypertrophy and proliferation, inflammation, and thrombosis in situ. Endothelial dysfunction shifts the balance between vasoconstrictors and vasodilators in favor of vasoconstrictors. All these changes lead to a progressive increase in pulmonary vascular resistance. Histological classification of pulmonary vascular disease was introduced by Heath and Edwards in 1958. It was suggested, that histological changes correlate with clinical severity of PAH. This classification involved 6 stages: the early lesions display medial hypertrophy (grade 1), progressing to intimal proliferation (grade 2), lumen occlusion (grade 3), progressive arterial dilatation and plexiform lesions (grade 4), thinning and fibrosis of the media (grade 5), and necrosis (grade 6). Changes in grade 1 to grade 3 were supposed to be reversible. In some patients, severe PAH can be detected after successful corrective cardiac surgery.

Management strategy

The diagnostic algorithm in PAH-CHD patients is the same as in other types of pulmonary hypertension.

The most common manifestations of PAH of all causes are exercise intolerance, dyspnea, and fatigue. Clinical symptoms of PAH-CHD may differ according to the underlying defect, severity of PAH, or patient's age [9].

Each patient after corrective cardiac surgery should undergo routine echocardiography examination; right ventricular function and right ventricular systolic pressure should be estimated. Transthoracic echocardiography is a cost-effective, time-efficient, and universal method to evaluate patients after surgery for the presence of PAH. Cardiovascular magnetic resonance imaging (CMR) and computed tomography (CT) can be used to complement echocardiography for the assessment of PAH-CHD. CT scans give information about cardiovascular structures, lung pathology, and the presence of thromboembolism. CMR provides precise assessment of cardiac structures without radiation exposure. However, the gold standard in establishing the diagnosis and severity of PAH is right heart catheterization, similarly to all other types of PAH [5].

Current management with PAH-CHD comprises pharmacological disease-targeted therapy. It should be emphasized that PAH after corrective cardiac surgery is similar to idiopathic PAH and should be treated according to the IPAH treatment algorithm with phosphodiesterase inhibitors, prostacyclin analogues, and endothelin receptor antagonists [5]. The only curative option for end-stage disease is heart and lung transplantation.

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