Pulmonary Arterial Hypertension in Adults with Congenital Heart Disease: Can we Predict its Development?

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Over the last decades, progress in pediatric cardiac surgery and interventional cardiology allowed reaching adulthood to a great number of children suffering from congenital heart diseases (CHD). Apart from corrected CHD patients, grown-up congenital heart diseases (GUCH) also comprise adults with newly diagnosed cardiac defect. Ebstein’s anomaly, coarctation of the aorta, atrial septal defect and congenitally corrected transposition of the great arteries may remain undiagnosed for many years or occasionally identified on echocardiographic evaluation and at least manifest in adult life for the first time with infective endocarditis or effort dyspnea [1]. Therefore it is difficult to estimate the exact prevalence of CHDs in adults. The management of GUCH subjects requires particular expertise by physicians in order to provide the most appropriate treatments.

It is known that patients over 60 years of age with moderate or severe CHD have worse survival prospective than general population: coronary artery disease, heart failure symptoms and NYHA class represent the strongest prognostic determinants. As compared to GUCH subjects aged between 20 and 60 years, those over 60 years of age need greater healthcare resources as outlined by considering the number of outpatient clinic visits and number and length of hospitalization of these patients [2]. The cardiovascular causes of admission to the hospital depend on complexity of CHD: congestive heart failure is the most frequent condition induced hospital admission and it is more frequent in patients suffering from complex disorders, including tetralogy of Fallot, truncus arteriosus and transposition of great arteries; valvular disease related cardiac decompensation is found in patients with simple disorder without atrial septal defect (ASD) or patent foramen ovale; finally, cerebrovascular event are the main cause of admission in case of patients suffering from simple atrial septal defect or patent foramen ovale [3]. Pulmonary arterial hypertension (PAH) represents an important complication of CHD, affecting about 10% of GUCH patients [4]. The risk of developing PAH is related to volume and pressure overload of the pulmonary circulation.

Size of defect, degree of blood shunting and repair status are the main key pathogenic factors inducing PAH and right cardiac chambers enlargement. When the left and right ventricular pressures become similar, the direction of blood flow across the defect depends on pulmonary vascular resistance: when the latter exceeds systemic vascular resistance the reversal of flow and cyanosis occur (Eisenmenger syndrome).

It has been estimated that about 44% of adult CHD subjects with a systemic-to-pulmonary shunt are at risk of PAH, and the prevalence of PAH in these subset of patients is 7.4% [5]. The beneficial effects in terms of pulmonary pressure values reduction in adults undergoing ASD occlusion are well known. Surgical closure of ASD significantly decreased right ventricular dimension and mean pulmonary pressure in patients over 35 years of age followed up for 1-11 years (mean 4.7) [6]. Percutaneous device occlusion of ASD has showed similar findings establishing itself as a valid alternative to surgery. A decrease in peak systolic pulmonary pressure to 54+21 mmHg
early after device implantation and to 31+11 mmHg after a mean follow-up of 21+14 months was observed in middle-aged patients (56+14 years) suffering from secundum ASD and peak pulmonary pressure >40 mmHg (mean 65+23 mmHg) [7]. Transcatheter ASD closure in 47 patients with mean age 69+5 years and pulmonary artery systolic pressure of 41.4+14.5 mmHg induced reverse remodelling of right-sided cardiac chambers and a decrease, but not a normalization, of PASP one month after closure [8]. Moreover, a study performed in 23 older patients (median age 70 years) with ASD and median pulmonary artery pressure of 22 mmHg demonstrated that device closure produces favorable cardiac remodeling without development of pulmonary hypertension at 1-year follow-up [9]. The European Society of Cardiology Guidelines for the management of GUCH consider transcatheter procedure as the method of choice for secundum ASD closure when applicable [1]. Although ASD repair provides positive effects on cardiac chambers dimension and PASP, magnitude of these benefits is greater in patients with less elevated PASP and less enlarged right ventricle and influenced by the age of patients [10]. Finally, according to the timing of surgery/catheter intervention it may be affirmed that “the earlier the better”.

Development of PAH after CHD repair is another aspect that deserves consideration. The abolition of left-to-right shunt is crucial for decreasing or normalizing the PASP value, although several evidences showed late onset PAH after successful correction of CHD, especially after correction of d-transposition of the great arteries [11,12]. It has been estimated a prevalence of PAH after corrective cardiac surgery of 5.7% [5].

A study carried out in 1.103 patients undergoing closure of systemic-to-pulmonary shunt (primum and secundum ASD, ventricular septal defect) showed an incidence of 2.1% in term of PAH occurrence immediately after the closure procedure, and a >15% incidence at 50 years follow-up. Moreover, the risk of PAH was reported also in subject with early closure of defect, i.e. < 25 years of age. The pre-existence of PAH and New York Heart Association functional class >I pre-closure were highlighted as main key worst predictive factors for PAH development after shunt closure. Finally, subject developing PAH showed a significantly lower 10-year survival as compared to controls [13].

The underlying mechanisms of PAH development after systemic-to-pulmonary shunt repair are still unknown. It may be hypothesized that continuous volume overload to the pulmonary circulation and consequent increased pulmonary pressure causes progressive changes in the wall arteries inducing PAH, such as endothelial dysfunction with increased expression of vasoconstrictor mediators and vascular remodeling due to increased intracellular matrix deposition and fibroblast and smooth muscle cells proliferation [14]. So the early repair, by reducing exposition of pulmonary arteries to such detrimental factor, might avoid the development of PAH.

This concept is supported by evidences showing positive outcome in young patient undergoing repair of cardiac defect [10]. A study performed in adults CHD patients (aged 59+15 years) with moderate or severe PAH showed that only 44% of patients had normalization (<40 mm Hg) of the right ventricular systolic pressure after percutaneous ASD closure [15]. Therefore, the correction of the cardiac defect should be performed before vascular changes become irreversible. However, the exact timing of surgery/catheter intervention is currently not established due to lack of parameters allowing evaluating early and reversible morphological changes in pulmonary vasculature.

Morbidity and mortality of PAH-CHD patients are still high despite advances in disease targeting therapies. In a 23 years of follow-up study in CHD adults, diagnosis of PAH was related to a more than 2-fold increase in all-cause mortality rate as compared to those without PAH, while the risk of complications such as heart failure and arrhythmia was 3-fold higher [16]. The outcome of these patients seems related to functional class, as showed by a 3-fold increased risk of death in subjects with NYHA functional class III-IV and regarding Eisenmenger subjects to location of the shunt. Moreover, the prognosis of postoperative-PAH patients was poor in a follow-up of 4.5 years as compared to patients with PAH associated with small defects [17].

Some biomarkers have been proposed as prognostic tools able to aid physicians in the management of this subset of patients and to provide them optimal medical treatments. C-reactive protein (CRP) has been evaluated as a reliable predictor for mortality in CHD-PAH patients. A CRP cut-off value >10 mg/L was associated with more than a threefold increased risk of death [18]. High-sensitivity troponin T (hsTnT) was also found to be associated with prognosis CHD-PAH patients: subjects with hsTnT level >0.014 μg/L had a significantly higher mortality rate as compared to those with normal hsTnT levels. Moreover, also NT-pro brain natriuretic peptide (NT-pro-BNP) and right ventricular function at baseline resulted determinants of death [19].

In conclusion, PAH represents an important cause of elevated morbidity and mortality in adults with CHD. This complication occurs especially in CHD with left-to-right shunt, and it can develop several years after the successful correction of cardiac defect. Although closure of shunt in childhood seems to avoid PAH, several evidences showed an increase in pulmonary pressure later in life. It remains difficult identifying patients at risk for developing PAH, and detecting PAH in an early stage it would allow starting prompt optimal therapeutic strategies. Pre-closure PAH and NYHA class >I have demonstrated to be predictive factors of PAH development after shunt closure. Serum levels of biomarkers such as CRP, hsTnT and NT-pro-BNP seem inversely related with survival of PAH-CHD patients and should be added to routine assessment of these patients in a model of risk stratification. Finally, although ESC Guidelines suggest that outcome is best when correction of CHD with shunt is performed at age <25 years, the aforementioned evidence showed the necessity of a close follow-up of all CHD patients, regardless of age at shunt closure, due to late risk of PAH development.

Declaration of Interest
The authors declare no conflicts of interest.

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