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Assessment of reversibility in pulmonary arterial hypertension and congenital heart disease

Diederik E van der Feen,[1] Beatrijs Bartelds,[1,2] Rudolf A de Boer,[3] Rolf M F Berger[1]

[1]Center for Congenital Heart Diseases, Department of Pediatric Cardiology, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[2]Division of Cardiology, Department of Pediatrics, Erasmus Medical Center—Sophia Children's Hospital, Rotterdam, The Netherlands
[3]Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Correspondence to
Dr Diederik E van der Feen, Center for Congenital Heart Diseases, University Medical Center Groningen, Groningen GZ 9713, The Netherlands; d.e.van.der.feen01@umcg.nl

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ABSTRACT

Pulmonary arterial hypertension (PAH) in congenital heart disease (CHD) can be reversed by early shunt closure, but this potential is lost beyond a certain point of no return. Therefore, it is crucial to accurately assess the reversibility of this progressive pulmonary arteriopathy in an early stage. Reversibility assessment is currently based on a combination of clinical symptoms and haemodynamic variables such as pulmonary vascular resistance. These measures, however, are of limited predictive value and leave many patients in the grey zone. This review provides a concise overview of the mechanisms involved in flow-dependent progression of PAH in CHD and evaluates existing and future alternatives to more directly investigate the stage of the pulmonary arteriopathy. Structural quantification of the pulmonary arterial tree using fractal branching algorithms, functional imaging with intravascular ultrasound, nuclear imaging, putative new blood biomarkers, genetic testing and the potential for transcriptomic analysis of circulating endothelial cells and educated platelets are being reviewed.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a lethal syndrome characterised by increased pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR) and normal pulmonary capillary wedge pressure. The diagnosis is essentially based on assessment of these haemodynamic values, and clinical presentation predominantly comprises symptoms of resulting right heart failure.[1] These symptoms however, are preceded by a progressively obstructive arteriopathy that may be clinically silent for many prior years. At diagnosis, most PAH aetiologies such as idiopathic PAH, have already progressed to an irreversible stage in which current targeted therapy may stabilise or decelerate progression, but cannot cure the disease.[2]

PAH in congenital heart disease (PAH-CHD) presents with unique features in this aspect. In these patients, the arteriopathy is triggered by increased pulmonary blood flow resulting from a left-to-right shunt due to an intracardiac or extracardiac defect. Early identification of the cardiac defect allows detection of the pulmonary arteriopathy in an early stage, and timely shunt closure can permanently reverse, thus cure the disease.[3] However, the beneficial effects of shunt closure seem lost after a certain point of no return, after which even accelerated PAH progression may occur months to years after surgery.[4] These observations underscore the critical importance of early and accurate detection of this '*window for reversibility*' in patients with PAH-CHD. The assessment of reversibility however, is nowadays primarily based on clinical judgement and measurements of haemodynamic variables, which have limitations as surrogates for the stage of the arteriopathy.[1 5] Techniques able to directly assess the pulmonary vasculature are still absent from clinical practice today. Reliable assessment of the vascular disease stage may improve identification of reversibility in PAH-CHD, and could help to detect disease development early in patients at risk for other forms of associated PAH (eg, in familial or HIV-PAH or connective tissue disease-PAH).

This review will evaluate the possibilities and limitations of the contemporary assessment of reversibility in PAH-CHD. First, we will provide a brief overview of the temporal structural, functional and cellular changes that occur during PAH progression in CHD. We will then provide a conceptual and practical approach to assess the pulmonary vasculature in PAH-CHD, using existing and new imaging modalities and biomarkers.

FLOW-INDUCED REMODELLING OF THE PULMONARY VASCULATURE: *A SEQUENCE OF EVENTS*

The normal pulmonary arterial (PA) tree (figure 1A) has a fractal branching structure that equally divides blood flow to the alveoli. The distal intra-acinar arterioles are non-muscularised and consist of a smooth endothelial cell (EC) layer (figure 2). More proximal pre-acinar arteries have a thin muscular medial vessel layer that becomes thicker and more elastic towards the PA trunk. The blood flow in the normal acinar pulmonary circulation is laminar: well-ordered and streamlined, pulsatile in the proximal pulmonary arteries, more continuous in the arterioles and capillaries, with a small pressure difference in the arterial and venous compartments.[6 7]

Blood flow and pressure are essential triggers for pulmonary vascular remodelling in CHD.[8] Increased pulmonary blood flow seems a prerequisite for the neointimal type remodelling, where increased pulmonary artery pressure functions as an accelerator. Non-restrictive, post-tricuspid shunts such as a ventricular septal defect (high flow/high pressure) induce advanced PAH-remodelling frequently and rapidly, usually within a few years. In contrast, pretricuspid high flow/normal pressure lesions like atrial septal defects induce advanced remodelling only in 5%–10% of the patients and generally only after two to four decades.[2] Increased flow, especially in combination with increased pressure, disturb blood flow throughout the PA tree,[6] leading to upregulation of flow-sensitive genes via mechanotransduction, such as early growth response-1[9] or p53.[10] These in turn induce pro-apoptotic, pro-proliferative and inflammatory signalling[2] and cause endothelial dysfunction. Morphological changes in cell surface, swelling and cohesion of ECs are one of the first structural changes visible,[11] followed by neomuscularisation

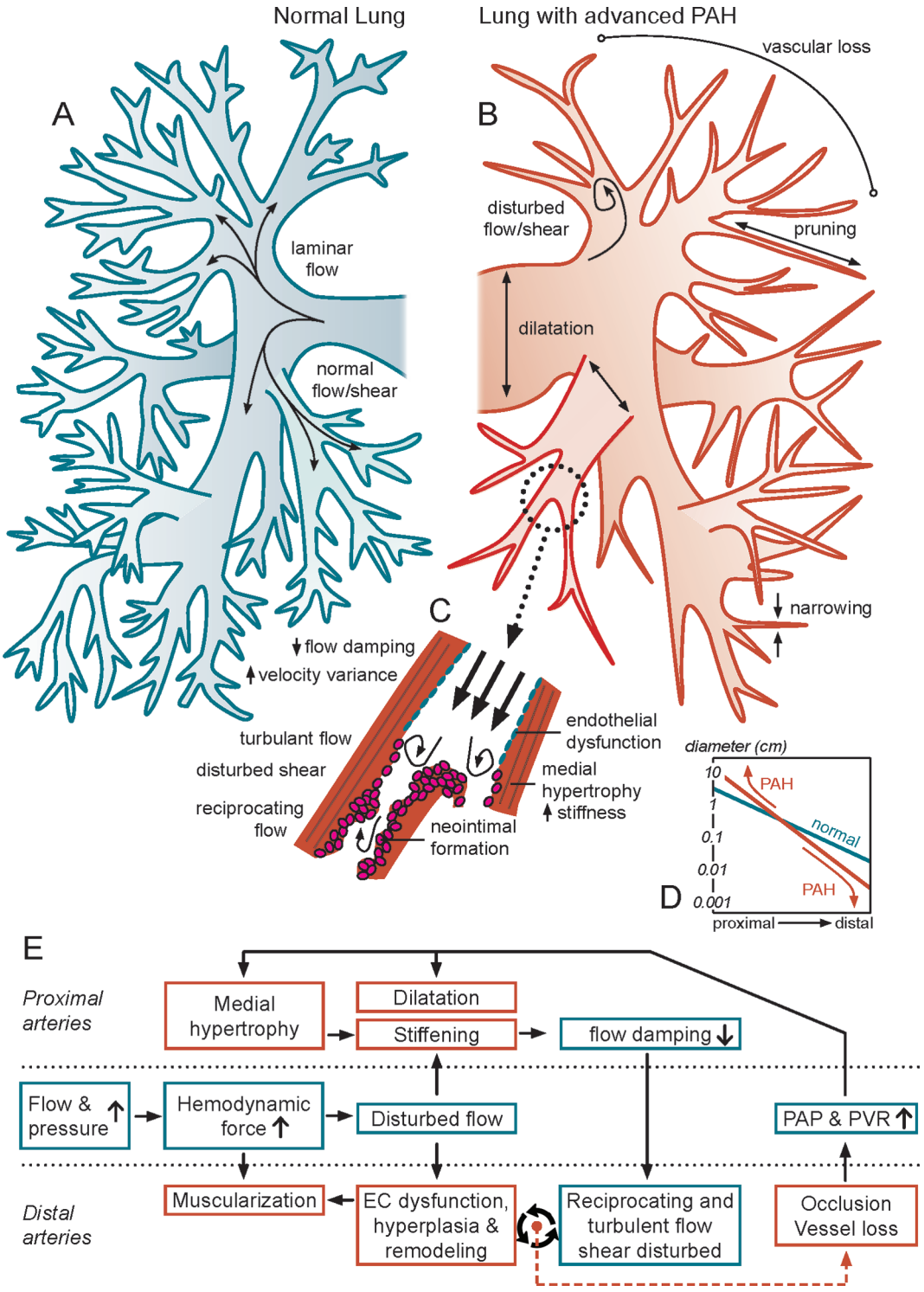

Figure 1 Schematic representation of the pulmonary arterial tree in the normal situation (A) and in pulmonary arterial hypertension (PAH) (B). PAH is characterised by proximal arterial dilatation, loss of fractal branching structure, distal arterial narrowing and pruning and peripheral vessel loss. (C) Increased haemodynamic force increases medial thickness and stiffness, this causes turbulent flow mainly at the branching points. Turbulent flow induces endothelial dysfunction and proliferation, which lead to neointimal lesions that occlude the vascular lumen and further disturb flow. (D) Logarithmic relationship of proximal arterial dilatation and distal occlusion in health and PAH. In PAH, the slope of this line increases. Adopted from Allen *et al*.[28] (E) Proposed sequence of haemodynamic (blue) and structural (red) events following increased flow. EC, endothelial cell; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance.

of the normally non-muscularised acinar arterioles and medial hypertrophy of pre-acinar arteries.[7] Proximal medial hypertrophy increases proximal PA stiffness, reducing physiologic proximal flow damping.[12] As a result, peak flow velocity and flow velocity variance are increased, amplifying the flow disturbance in the distal PAs[12] (figure 1C,E, figure 2).

Neointimal remodelling, the pathohistological signature for any form of progressive PAH, occurs when blood flow remains

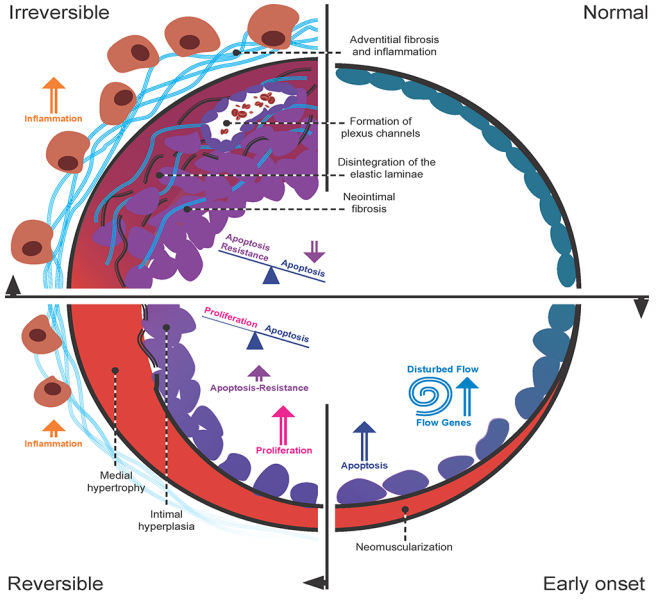

Figure 2 Concise scheme of the progression of pulmonary arterial hypertension (PAH) in response to flow at the intra-acinar level of the pulmonary arterial (PA) tree. The normal arteriole has a smooth single layer of endothelial cells (EC) and no medial layer. Increased flow leads to the upregulation of numerous flow-sensitive genes and induces EC apoptosis and EC dysfunction, and neomuscularisation. Reversible PAH is characterised by medial hypertrophy and EC proliferation. The shifting balance between EC proliferation and apoptosis induces intimal hyperplasia. Irreversible PAH is characterised by neointimal fibrotic lesions and adventitial fibrosis and inflammation. ECs have become resistant to apoptosis and progressively occlude the vascular lumen. Plexus channels start to form within the vessel, eventually leading to the characteristic plexiform lesion.

disturbed. Neointimal lesions are found primarily at branching points in the distal PAs.[13] This process involves intimal hyperplasia, degradation of the elastic laminae, infiltration of pericytes into the intima and encroachment of smooth muscle cells into the lumen and is driven by a prolonged misbalance in proliferation and apoptosis, upregulation of anti-apoptotic signalling and ongoing inflammation.[14–16] Neointimal remodelling disrupts the vascular luminal surface, which further disturbs local flow patterns, causing a vicious cycle of disturbed flow on a progressively remodelling intimal layer,[6] which ultimately leads to the development of a fibrotic neointimal layer and luminal occlusion (figure 2).

These local distal arteriolar changes affect the structure and function of the whole PA tree, the most marked being reduced branching complexity, occlusion of supernumerary arteries, pruning and loss of distal vasculature and dilatation and stiffening of the proximal arteries[17] (figure 1B). The *human model* of PAH-CHD offers the unique opportunity to study these structural, functional and molecular changes in all different stages of disease progression: from disease initiation and the reversible phase in infancy and childhood, throughout the progression towards advanced, irreversible disease.[2]

CONTEMPORARY HAEMODYNAMIC ASSESSMENT OF PAH-CHD AND ITS UTILITY FOR REVERSIBILITY

The assessment of reversibility is a crucial part in the decision for shunt closure (often referred to as 'operability') in patients with PAH-CHD. An algorithm for the assessment of reversibility is presented in figure 3. In essence, operability of CHD associated with PAH involves the possibility to successfully perform the operative correction of the heart defect and for the patient to survive that procedure, where reversibility of PAH-CHD refers to the normalisation of the pulmonary vasculature, directly but also long term after correction of the heart defect. At present, no gold standard exists for the assessment of reversibility. Contemporary assessment of reversibility relies on the integration of clinical variables (including age, type of CHD, central cyanosis at exertion, clubbing, right ventricular heave, accentuated pulmonary second heart sound component, fading of a ventricular murmur, associated comorbidities such as genetic or chromosomal abnormalities), laboratory variables (including haemoglobin, haematocrit) and haemodynamic evaluation by echocardiography and heart catheterisation (HC).[5 18] Currently, HC is regarded the cornerstone in the diagnosis and prognostication of PAH-CHD.

According to current guidelines, assessment of reversibility is limited to haemodynamic variables: those in favour of reversible PAH-CHD are a left-to-right shunt and a PVR index <4 WUm^2. Shunt closure is contraindicated when the net shunt is directed right-to-left, and is discouraged when PVR index is >8 WUm^2. When the PVR index is between 4 and 8 WUm^2, 'individual patient evaluation in tertiary centres' is advised.[19] These recommendations however, are predominantly based on expert opinion and are hardly supported by data. In fact, in PAH-CHD, no prospective studies have yet identified reliable haemodynamic cut-offs that predict reversal of pulmonary vascular disease and normalisation of haemodynamics after cardiac correction.[2] Available retrospective studies are seriously hampered by selection bias, lack of preoperative characteristics or incomplete follow-up.

Acute pulmonary vasodilator tests (AVT) are performed during HC to test the effect of short-acting pulmonary vasodilators (inhalation of nitric oxide or epoprostenol) on PVR, PAP and shunting. Although the use of AVTs to estimate reversibility prior to corrective surgery is widespread in current clinical practice, no haemodynamic cut-offs have shown sufficient accuracy in predicting reversal after shunt correction. The use of AVTs to assess reversibility/operability in PAH-CHD should not be confused with AVTs in idiopathic PAH, which are indicated to predict prolonged beneficial effects of calcium channel blocker therapy and where specific criteria for acute responders have been defined.[20] However, these response criteria cannot be extrapolated to assess reversibility in PAH-CHD.[21] Considering the heterogeneity in CHD and the complexity and limitations of haemodynamic measurements (especially when performing AVTs) in the situation of a shunt,[22] it might be an illusion to expect a single haemodynamic parameter to distinguish reliably between reversible and irreversible PAH-CHD.

STRUCTURAL, FUNCTIONAL AND MOLECULAR ASSESSMENT OF THE PULMONARY VASCULATURE IN PAH

The following paragraphs present an overview of methods to analyse structural, functional and molecular changes at the different anatomical levels of the PA tree in PAH, and their potential to assess reversibility. We summarised the indices evaluated in this review, and the current indices for reversibility in table 1.

Structural markers

The assessment of vascular morphology via lung biopsy has long been considered the gold standard for phenotyping pulmonary

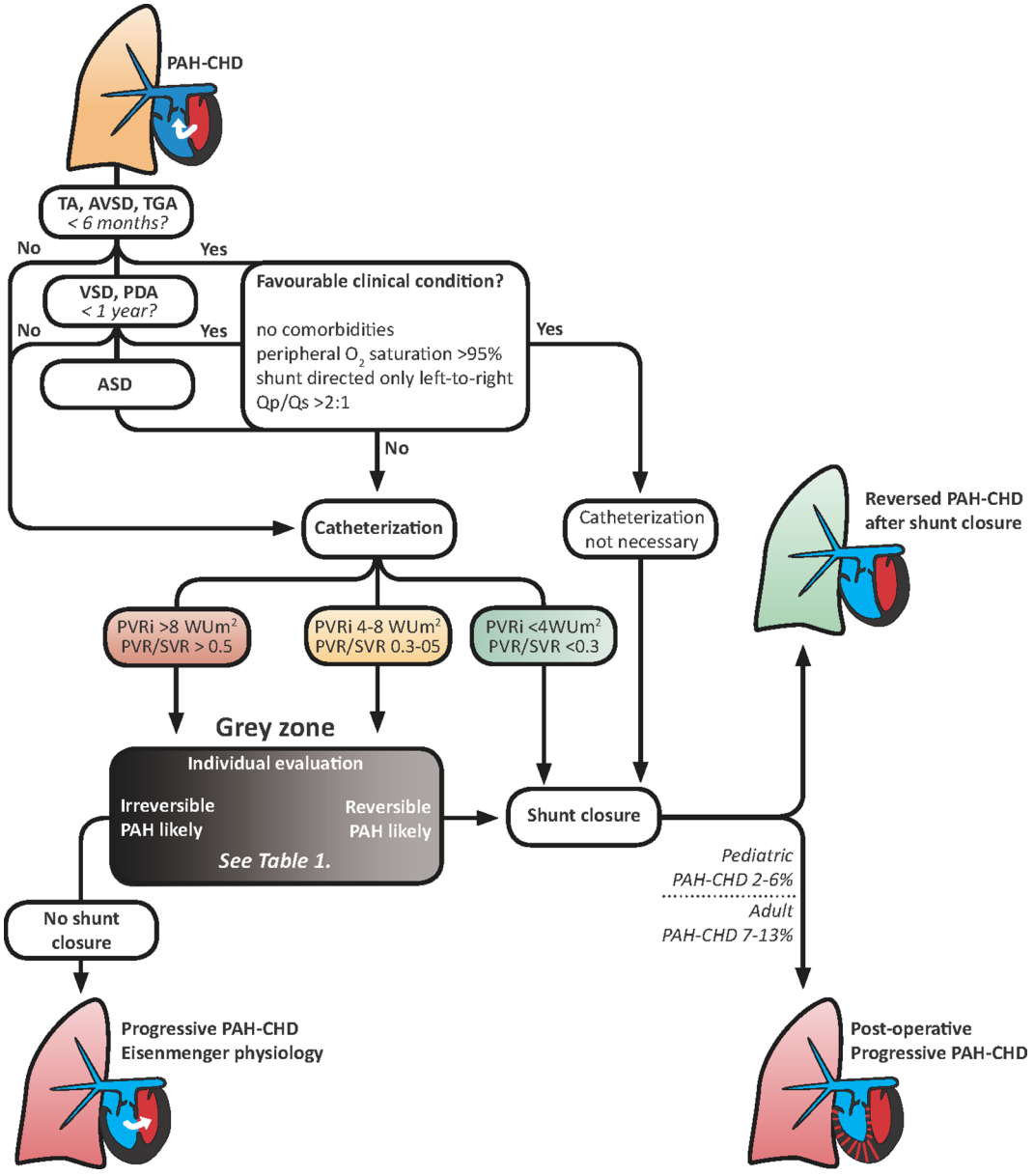

Figure 3 Algorithm for the assessment of reversibility in pulmonary arterial hypertension in congenital heart disease (PAH-CHD). Currently, a large grey zone exists for patients with PAH-CHD with a PVR index>4 WUm^2. Table 1 provides a summary of possible methods to discern reversibility, but more research is needed to accurately predict a reversible response to shunt closure; 2%–6% of children and 7%–13% of adults with PAH-CHD develop postoperative PAH after shunt closure, which is associated with a significantly worse prognosis than patients with uncorrected Eisenmenger syndrome. ASD, atrial septal defect; AVSD, atrioventricular septal defect; PVR/SVR, pulmonary-to-systemic vascular resistance ratio; Qp/Qs, pulmonary-to-systemic blood flow ratio; RV, right ventricular; TA, truncus arteriosus; TGA, transposition of the great arteries; VSD, ventricular septal defect; WU, Woods Units×m^2.

vascular disease.[2] In patients with PAH-CHD, a lung biopsy showing neointimal fibrosis and plexiform lesions predicts progression, also after shunt closure, whereas isolated medial hypertrophy and mild intimal proliferation are likely, but not sure, to improve.[3 23] Although this morphological approach to reversibility is still widely accepted as a concept, its practical limitations have led to its abolishment from clinical practice. Morbidity and mortality in PAH-CHD has been reported as high as respectively 13% and 20%.[24] The patchy distribution of advanced vascular lesions in the PAH lung further limits the reliability of judging reversibility from a single or multiple biopsy specimen. Hence, less invasive methods to assess the structural changes of the PA tree have been developed.

Main PA dimensions can be readily visualised by MRI, CT, plain radiography and echocardiography. A longitudinal CT study in patients with pulmonary hypertension (PH) showed that main PA dilatation already occurs at an mPAP of 21–24 mm Hg,[25] and correlates with mPAP and PVR during disease progression, indicating applicability for early PH detection. However, the value of main PA dimension as a predictor of reversibility in PAH-CHD is likely limited, as pressure and volume overload is involved, and the dimensions change with age.[26]

The distal PA tree with advanced PAH shows progressive reduction in fractal branching structure (pruning) and arteriolar cross-sectional area (vascular loss, see figure 1). These features can be visualised by wedge angiography and quantified by

Table 1 Contemporary and possible additional indices for the assessment of reversibility in PAH-CHD.

Variable	Effect on/indicative of reversibility	Level of evidence*
Contemporary indices		
Age and CHD type	Younger age at shunt correction favours reversibility. High flow+high pressure lesions more rapidly lead to irreversible PAH than high flow only. *Age below which reversible PAH is likely.* *TA, AVSD, TGA: <6–12 months. VSD, PDA: <1–2 years. ASD: 30–40 years.*	C
Comorbidities	Comorbidities such as Down syndrome, congenital diaphragmatic hernia, bronchopulmonary dysplasia, arteriovenous malformations, hereditary telangiectasia, hyperthyroidism or rheumatoid arthritis are associated with increased risk to develop irreversible PAH in CHD.	C
Physical examination	*Indicative of irreversible PAH:* cyanosis at exertion, peripheral oxygen saturation <90%, clubbing, RV heave, accentuated pulmonary 2° heart sound component, fading of ventricular murmur.	C
Echocardiographic evaluation	*Indicative of reversible PAH:* Net shunt direction is left-to-right. Pulmonary to systemic blood flow ratio (Qp/Qs) is 2:1.	C
Right heart catheterisation	*Indicative of reversible PAH: PVR<4 WU.* *Indicative of irreversible PAH: PVR>8 WU.* PVR 4–8 WU: further evaluation in tertiary centres.	B
Evaluated indices		
Genetic evaluation	BMPR2 and Sox17 mutations predispose to PAH in CHD. Other mutations associated with PAH, but not (yet) with PAH-CHD include: BMPR1B, ACVRL1, TBX4, EIF2AK4, KCNK3, ALK5, SMAD4, SMAD9, AGTR1, CAV1, EDN1, EDNRA, ENG, KCNA5, NOS2, NOTCH3, SERPINE1, SIRT3, THBS1, TOPBP1, TRPC6.	C
Vascular morphometry on lung biopsy	*Indicative of reversible PAH:* Medial hypertrophy and mild intimal proliferation. *Indicative of irreversible PAH:* Neointimal fibrosis and plexiform lesions.	Not recommended due to procedural risks.
Structural evaluation of the PA tree	Integration of main PA dilatation, vascular loss and reduced fractal branching.	Further exploration needed.
PA stiffness indices	*Indicative of reversible PAH:* PA-distensibility>0.95 %/mm Hg. PA-compliance>0.08 mm^2/mm Hg.	C
Nuclear imaging	Hypothetical potential for tracers of molecular processes associated with reversibility. Limited applicability in paediatric PAH-CHD.	Not recommended in children.
Blood biomarkers	*Indicative of irreversible PAH:* Increased CEC count. Increased levels of asymmetric dimethylarginine, caveolin-1, filamin-1A, cathepsin-D. Decreased levels of grehlin and glutathione S-transferase mu1.	C
Transcriptomic profiling of circulating ECs and platelets	Hypothetical potential to identify transcriptomic profiles associated with PAH reversibility in circulating ECs and 'educated' platelets.	Further exploration needed.

*Levels of evidence: (A) based on data from multiple randomised clinical trials or meta-analyses. (B) Data from a single randomised clinical trial, multiple trials with heterogeneous results, or observational studies. (C) Consensus of opinion of the experts and/or small studies, retrospective studies, registries.
ASD, atrial septal defect; EC, endothelial cell; PA, pulmonary arterial; RV, right ventricular; TA, truncus arteriosus; AVSD, atrioventricular septal defect; TGA, transposition of the great arteries; VSD, ventricular septal defect; WU, Woods Units.

calculating tapering (rate of reduction in vessel diameter), background haze (contrast fluid intensity in peripheral lung fields) and circulation time.[27] At present, reduction in fractal branching can be calculated using a fractal dimension algorithm on CT angiography.[17] A reduction in fractal branching correlates with PVR and functional class in idiopathic pulmonary arterial hypertension (IPAH) and PAH-CHD.[17]

Main PA dilatation and fractal branching have limitations as separate indices in the context of reversibility, but combined they justify further investigation. A power-law model integrated both parameters showing a logarithmic linear correlation: small increments in main PA diameter correspond to relatively large changes in the distal PA tree; and the slope of this line (X) decreases during disease progression (figure 1D). Comprehensive analysis showed that the largest decrements in X happen in the earliest phases of the PAH development, before any elevation in resting PVR, indicating X as a sensitive marker for early remodelling of the distal pulmonary vasculature.[28] These insights rationalise prospective studies in animal models and human PAH to validate their predictive value with regard to reversibility.

Functional markers

Vascular stiffness indices such as distensibility and compliance are functional parameters for the PA tree that can be assessed by intravascular ultrasound (IVUS) or by integrating dynamic MRI and HC data. In PAH, arterial stiffening was shown to occur early in the disease, when mPAP and PVR are still within normal range.[29] In 41 children with various stages of PAH-CHD, distensibility and compliance, measured by IVUS at baseline, correlated with progressive PAH and mortality after a 20-year follow-up. Interestingly, IVUS could also predict disease progression in patients with a presupposed favourable haemodynamic profile at HC.[30] IVUS has been shown safe and applicable even in small children with PAH-CHD.[31] These data support a role for PA stiffness indices in the assessment of reversibility.

Molecular markers

The increasing comprehension of the molecular biopathology associated with early progression, reversal or irreversibility of PAH, provides a theoretical basis to stage PAH using nuclear

imaging, circulating biomarkers and profiling of the transcriptome or metabolome.

Nuclear imaging

Nuclear imaging techniques like positron emission tomography (PET) and single photon emission computed tomography allow in vivo assessment of pathophysiologic processes and responses. Nuclear imaging could identify patients with PAH with molecular profiles favourable for reversibility using a variety of tracers such as ^{18}F-Fluorothymidine (proliferation), ^{18}F-flucicatide (neoangiogenesis) and annexin-tracers (apoptosis).

The first trial with nuclear imaging in PAH, involved a PET study with fluorine-18-labelled 2-fluoro-2-deoxyglucose-tracer (^{18}F-FDG). ^{18}F-FDG uptake is increased in cells with high aerobic glycolysis, which has also been observed in ECs of patients with PAH.[32] In rats with PH, ^{18}F-FDG signal positively correlated with PA muscularisation.[32] ^{18}F-FDG signal was also increased in patients with end-stage IPAH compared with controls.[33] A subsequent study however, showed that among patients with IPAH, ^{18}F-FDG uptake is highly heterogeneous.[34] Hurdles of pulmonary nuclear imaging in PAH include the influence of target site perfusion on tracer uptake and the limited spatial resolution of current nuclear imaging techniques. In addition, the radiation exposure limits its applicability in paediatric PH.

Blood biomarkers

Blood biomarkers currently incorporated in clinical PAH guidelines are brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP).[35] NT-proBNP correlates with haemodynamic parameters and survival, and parallels a treatment effect with vasodilator therapy.[35] These data confirm the utility of the BNPs as a biomarker for the pressure-loaded RV, but being markers of cardiac stretch, their role in the assessment of pulmonary vascular disease is limited.

Biomarkers for EC damage

In PAH, damaged pulmonary ECs detach and become detectable in the peripheral blood.[36] In PAH-CHD, circulating EC (CEC) count in peripheral blood was 10-fold higher in irreversible versus reversible PAH and controls.[37] Both in PAH-CHD and IPAH, clinical deterioration was associated with increased CEC count, while treatment with PAH-targeted therapy was associated with a decrease.[36] The number of circulating endothelial progenitor cells, recruited from the bone marrow (indicating reduced capacity to maintain EC homeostasis), is significantly reduced in Eisenmenger PAH compared with healthy controls,[38] but did not differentiate in reversibility in a cohort of reversible and irreversible PAH-CHD.[37] Other suggested circulating biomarkers for EC damage are asymmetric dimethylarginine (ADMA) and ghrelin. ADMA levels were significantly higher in end-stage versus early PAH-CHD.[39] Conversely, ghrelin levels were increased in paediatric early PAH-CHD versus CHD without PH, and decreased in end-stage versus early PAH-CHD.[40]

Other biomarkers

A recent study compared the metabolomics blood profiles of 10 early, reversible and four patients with advanced, irreversible PAH using mass spectrometry.[41] In this small cohort, four candidate proteins were found with discriminative potential between groups: caveolin-1, filamin-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 signalling in ECs,[42] and mutations or loss of caveolin-1 in ECs are generally associated with the development of PAH. However, caveolin-1 expression was indeed found to increase with disease progression in the media of remodelled arteries in end-stage IPAH and PAH-CHD.[41] This temporal expression pattern makes caveolin-1 a potential marker to distinguish reversibility. Filamin-1A is associated with apoptosis-resistance, and cathepsin-D to elastin and collagen degradation, and to vascular remodelling: processes all consistent with end-stage PAH pathology. GSTM1 finally is associated with protection against reactive oxygen species (ROS).[41] ROS induces DNA damages which propagates the progression of PAH.[43] Loss of GSTM1, as found in the blood of patients with irreversible PAH, may therefore be an appropriate biomarker for PAH progression. Larger prospective clinical studies, ideally with incorporation in a therapeutic algorithm, are needed to confirm the value of these biomarkers for clinical practice.

Next-generation sequencing of circulating cellular RNA and educated platelets

Recent observations in lung cancer indicate that lung tumours shed cells and circulating tumour DNA into the bloodstream and 'educate' platelets with tumour-RNA as they scrape past the tumour.[44] These factors can be isolated from a standard peripheral blood sample. Next-generation sequencing (NGS) then allows to identify tumour profiles that can be used for staging, to determine treatment strategy and to predict treatment response.[44] Pulmonary ECs also shed into the bloodstream in PAH (see the 'Biomarkers for EC damage' section) and platelets from patients with PAH are significantly altered compared with controls as well.[45] These observations rationalise NGS studies of CECs and platelets in PAH, to detect transcriptomic profiles that are associated with reversible or irreversible disease.

Genetic evaluation

An increasing number of genetic mutations is associated with PAH (also see table 1). If this mutation leads to PAH, the phenotype is usually severe and progressive.[46] Genetic mutations are not common in PAH-CHD,[47] and available data are controversial. Nevertheless, the presence of a mutation in the context of PAH-CHD could predispose for or accelerate progressive, thus irreversible disease. Mutations in BMPR2,[48 49] and recently in the transcription factor Sox17,[50] have been associated with PAH in CHD specifically. Whether this provides sufficient rationale to screen for these variants in the assessment of PAH reversibility remains to be determined.

CONCLUSION

Early and accurate detection of *the window for reversibility* is critical in patients with PAH-CHD, but up to the present day there is no evidence, nor consensus, how to define this window. The current clinical tools including invasive haemodynamic evaluation do not suffice and are prone for improvement. Insights in the structural, functional and the molecular changes that occur in the PA tree during the progression of PAH, open windows for less invasive imaging techniques and exploration of new biomarkers. Extensive mapping of the metabolomic or transcriptomic profile of the peripheral blood in patients with PAH-CHD, enables a promising opportunity to determine a signature for reversibility that aids therapeutic decisions in the clinic. Prospective trials to address this clinical need are highly warranted.

Contributors DEvdF has drafted the manuscript. RMFB, RAdB and BB have revised the manuscript. RMFB gave final approval of the version published.

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