Pulmonary Arterial Hypertension In Adults With Congenital Heart Disease: General Overview of Disease Mechanisms

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Adults with congenital heart disease (CHD) have become a rapidly expanding group of complex patients requiring multidisciplinary care in specialty centers by those trained in CHD. They represent one of the most challenging subgroups of patients with pulmonary arterial hypertension (PAH) due to the presence of structural heart disease with or without coexisting cyanosis and its complications. The primary focus of attention for these patients is the lungs, whose vascular system is affected by shunt flow, or is also congenitally malformed, or has been altered by surgical procedures. When PAH develops, it affects physical exercise tolerance, travel to high altitudes, pregnancy, operability, and anesthesia (myocardial failure due to pulmonary hypertensive crisis), and thus general morbidity and mortality in this special patient group.

Incidence of PAH in Adults with CHD

Congenital heart disease is the most common major congenital malformation, occurring in approximately 6 per 1000 live births.[1] In up to two thirds of patients with CHD, there is pathology of the pulmonary vascular system: it is hypoplastic, anatomically wrongly connected, or a shunt defect is present. In a very small percentage of cases the heart disease is accompanied by PAH despite there being no significant strain on the hemodynamic system. Despite successful corrective surgery and a decrease in the occurrence of immediate acute postoperative pulmonary hypertension from 25%[2,3] formerly to 2% today,[4] approximately 10% to 20% of such patients have increased pulmonary vascular resistance. As a result of advances in diagnostics and surgery, approximately 85% to 90% of patients with CHD currently live into adulthood. It has been estimated that every year, of the approximately 5500 patients with CHD,[1,5,6] approximately 400 to 500 have significant PAH that warrants treatment.

Key Words—Congenital heart disease; Eisenmenger syndrome; pulmonary arterial hypertension; pathophysiology.

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Definition and Application to Adults with CHD

Since the classification of all forms of pulmonary hypertension at the working symposia of the World Health Organization (WHO) in 1998 in Evian and 2003 in Venice, pulmonary hypertension associated with CHD has been categorized under WHO group I, *pulmonary arterial hypertension (PAH)*. The WHO classification has also placed under this heading idiopathic PAH and familial pulmonary hypertension; PAH due to autoimmunologic, hepatologic, infectious (HIV, schistosomiasis), hematologic (sickle cell anemia, thalassemia, hemolytic anemia), and toxic causes; and persistent neonatal pulmonary hypertension. Similar to these other forms of WHO group I PAH, the PAH associated with CHD manifests as a pulmonary arteriolar vasculopathy. Primary forms and a number of secondary forms of PAH are thus assigned to *one* class, which combines the histopathologic characteristics with aspects of the clinical therapeutic response. It also includes those cases of PAH that are caused by problems of the left or systemic arterial side of the heart (including pulmonary vein stenoses, cor triatriatum, mitral stenosis or stenosis of the systemic arterial atrioventricular valve, hypoplastic or hypocontractile left or systemic arterial ventricle, and aortic valve and isthmus stenosis) if they are accompanied by an independent and inappropriate increase in pulmonary vascular resistance.

The hemodynamic definition of idiopathic PAH (mean pulmonary arterial pressure greater than 25 mmHg at rest and greater than 30 mmHg during exercise) also is applied to PAH in adults with CHD.[7] However, one must be aware that the pulmonary arterial pressure results from the ratio of pulmonary blood flow to pulmonary vascular resistance, and thus per se does not permit any statement about pulmonary vascular resistance in cases of shunt defects, and that, furthermore, pulmonary vascular pressure is a result of myocardial contractility, ie, the maximum wall tension that the subpulmonary ventricle can generate. Thus, each measurement of pulmonary vascular resistance at rest should be accompanied by a measurement under an increased pulmonary blood flow situation, not only because latent PAH can be revealed during increased flow stress to the pulmonary vascular bed,[8] but also because only the two-point determina-

tion of the pulmonary flow-pressure ratio can permit a most correct estimation of the change during pharmacologic determination of the pulmonary vascular reserve.[9]

Idiopathic PAH versus PAH in CHD

Common Features

Disturbances of intimal function of the pulmonary arteries and arterioles can already be demonstrated by electron microscopy and functionally at an early stage. In the early stage a criss-cross pattern of the originally parallel endothelial cell arrangement can be observed,[10] which is accompanied by loss of the function of the vasodilative L-arginine-NO-metabolic pathway and reduction of other vasodilator substances (prostacyclins). Associated pulmonary endothelial dysfunction[11] may lead to a predominance of vasoconstrictor mediators such as endothelins and thromboxanes.[12] Increasing damage is recognizable through pulmonary vascular medial hypertrophy. At the same time, there is an increase in the distances between cells and in gaps in the intima lining of the vessels, and transudation of growth factors into the adventitia.[13] Finally, the vessel occludes as a result of the formation of intraluminal *plexiform lesions*, at which time increasing fibrosis of the surrounding connective tissue occurs, so that dilatation of the pulmonary vessel is impossible and pulmonary vascular resistance is fixed, though some residual function of the pulmonary endothelial vasodilator metabolic pathways may be detectable.[14, 15]

Dissimilar Features

In contrast to knowing what the stimulus for the development of PAH in CHD is, namely, the pressure and volume load on the pulmonary vascular bed, the initiating stimulus of idiopathic PAH is unknown. Various authors position idiopathic PAH between a cancer and an inflammatory disease.[16] Consistent with this seems to be the clonality of the cells that are involved in the formation of the plexiform lesions, which in PAH associated with CHD are said to be of multiple polyclonal origin, but monoclonal in idiopathic PAH.[17] The theory of polyclonal origin would fit with the fact that PAH in CHD is associated with reduced responsiveness to treatment in many studies,[18] while the monoclonal origin in idiopathic PAH would be associated with a very rapid course of the disease. Despite improvement in median survival from time of diagnosis for patients with idiopathic PAH from 2.8 years in a 1991 NIH study[19] to 5.6 years at present,[20] this course still constitutes a much more urgent need for therapeutic intervention than in adults with CHD and PAH with their slower and less dramatic course. The substantially more favorable natural history for adults with CHD and PAH is an important consideration when making treatment decisions, such as timing of transplantation.

Pathophysiology of Right Ventricular Function

In idiopathic PAH, a large percentage of patients die of right ventricular decompensation.[23] With disease progression, right ventricular wall tension and pressure in the idiopathic PAH patient increase in response to the concomitant rise in pulmonary vascular resistance to maintain cardiac output. Subsequently, there follows a stable phase of more or less unchanged pulmonary arterial pressure and the same wall tension, but increasing right ventricular diameter, while the disease progresses and pulmonary vascular resistance increases further.[24] Finally, however, in the late stages of disease, any further increase in pulmonary vascular resistance results in a decrease in right ventricular ejection, with increasing end diastolic values, an increase in central venous pressure, and thus the clinical symptoms of right heart failure.[25]

The reduction in right ventricular ejection as a result of the massively increased pulmonary vascular resistance causes a reduced pulmonary venous return to the left ventricle and a low cardiac output. The left ventricle becomes small and banana-shaped, the curvature of the septum follows the right ventricle and is curved into the left ventricle (visible on echocardiographic and magnetic resonance tomographic imaging). These are ventriculo-ventricular interactions that additionally lead to a functional disturbance (reduction of diastolic compliance, increasing left ventricular dysfunction) that can be so pronounced that they themselves can become the cause of venous pulmonary hypertension, and thus, in a vicious circle, add to the process of PAH. In this situation a carefully performed balloon atrial septostomy can relieve the congestion in front of the right ventricle and ensure a cardiac output adequate for the systemic circulation, which is therefore obtained by accepting desaturation that has to be exactly balanced, and the time to the necessary lung transplantation is bridged and prolonged.[26]

In contrast, in adults with CHD and PAH who have a corrected circulatory situation and would therefore be comparable hemodynamically with patients with idiopathic PAH, the progress of the disease is less rapid and dramatic. Although there are still no systematic data on the long-term course, in most cases the rise in pulmonary vascular resistance is gradual and is well compensated for a long time by the already preoperatively hypertrophic right ventricle. Patients with trisomy 21 appear to be the exception to the rule; despite removal of the hemodynamic stimulus after surgical correction, their increase in pulmonary vascular resistance can rapidly progress further.

Compared with patients with idiopathic PAH, patients with Eisenmenger syndrome (as a result of a major shunt defect at the *ventricular level)* have the same afterload for both ventricles hemodynamically interconnected from birth. In a sense these ventricles exhibit "univentricular" function and exhibit similar hypertrophy and functional reserve.[27] As a result, compensated cardiac function is maintained for decades, and isolated right heart decompensation with consecutive low cardiac output virtually never occurs; instead, the patients desaturate more and more through the increasingly reduced proportion of the pulmonary blood flow. The smaller the defect, the more the hemodynamic situation resembles not univentricular function, but that of a serial circulatory function as in idiopathic PAH.

In patients with a shunt defect at the *atrial level* this mechanism is absent; the volume load on the right ventricle positions it close to the descending branch of the Frank-Starling curve, while the hypertrophic stimulus is absent due to the pulmonary vascular resistance hardly increasing for

decades on account of the exclusive volume load. When the pulmonary vascular resistance eventually increases, this affects the now reduced compensatory ability of this dilated right ventricle, and right ventricular decompensation therefore immediately takes place, while pulmonary arterial pressures that are still only low continue to rise.[28-30] With increasing central venous pressures and increasingly impaired cardiac output as a result of the increase in pulmonary vascular resistance, this atrial shunt defect at the same time acts like a balloon atrial septostomy, so that the clinical signs of right heart compensation and low cardiac output occur later than the increasing desaturation obtained by means of the balloon atrial septostomy mechanism.

Therefore, for a "pretricuspid" defect at the atrial level such as an atrial septal defect, right-to-left shunting occurs only after right ventricular decompensation occurs. This is quite unlike the case of a large "post-tricuspid" defect at the ventricular or great arterial level where cyanosis is caused by mixing. In left-to-right shunting at the atrial level, ie, pretricuspid, the amount of shunting is not influenced by the relation PVR:SVR, or RVSP:LVSP; rather, it is guided by the overall capacity of the right atrium and the diastolic compliance of the right ventricle. These cavities take up, in their respective hemodynamic phase, the left-to-right shunted blood and give it to the right ventricle depending on its diastolic compliance. As soon as systole begins, a fraction of that volume is ejected, depending on the right ventricle's position on the Frank-Starling curve, ie, the central venous pressure will only rise once the right ventricle begins to fail. Thus, the rise of the central venous pressure does not reflect pulmonary artery pressure or pulmonary vascular resistance, but rather right ventricular function.

PAH in CHD: Subgroups

As a result of the combination of cardiac and pulmonary malformations and possibilities for surgical correction there are various possibilities for how the condition of the pulmonary vascular system can influence the function of the circulation.

Cyanosis as a Result of Eisenmenger Syndrome

The term "Eisenmenger syndrome" was coined by Paul Wood for patients with systemic to pulmonary connections who have reversal of shunting (right-to-left) as a result of a progressive increase in pulmonary vascular resistance.[31] The blood flow to the lung is unifocal, and cardiac function is not univentricular, ie, the patient's cyanosis is not present from birth and due to obligate mixing of the venous returns on an intracardiac level, but is due to a previous left-to-right shunt that has led "secondarily" to a suprasystemic increase in pulmonary vascular resistance with a shunt reversal, the discrete cyanotic desaturation reflecting the massively increased pulmonary vascular resistance only incompletely. In the hemodynamic sense this term also applies to patients with surgical correction of a shunt defect and a significant right-to-left shunt as a result of a residual defect, and includes diagnoses

such as ventricular septal defect, atrioventricular septal defect, truncus arteriosus, and aortopulmonary window, but also atrial septal defect and transposition of the great arteries after atrial or arterial reversal surgery.

However, if cardiac function is *univentricular*, there is intracardiac mixing of venous return and thus neonatal cyanosis in approximately 7% to 10% of cases in which the pulmonary resistance does not decrease postnatally[32]. In these rare cases, heart failure symptoms may not be apparent because of the absence of a large left-to-right shunt secondary to elevated pulmonary vascular resistance. These cases may be missed because of the absence of clinical symptoms. Instead a very early "primary" Eisenmenger syndrome develops, in which there can be balanced ventricular function for a very long time[33] and good survival[27] despite considerable cyanosis.

Cyanosis as a Result of Shunt at an Atrial Level

Approximately 17% to 19% of cases of shunt defects at the atrial level are accompanied preoperatively by PAH,[34] with approximately two thirds of these in each age group having increased pulmonary vascular resistance, increasing from the 4th decade of life. Sinus venosus defects have an earlier and higher development of increased pulmonary vascular resistance as a result of the additional pulmonary venous volume load.[35] Cyanosis in an atrial septal defect patient can develop as a result of "streaming" in the atrial region, as a result of concomitant tricuspid insufficiency, or as a result of differences in ventricular compliance, and does not necessarily reflect the pulmonary vascular resistance.[36] Further investigation would be warranted in these cases to determine operability.

Postoperative Chronic Persistent PAH

For all shunt defects at a ventricular or arterial level, persistence (approximately 15% to 18%[37]) and progression of the increased pulmonary vascular resistance following successful surgical correction have been described; the prevalence varies according to the size of the shunt defect, the age of the patient, and additional malformations; they are combated by the modern strategy of correcting such defects by the age of 6 months. In patients with transposition and atrial reversal surgery[38] (but also after arterial switch surgery[39]) PAH is known to develop in approximately 7% to 10%, and this also includes patients who had a favorable neonatal course as a result of a failure of pulmonary vascular resistance to decrease. Hemodynamically, patients with such postoperative defects with increased pulmonary vascular resistance must be classified as having idiopathic PAH, and they benefit from a residual defect, either created intraoperatively (flap valve double patch[40]) or developed postoperatively through a balloon atrial septostomy.

PAH Due to Pulmonary Venous Hypertension

A chronic pressure load on the pulmonary venous compartment (as a result of pulmonary venous stenoses, cor triatriatum, mitral stenosis, or left heart dysfunction sui generis or due to subsequent stenoses) also involves, depending on the duration and extent of the load, the arterial side, with corresponding histological changes. But the plexiform lesions typical of PAH are absent,[41, 42] which is given as the reason this form of PAH rapidly normalizes after surgical correction.[43]

Unilateral PAH

As a result of pulmonary blood flows that transmit the arterial systemic pressure to the pulmonary vascular system, local PAH can develop in the corresponding dependent area of the lung. This applies for unilateral systemic-to-pulmonary arterial shunts[44] (Blalock-Taussig, Waterston, Pott) and congenital aortopulmonary collaterals (major aortopulmonary collaterals, or MAPCAs) or could be due to differing lung perfusion (right pulmonary artery originates from the aorta; bifurcation obstruction with differing stenosis of the left or right pulmonary arteries and pulmonary hyperperfusion of the contralateral side). Paradoxically, in the "protected," unaffected side of the lung, PAH often develops histologically as well,[45] for which circulating or local neurohormonal factors may be responsible as a cause. Patients with hypoplasia of the pulmonary artery region and who undergo appropriate palliative surgery (Fallot disease, pulmonary atresia) often display a combination of all these possibilities.

PAH Hemodynamics in Cases of Low Pulmonary Vascular Resistance

If the right ventricle is weak, or if it is absent altogether, even slight increases in pulmonary vascular resistance can significantly lower the transpulmonary blood flow. The Fontan procedure represents the extreme end of this spectrum. The hemodynamic success of this palliative operation are known to be dependent on the hemodynamic and mechanical intactness of the mechanical and vascular function of the lung.[46] It is physiologically plausible, but still speculative on account of insufficient data, that this also applies for defects with impaired right ventricular (mechanical or contractile) function (Ebstein anomaly,[47] Uhl anomaly of the right ventricle, postoperative tetralogy of Fallot,[48] or atrial septum defect[49]), with corresponding implications for a therapeutic or prophylactic strategy.

Conclusion for Cardiologic Practice

Adult patients with congenital heart disease display multiple problems in the long term. Pathologically increased pulmonary vascular resistance, with its manifestation as PAH and its consequences with regard to right ventricular function, systemic oxygen supply, and the consecutive effects on physical exercise tolerance and general clinical condition must not be underestimated. The specialist for patients with congenital heart disease should be very familiar with the possible forms of PAH and understand the interplay between right (subpulmonary) ventricle and pulmonary vascular resistance. Pulmonary vascular resistance can be successfully influenced by means of a wide variety of specifically and selectively effective pulmonary substances. An enormous amount of research on novel targeted agents is being carried out, with a large amount of clinical knowledge being gained. Additional areas of use such as in patients with PAH associated with CHD are currently being investigated as well. ■

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