Assessment of the Reversibility of Pulmonary Hypertension in Adult Congenital Heart Defects: When, how and why?

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Abstract: Pulmonary arterial hypertension (PAH) in the context of adult congenital heart disease (ACHD) can be reversed by early closure of the communication or pre-existing shunt. This "window of opportunity" is lost beyond a certain point of no return. Therefore, it is crucial to accurately assess the reversibility of this progressive vascular disease, which usually begins in early stages. The reversibility assessment is currently based on a combination of clinical symptoms, hemodynamic changes and fundamental variables such as pulmonary vascular resistance. However, its measurement has limited predictive value and leaves many patients in a “gray area” regarding decision-making. This review provides a concise overview of the mechanisms involved in the flow-dependent progression of PAH in CHD and assesses existing and future alternatives for a thorough assessment of existing pulmonary artery disease. The structural quantification of the pulmonary arterial tree using fractal branching algorithms, functional images with intravascular ultrasound, nuclear imaging, new serum biomarkers, genetic tests and the potential for transcriptomic analysis of circulating endothelial cells and platelets are being incorporated into the evaluation of this type of patients.

Keywords: Pulmonary Hypertension-Congenital Heart Diseases-Pulmonary Vasculature-Heart Failure.

INTRODUCTION

The prevalence in the diagnosis of congenital heart defects (CHD) has increased from 1 child per 1,000 live births in 1930 to 9 per 1,000 live births in 1995 and has remained constant since then. The incidence of CHD varies from 7 to 9 newborns per 1000 live births. Although the exact prevalence of Adult Congenital Heart Disease associated with Pulmonary Hypertension (ACHD-PAH) remains unknown, it is estimated that approximately 4 to 10% of adults with CHD will eventually develop ACHD-PAH. These figures are repeated in underdeveloped countries [1].

Eisenmenger syndrome (ES) comprises 58% of patients with ACHD-PAH, while ventricular septal defect (CIV) is the most common underlying congenital anomaly (42%). It is noteworthy that the distribution of the causes of ACHD-PAH has changed over the years and is likely to change in the future [2]. Early diagnosis and treatment of CHD have resulted in a decrease in the number of patients with ES and an increase in the number of patients with pulmonary hypertension (PH) after surgical repair of CHD. Furthermore, as mortality in pediatric patients with CHD continues to decrease, a reduction is expected in patients with ACHD-PAH with simple defects and an increase in patients with ACHD-PAH with complex lesions [3].

Flow-Induced Remodeling in the Pulmonary Vasculature: A Sequence of Events

The normal pulmonary arterial (PA) tree has a fractal branching structure that manages to homogeneously perfuse the blood flow to the entire alveoli. The distal intra-acinar arterioles are not muscled and consist of a layer of endothelial cells (EC). The pre-acinar arteries contain a thinner muscular medial vasa that becomes thicker and more elastic when we advance into the AP trunk [4]. The normal blood flow in the pulmonary circulation is laminar: well ordered and streamlined, pulsating in the proximal lung arteries, more continuous in the arterioles and capillaries, with a small difference in pressure in the artery and venous compartments. Blood flow and pressure are essential triggers for pulmonary vascular remodeling in CHD [1]. Increased pulmonary blood flow appears to be a prerequisite for neointimal-type remodeling, where increased pulmonary artery pressure functions as an accelerator [5].

Non-restrictive post-tricuspid shunts such as ventricular septal defect (high flow / high pressure) induce rapid advanced remodeling of PAH. In contrast, pre-tricuspids (high-flow / normal-pressure lesions) as septal atrial defects induce advanced remodeling in only 5% to 10% of patients and generally only after two to four decades [6].

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Increased flow, especially in combination with increased pressure, definitively alters blood flow throughout the pulmonary vascular tree, leading to positive regulation of flow-sensitive genes by mechano-transduction, such as those of the early growth response p19 or p53. These in turn induce pro-apoptotic, pro-proliferative and inflammatory effects causing endothelial dysfunction. Morphological changes on the cell surface such as inflammation and cohesion of endothelial cells constitute one of the first visible structural changes, followed by neomuscularization of the acinar arterioles (usually not muscled) and medial hypertrophy of pre-acinar arteries. Proximal medial hypertrophy increases the rigidity of the AP, reducing the proximal physiological flow and accelerating the maximum distal flow rate. Neo-intimal lesions are found mainly on the distal branches. This process involves intimal hyperplasia with degradation of the elastic laminae, infiltration of pericytes in the intima and invasion of smooth muscle cells in the vascular lumen [7].

The human ACHD-PAH model offers a unique opportunity to study these structures, with their functional and molecular changes at all different stages of disease progression: from the early reversible stages in childhood to advanced and later irreversible disease.

Contemporary Hemodynamic Evaluation of PH in CHD and its Utility for the Evaluation of Vascular Reversibility

Assessment of vascular reversibility is a crucial part of the decision for closure of a shunt (often called "operability") in patients with ACHD-PAH. In essence, the operability of a CHD associated with PAH implies the possibility of successfully performing the surgical correction of the heart defect with low morbidity and mortality during the procedure and its immediate evolution, but also to evaluate the response without complications in the medium and long term.

There is currently no "gold standard" for reversibility assessment. The contemporary evaluation of reversibility is based on the integration of clinical variables (including age, type of CHD, central cyanosis on exertion, increased R2, syncope, systolic murmur, associated comorbidities and defined genetic patterns or chromosomal abnormalities), laboratory variables. (hemoglobin, hematocrit) and hemodynamic evaluation using cardiovascular imaging (echocardiography, CT, MRI) and cardiac catheterization.

According to current guidelines, the evaluation of reversibility is limited to hemodynamic variables: left / right shunt, a PVR index <4 WU/m2. The closure of the lead is contraindicated when the net lead is directed from right to left, and is not recommended when the PVR index is> 8 WU/m2. When the PVR index is between 4 and 8 WU/m2, an “individual” evaluation in a specialized center is recommended [8].

Recommendation for shunt closure in Congenital Heart Diseases [8]

Recommendation			Class	Level
PVR_i (WU/m2)	PVR	To correct		
<4	<2.3	Yes	IIa	C
4-8	2.3-4.6	Evaluate in Reference Centers	IIa	C
>8	>4.6	No	IIa	C

These recommendations, however, are predominantly based on expert opinion and are hardly compatible with the data. In fact, in the ACHD-PAH, prospective studies have not yet identified hemodynamic variables with reliable cut-off points that are able to predict with certain accuracy the reversibility of changes in the pulmonary vasculature after shunt correction. The retrospective studies available are seriously hampered by selection bias, the lack of an adequate description of the preoperative characteristics or an incomplete follow-up of their evolution.

For the evaluation of reversibility, acute pulmonary vasodilator tests (PVT) are performed using short-acting pulmonary vasodilators: inhalation with nitric oxide or epoprostenol. Although the use of PVT to estimate reversibility before corrective surgery is widespread in current clinical practice, no hemodynamic variable has been shown to be accurate enough to predict definitive reversibility after shunt correction [9]. The use of PVT to assess reversibility and eventually operability in ACHD-PAH should not be confused with PVT applied in idiopathic PH. In idiopathic PH, they are used to predict the prolonged beneficial effects of pharmacological therapy with calcium channel blockers where there are specific criteria that define those who respond acutely clearly and precisely.

However, these response criteria cannot be extrapolated to assess pulmonary vascular reversibility

in ACHD-PAH. Considering the heterogeneity of the pathophysiological processes that occur in the different congenital heart diseases and the complexity and limitations that the different hemodynamic measurements entail (especially when performing a test of these characteristics), it would not be appropriate to rely on a single hemodynamic parameter to assess reversibility of the pulmonary vascular bed in the context of ACHD-PAH.

Structural, Functional and Molecular Evaluation of the Pulmonary Vasculature in PAH

Next, we develop an overview of the methods to analyze structural, functional and molecular changes at the different anatomical levels of the pulmonary vascular tree in PH and their potential to evaluate their possible reversibility through different interventions.

Structural Markers

The evaluation of vascular morphology by lung biopsy has been considered the gold standard for phenotyping pulmonary vascular disease. In patients with CHD-PAH, a lung biopsy demonstrating neointimal fibrosis and plexiform lesions predict the progression of proliferative phenomena that do not reverse after shunt closure. However, the presence of medial hypertrophy and mild intimal proliferation generally indicate a favorable evolution after resolution of the shunt [10].

Although this morphological approach to evaluating reversibility is still widely accepted as an academic concept, the obvious practical limitations have led to its abolition of healthcare practice. The irregular distribution of advanced vascular lesions in the lung with PH limits its reliability, and even more so by means of a biopsy with a single or multiple sample. Therefore, less invasive methods have been adopted in order to evaluate structural changes with less risk and a similar capacity for discrimination [11].

The main dimensions of AP can be easily visualized by Nuclear Magnetic Resonance (NMR), Computed Tomography (CT), plain radiography and Echocardiography. A longitudinal CT scan in patients with PH showed that the main dilatation of the PA is already present with a mPAP of 21–24 mm Hg, and is correlated with the PVR during the progression of the disease, indicating its applicability for early detection of PH [12].

However, the value of the PA dimension as the main predictor of reversibility in a ACHD-PAH is probably limited, since the pressure-volume overload and the dimensions change with age. The distal pulmonary tree with advanced PH shows a progressive reduction in its fractal ramification (amputation) and in the arteriolar cross-sectional area. These characteristics can be visualized by wedge angiography and quantified by calculating the gradual decrease (rate of reduction in the diameter of the vessel), the background (contrast of fluid intensity in the peripheral lung fields) and the circulation time. A reduction in fractal branching is correlated with PVR and functional class in idiopathic PH (IPAH) and in ACHD-PAH [13]. The main PA dilation and fractal branching have limitations as separate indices in the context of reversibility, but combined they would justify the development of Randomized Clinical Trials (RCTs) that justify their application.

Functional Markers

Vascular stiffness indices such as compliance are functional parameters of the pulmonary vascular bed that can be evaluated using intravascular ultrasound (IVUS) or dynamic MRI along with data from the patient's medical history.

In PH it has been shown that the increase in arterial stiffness occurs early in the development of the disease when the mPAP and the PVR are still within the normal range. IVUS could also predict disease progression in patients with a favorable hemodynamic response. These data support a role for PA stiffness indices in the assessment of reversibility.

Molecular Markers

The increasing understanding of molecular biopathology associated with the early progression, reversal, or irreversibility of HP provides a theoretical basis for staging HP using nuclear imaging, circulating biomarkers, and transcriptome or metabolome profiling [14].

Nuclear Images

Nuclear imaging techniques such as Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) allow evaluating pathophysiological processes and responses "*in vivo*". Nuclear imaging could identify PH patients with favorable molecular profiles for reversibility using a variety of tracers such as 18F-Fluorothymidine (marker of proliferative processes), 18F-flucicatide (neoangiogenesis), and annexin tracers

(apoptosis) [15]. The first PH nuclear imaging assay involved PET with a fluorine-18-labeled 2-fluoro-2-deoxyglucose marker (18F-FDG). The absorption of 18F-FDG increases in cells with high aerobic index and glycolysis, which has also been observed in the endothelial cells of patients with PH. In rats with this pathology, the 18F-FDG signal was positively correlated with an increase in the PA muscle mean. The 18F-FDG signal also increased in patients with end-stage idiopathic PH compared to controls.

However, the study showed that among patients with idiopathic PH, the uptake of 18F-FDG is highly heterogeneous [16, 17].

Serum Biomarkers

Cerebral natriuretic peptide (BNP) and pro BNP N-terminal (NT-proBNP) have recently been incorporated into the Guidelines and Consensus on this pathology.

NT-proBNP correlates with hemodynamic parameters and survival in right failure and correlates adequately with the therapeutic response to the available pharmacological arsenal. These data confirm the usefulness of natriuretic peptides as biomarkers that reflect the pressure overload of the right chambers, but considering that they are markers of cardiac stretching, their role in the evaluation of pulmonary or vascular disease is limited [18].

Biomarkers of Endothelial Dysfunction

In PH, damaged lung endothelial cells (EC) detach and become detectable in the peripheral blood. In ACHD-PAH, the peripheral blood count of the circulating EC (CEC) was 10 times higher in irreversible PH than in reversible PH. In both ACHD-PAH and idiopathic PH, clinical deterioration was associated with an increased CEC count, whereas treatment with therapy directed at PH was associated with a decrease. The number of circulating progenitor endothelial cells recruited from the bone marrow (indicating reduced ability to maintain EC homeostasis), is significantly reduced in

Eisenmenger Syndrome compared to healthy controls [19].

Other Suggested Circulating Biomarkers for CD

Damage markers are asymmetric dimethylaginine (ADMA) and ghrelin. ADMA levels were significantly higher in the final stage versus early in the ACHD-PAH. In contrast, ghrelin levels increased in children with early CHD-PH versus non-CHD-PH and decreased in late versus early stage [20].

A recent study compared the blood metabolomic profiles of 10 patients with reversible HP and four patients with irreversible HP using mass spectrometry. In this small cohort, proteins with discriminatory potential between groups were found in four candidates: caveolin-1, phylamine-1A, cathepsin-D (increased in irreversible PAH) and glutathione S-transferase mu1 (GSTM1; decreased in irreversible PAH). Seemingly contradictory, caveolin-1 is known to amplify beneficial BMPR2 signaling in ECs, and caveolin-1 mutations or loss in ECs are generally associated with the development of PH. However, expression of caveolin-1 was increased with disease progression in the mean of remodeled arteries in end-stage idiopathic PH and in ACHD-PAH. This temporal expression pattern makes caveolin-1 a potential marker to distinguish reversibility. Filamin-1A is associated with resistance to apoptosis and cathepsin D and elastin to collagen degradation and generates vascular remodeling. GSTM1 is finally associated with protection against reactive oxygen species (ROS). ROS induces DNA damage that propagates the progression of PAH. Loss of GSTM1, as found in the blood of patients with irreversible PH, therefore, may be an appropriate biomarker for the progression of PH. Larger prospective clinical studies, ideally incorporating into a therapeutic algorithm, are necessary to confirm the value of these biomarkers for clinical practice [21].

Next Generation Sequencing of Circulating Cellular RNA and Platelets

Recent observations in lung cancer indicate that lung tumors dump cells and circulating tumor DNA into the bloodstream and "educate" platelets with tumor RNA as they pass the tumor. These factors can be isolated from a peripheral blood sample standard and next generation sequencing (NGS) can be performed that allows us to identify tumor profiles that can be used for "staging", and determine the specific treatment strategy with even the ability to predict the answer to it.

Pulmonary EC is also discharged into the bloodstream in PH and platelets from PAH patients are significantly altered compared to controls too. These observations streamline NGS studies of CEC and platelets in PH to detect transcriptomic profiles that are associated with reversible or irreversible diseases [22].

Genetic Evaluation

An increasing number of genetic mutations is associated with PH. If this mutation leads to PH, the phenotype is usually severe and progressive. Genetic mutations are not common in ACHD-PAH and the available data is controversial. However, the presence of a mutation in the context of a patient with ACHD-PAH could predispose or progressively accelerate the pre-existing clinical picture and therefore transform the disease into an irreversible process. Mutations in BMPR2, and recently the transcription factor Sox17, have been associated with PH in CHD specifically. Whether this provides sufficient justification for detecting these variants in the PH reversibility assessment remains to be determined [23].

Despite the progress being made, the criteria used to date for the safe closure of intracardiac shunts continue to require some of those described here, namely:

Criteria for Greater Security to Close the Shunts

Ideal parameters for safe closure of patients with CC [4]

1. Normal saturation at rest and exercise
2. Left-right shunt on echocardiogram
3. Increased pulmonary flow (Qp / Qs by Echo): Ideally> 3 in large non-restrictive defects, but beware of <2 and large volume defects
4. Integral of velocity flow in pulmonary veins increased (> 30 cm)
5. PASP not greater than 70 mm Hg
6. PASP / PDAP ratio> 2: 1 PADP is usually low in uncomplicated shorts
7. PVRi <6 WU/m2 (ideally 4 WU/m2)
8. Normal PCP and normal LVEDP. Without MI or LV dyastolic dysfunction
9. Absence of restrictive physiology in the LV
10. Absence of advanced LV dysfunction, severe arrhythmias or comorbidities that justify it

Alternatives to Patient Inoperability

Given the definitive impossibility of reversing the changes produced in the pulmonary vasculature, the start of pharmacological therapy is now mandatory. The different guidelines indicate this by offering a large number of prognostic markers with which to assess the evolution of our patients.

Clinical guideline on progression of pulmonary vascular disease and initiation of therapy in patients with ACHD-PAH[1]		
	NT pro BNP >500 ng/l o BNP > 13.9 ng/ml	Combined pharmacological therapy in the presence of any of the following variables
	TAPSE < 15 mm	
	6MWT < 350 mtrs	
	SO_2 <85%	
	RA area >25 cm^2	
	RA vs LA area >1.5	
	Functional class NYHA > III	
	Absence of sinus rhythm	
	Ferritin < 30 ng/ml o Ferritin betwen 30 y 100 ng/ml with saturation of Transferrine < 20%	Iron replacement therapy

TAPSE: tricupid annular plane systolic excursion; 6MWT: 6-minute walk test; SO_2: oxygen saturation; RA: right atrium: LA: left atrium.
[1]Adult congenital heart disease with pulmonary arterial hypertension: mechanisms and management Papamichalis M Heart Failure Reviews Springer Nature 2019.

The combination of drugs that act on the three pathophysiological pathways currently described (nitric oxide, endothelin and prostagalandin) results in an effective option until the appearance of significant functional class deterioration that requires us to submit the patient to a pre-transplant lung evaluation.

Shunts and PAH have a complex relationship that evolves with time. In the early stages of PH secondary to left-to-right shunt, the best therapeutic option remains closing the shunt. When PH has developed with concomitant significant pulmonary vascular disease, the shunt should not be closed and patients should be treated with specific therapies. In severe cases of idiopathic PH, shunt creation (atrial septostomy or reversed *Potts* shunt) may represent a therapeutic option that improves functional status and may delay the need for lung transplantation in those who survive the high-risk procedure. Further studies are needed to assess the indications for shunt creation, as well as the long-term effects of this approach [24].

Recommendations for the Treatment of Patients with HP and Congenital Heart Disease		
Recommendations	**Class**	**Level**
Bosentan is recommended in Eisenmenger's Syndrome in FC III	I	B
Other BRE, iPDG5 or Prostanoids may be indicated in Eisenmenger Syndrome	IIc	C
In the absence of significant hemoptysis, oral anticoagulation can be used in patients with signs of thrombosis or HF.	IIb	C
Supplemental O2 may be used to improve saturation and HF signs	IIa	C
In the presence of signs of hyperviscosity in blood, phlebotomy with isovolumetric replacement may be used, with a hematocrit> 65%	IIa	C
Iron supplements with low serum ferritin may be used	IIb	C
Combined drug therapy may be used in Eisenmenger Syndrome	IIa	C
Calcium antagonists are not indicated in Eisenmenger Syndrome	III	C

CONCLUSION

Early and accurate detection of the reversibility window is a critical challenge in patients with ACHD-PAH, but to date there is no evidence or consensus on how to define this window. Only approximations as a result of isolated cohort studies. Current clinical tools, including invasive hemodynamic evaluation, are not sufficient to adopt a specific definition in this area. Future prospects include a detailed study of the structural, functional, and molecular changes that occur in the pulmonary vascular tree during PH progression. This opens new windows of opportunity for invasive imaging techniques and exploration of new biomarkers, for the extensive mapping of the metabolic or transcriptomic profile of peripheral blood in these patients, offering a promising opportunity to determine the reversibility of their pulmonary vasculature. Thus, a broad field of basic and clinical research is defined that must be addressed in the coming years.

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