Assessment of pulmonary vasoreactivity in children with pulmonary hypertension

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Purpose of review

With the current advance in understanding and treatment of pulmonary arterial hypertension in children, pulmonary vasoreactivity testing would navigate the treatment option. An inclusive review of the milestone studies and also recent literature over the last few years on the pulmonary vasoreactivity testing in children will provide the update on various available pulmonary vasodilator agents, markers related to vasoreactivity response, the implication of the testing result on child management and outlook for the long-term outcome.

Recent findings

There continue to be emerging data regarding pulmonary vasodilators for vasoreactivity testing in children and the genetic predictor of pulmonary vasoreactivity response, particularly in children with idiopathic and familial pulmonary hypertension. Despite a recent advance in pulmonary hypertension therapy leading to improved prognosis in children, the novel knowledge on standardized pulmonary vasoreactivity testing in children and its interpretation remain limited and controversial.

Summary

The precise definition of pulmonary vasoreactivity testing remains debatable, particularly in children with pulmonary hypertension related to congenital heart defect. Defining the responder, in order to navigate the treatment option, is frequently dictated by institutional experience and facilities. Meanwhile, the criteria for responder in children with idiopathic pulmonary artery hypertension are reasonably consistent. In general, responders seem to have less severe disease and better prognosis.

Keywords

Eisenmenger's syndrome, idiopathic pulmonary artery hypertension, pulmonary hypertension, pulmonary vasoreactivity test

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Introduction

Pulmonary arterial hypertension (PAH) is defined as the elevated mean pulmonary artery pressure (mPAP) of more than 25 mmHg at rest, a normal pulmonary capillary wedge pressure (less than 15 mmHg) and a pulmonary vascular resistance (PVR) of more than 3 Wood units (WU) [1]. These criteria have also been applied to diagnose children with PAH. Idiopathic PAH (IPAH) and PAH related to congenital heart disease (CHD) are the two major forms of PAH predominantly classified in children. IPAH is initially believed to be a rare disease until recently when it is now being diagnosed with greater frequency. In contrast, PAH related to CHD, which was once considered to be the most common form of PAH in children, is in decline over the last decade due to the early access and advance in congenital heart surgery. Survival of PAH children has significantly improved due to the current development in pulmonary vasodilator-targeting therapy, particularly IPAH [2•]. Meanwhile, the surgical corrections of CHD in children with severe and longstanding PAH have simultaneously evolved successfully. Assessing pulmonary vasoreactivity remains an important tool to evaluate the pulmonary vascular beds as it leads to assist in defining the best treatment option and prognosis.

Pathology and pathogenesis of pulmonary arterial hypertension

PAH is a panvasculopathy predominantly affecting small pulmonary arterioles [3], which leads to pathological increases in PVR resulting in restricted flow through the pulmonary arterial circulation. Various pulmonary arteriopathies are characterized as pathological features of PAH, including medial hypertrophy, intima–media thickness, adventitial proliferation, thrombosis *in situ*, inflammation and plexiform lesion. An individual patient

may develop a diverse degree of lesions heterogeneously in various segments of the lung. Constrictive lesion including medial hypertrophy is considered to be an earlier and more reversible form [4]. As they are diffuse lesions, they are hemodynamically important in pulmonary vasoreactivity testing.

Pathogenesis of PAH is characterized by endothelial dysfunction causing imbalance in pulmonary vasoactive substances [5,6], a decreased ratio of apoptosis/proliferation in pulmonary arterial smooth muscle cells (PASMCs) [7,8] and disordered adventitia [9]. The pulmonary vasoactive substances are currently classified according to their mechanisms into three major pathways specifically via the prostacyclin, endothelin and nitric oxide. PASMC abnormalities mostly manifest via abnormal regulation of K^+, Ca^{++} and Na^+ channels [10]. Moreover, genetic mutation has been implicated in pathogenesis of familial PAH (FPAH), particularly gene mutations in the transforming growth factor beta-receptor pathway, bone morphogenetic protein receptor type II (BMPR2) and activin-like kinase 1 [11–13]. Therefore, the pathogenesis of the PAH currently is considered to be multiple hits in mechanism. Relevant cellular pathways in the pathogenesis of PAH are summarized in Fig. 1 [14•].

Hemodynamic assessment and acute pulmonary vasoreactivity testing

Several noninvasive tests, particularly the echocardiography, have markedly contributed and played a major role in screening and assisting in diagnosis of PAH. The Doppler echocardiography can provide an estimate of the right ventricular and systolic PAPs. However, all patients with suspected PAH are recommended for pulmonary hemodynamic assessment to evaluate the PVR. Calculated PVR reflects the influence of transpulmonary pressure gradient and pulmonary blood flow and is only elevated in the PAH, a predominant pediatric age group in pulmonary hypertension classification.

Acute pulmonary vasoreactivity testing is usually performed during the same procedure as the diagnostic cardiac catheterization to define the component of constrictive lesions, which are known to be reversible.

Indication for acute pulmonary vasoreactivity test

The rationale for pulmonary vasoreactivity testing in children with PAH is two-fold: management option and prognosis. Children with PAH undergoing acute vasoreactivity test deserve to be discussed separately from children with IPAH and those with CHD. Every child with IPAH should undergo pulmonary vasoreactivity testing. This is because the positive response to a pulmonary vasodilator indicates the likelihood that the child would have a favorable response to high-dose calcium channel blockers (CCBs) long-term therapy [15,16].

In children with PAH related to CHD, approximately one-third with uncorrected CHD died from pulmonary vascular obstructive diseases [17]. Surgical correction for those with advanced and irreversible pulmonary vasculopathy is contraindicated due to the high morbidity and mortality. The vital part of the assessment of surgical operability requires an accurate determination of the degree of pulmonary vasoreactivity or reversibility. Moreover, the test would also provide a prediction whether postoperative pulmonary hypertensive crisis will response favorably to a pharmacological agent.

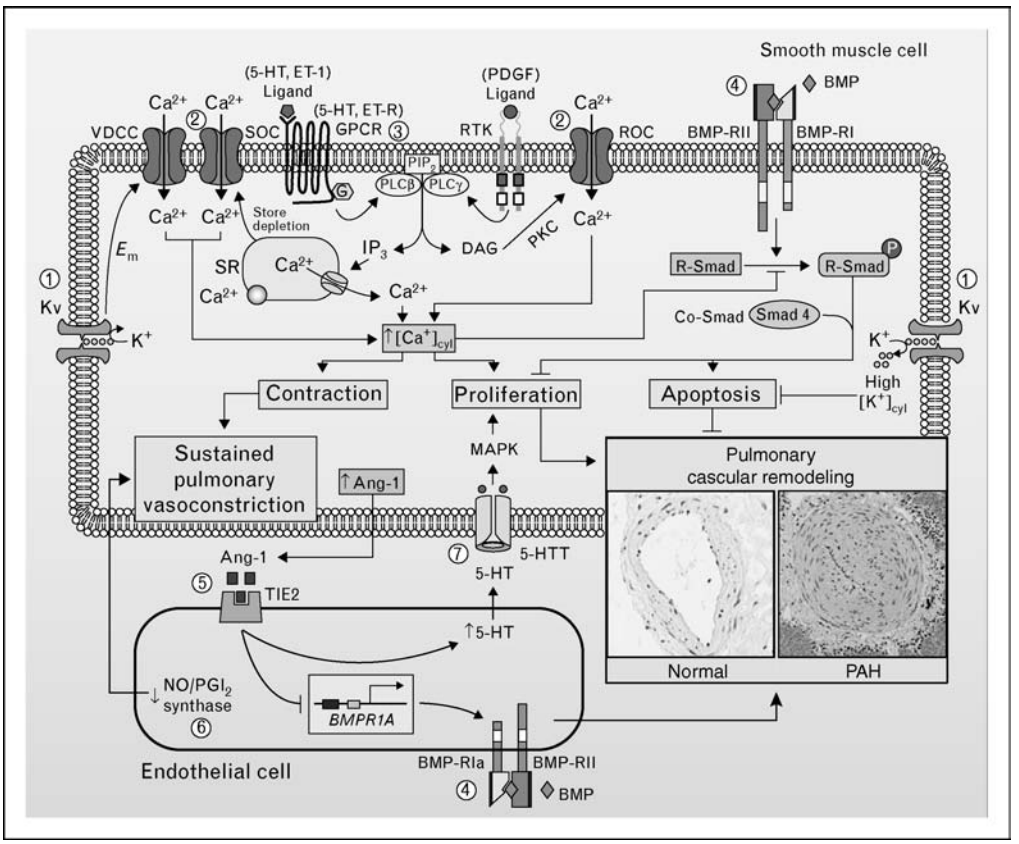
Criteria of responder for pulmonary vasoreactivity test

The definition of a 'positive' response is debatable. However, the European Society of Cardiology and the American College of Cardiology guidelines have proposed that an acute response to vasodilator challenge in IPAH should be a reduction of the mPAP by at least 10 mmHg to an absolute level of less than 40 mmHg with a concomitant normalization of cardiac output. The support for this definition is based on the clinical outcome of a retrospective analysis [18] of 557 patients who had received high-dose CCB treatment. The reliance on the mere change of mPAP without determination of PVR is arguable whether it will define IPAH patients with long-term benefit of CCB treatment [19••]. Modified criteria have been used in a recent study by Rosenzweig *et al.* [20••] by adding more specific criteria to define responder in children with IPAH whose mPAP is 40 mmHg or less by using the mPAP and PVR index, which had to decrease by at least 20%.

The major indication for pulmonary vasoreactivity testing in children with severe PAH related to the CHD is the part that evaluates the operability of the cardiac lesion. The general concept covers that the determination of the indexed PVR of 6–8 WU m^2 or lower is indicative of reversibility of the pulmonary vascular disease and thus eligible to the biventricular repair [21].

It is important to emphasize that the evaluation of vasoreactivity response in PAH related to the CHD patient should focus on the alternation of PVR and the blood flow to both systemic and pulmonary circulations, as these patients could respond to pulmonary vasodilator agents with decreasing of the PVR and increasing of pulmonary blood flow without significant PAP change. So far, there have been no standard criteria to define positive pulmonary vasodilator responder to indicate the

Figure 1 Cellular pathways in the pathogenesis of pulmonary arterial hypertension



A rise in [Ca^{2+}]cyt in PASMCs [due to decreased Kv channel activity ① and membrane depolarization, which opens VDCCs; upregulated TRPC channels that participate in forming receptor and store-operated Ca^{2+} channels ②; and upregulated membrane receptors (e.g., serotonin, endothelin or leukotriene receptors) ③; and their downstream signaling cascades] causes pulmonary vasoconstriction, stimulates PASMC proliferation and inhibits the BMP-signaling pathway that leads to antiproliferative and proapoptotic effects on PASMCs. Dysfunction of BMP signaling due to BMP-RII mutation and BMP-RII/BMP-RI downregulation ④ and inhibition of Kv channel function and expression ① attenuate PASMC apoptosis and promote PASMC proliferation. Increased Ang-1 synthesis and release ⑤ from PASMCs enhance 5-HT production and downregulate BMP-RIA in PAECs and further enhance PASMC contraction and proliferation, whereas inhibited nitric oxide and prostacyclin synthesis ⑥ in PAECs would attenuate the endothelium-derived relaxing effect on pulmonary arteries and promote sustained vasoconstriction and PASMC proliferation. Increased activity and expression of the 5-HTT ⑦ would serve as an additional pathway to stimulate PASMC growth via the MAPK pathway. In addition, a variety of splicing factors, transcription factors, protein kinases, extracellular metalloproteinases, and circulating growth factors would serve as the 'hits' to mediate the phenotypical transition of normal cells to contractive or hypertrophied cells and to maintain the progression of PAH. 5-HT, 5-hydroxytryptamine; 5-HTT, 5-HT transporter; 5-HTR, 5-hydroxytryptophan; Ang-1, angiopoietin; AVD, apoptotic volume decrease; BMP, bone morphogenetic protein; BMP-RI, BMP type 1 receptor; BMP-RII, BMP type II receptor; BMPR-IA, BMP receptor 1A; Ca^{2+}, calcium ion; Co-Smad, common smad; cyt, cytosine; DAG, diacylglycerol; E_m, membrane potential; ET-1, endothelin-1; ET-R, endothelin receptor; GPCR, G protein-coupled receptor; IP_3, inositol 1,4,5-trisphosphate; K, potassium; Kv, voltage-gated potassium channel; MAPK, mitogen-activated protein kinase; NO/PGI_2, nitric oxide/prostacyclin; PAEC, pulmonary arterial endothelial cell; PAH, pulmonary arterial hypertension; PASMC, pulmonary artery smooth muscle cell; PDGF, platelet-derived growth factor; PIP_2, phosphatidylinositol biphosphate; PLC, phospholipase C; PLCβ, PLC-beta; PLCγ, PLC gamma; PKC, protein kinase C; ROC, receptor-operated calcium channel; R-Smad, receptor-activated smad signaling pathway; RTK, receptor tyrosine kinase; SOC, store-operated channel; SR, sarcoplasmic reticulum; TIE2, tyrosine-protein kinase receptor; TRPC, transient receptor potential channel; and VDCC, voltage-dependent calcium channel. Data from McLaughlin *et al.* [14•].

risk of corrective surgery. In conventional consensus, the decision on operability of children with severe PAH depends on the actual value of indexed PVR of less than 6 WU m^2 or the pulmonary-to-systemic vascular resistance ratio (Rp/Rs) of less than 0.3 after the acute vasodilator test [22,23•]. These criteria are not universally standardized due to the advance in surgical technique and perioperative care. Some medical institutes have even surpassed the conventional criteria to offer corrective surgery to patients with more advanced pulmonary vasculopathy. It would, therefore, be impractical to define the universal criteria in order to ensure the operability in all patients with PAH related to CHD.

The positive response criteria in children with PAH related to CHD may also differ depending on the pulmonary vasodilator agent used for the test. The Inhaled Nitric Oxide as a Preoperative (INOP) Test Study group, a multicenter study collecting data on preoperative hemodynamics including the vasoreactivity testing using

oxygen, inhaled nitric oxide (iNO) and combination of these two agents in CHD patients with PAH chose the Rp/Rs of less than 0.33 and a 20% decrease in Rp/Rs from baseline as the two criteria for operability [24]. In our recent report on the pulmonary vasoreactivity testing using iloprost, we used the criteria of the concomitant PVR of less than 6 WU m^2 and the Rp/Rs of less than 0.3 to refer the patient for surgical correction [23•]. Nine of the 11 children who underwent corrective operations had normalized PAP in postoperative follow-up, whereas the other two remained having elevated PAP and required pulmonary vasodilator treatment.

One needs to be cautious and aware that evaluation of a given potential vasodilator for the reactivity testing may define the responder to each agent differently. As iNO was initially introduced to test the pulmonary vascular bed in children with PAH related to CHD, the simultaneous fall of PVR and Rp/Rs of more than 10% is used to define the positive responders [25].

Agents used to determine acute pulmonary vasoreactivity

The ideal vasodilator agent for pulmonary vasoreactivity testing should be very selective for pulmonary vascular beds and has rapid onset and offset of effect. Agents commonly used in acute vasoreactivity test are oxygen, iNO, inhaled iloprost, intravenous prostacyclin and intravenous adenosine. The details of these agents are summarized in Table 1 [19••].

In patients with CHD, pure oxygen has been originally used to test pulmonary vasoreactivity. It has the advantage of being available in all institutes, being easily administered and having almost unknown side effect. Despite oxygen having been widely used to assess the pulmonary vasoreactivity, the precise mechanism involved in its pulmonary vasodilator effect remains unclear; a number of pathways have been proposed, including the oxygen sensor in PASMCs-regulated pulmonary vascular tone through the K^+ channel via a cyclic nucleotide-dependent kinase [26]. When pure oxygen is used to test pulmonary vasoreactivity in children with CHD, the dissolved oxygen must be included in the calculation in order to avoid false-positive result.

iNO has become widely used as an agent for pulmonary vasodilator testing. Although there is no evidence-based guideline for selection of vasodilators, the panel of experts considered iNO as the preferred vasodilator to predict the long-term responder to CCB treatment in IPAH patients [14•]. Haworth and Hislop [2•] reported only 7.4% of IPAH children who underwent cardiac catheterization responded positively to iNO, whereas the INOP study, retrospective data from 10 institutions, evaluated effect of pure oxygen, and combination of oxygen and iNO (mean 60 ppm) as agent for preoperative vasodilator test in 124 children with PAH related to CHD suggested that combined use of oxygen and iNO increased the sensitivity in defining the candidate for corrective surgery rather than oxygen alone [24].

Inhaled iloprost has previously been evaluated as an effective pulmonary vasodilator in children [27]. Our group recently reported the use of aerosolized iloprost (0.5 μg/kg administered over 10 min) as a vasodilating agent to test the pulmonary vasoreactivity in children with PAH related to CHD [23•]. In 18 PAH related to CHD children, 13 had a positive response to iloprost in terms of the simultaneous decrease in both PVR and Rp/Rs of more than 10%, but only nine of the 13 iloprost responders had PVR of less than 6 WU m^2 and Rp/Rs of less than 0.3 as the criteria for corrective surgical operability. In contrast, three out of five children who were iloprost nonresponder had a positive response to 100% oxygen and considered to be operable and underwent surgical correction with normalized PAP in mid-term follow-up.

Correlation between genetic basis of pulmonary arterial hypertension and vasoreactivity test

Rosenzweig *et al.* [20••] investigated the role of BMPR2 mutations on acute vasoreactivity test and disease severity in IPAH/FPAH children and adults. In this study, from

Table 1 Agents used for determination of acute pulmonary vasoreactivity

Agent	Administration	Dosage	Advantages	Drawbacks
Prostacyclin	Intravenous	2 ng/kg/min (stepwise increase every 10–15 min); maximum dose 10 ng/kg/min	Affects PAP and *CO*, can be used as a chronic therapy	Systemic hypotension, gas-exchange disturbances
Adenosine	Intravenous	50 μg/kg/min increased by 50 μg/kg/min every 2 min; maximum dose of 500 μg/kg/min	Affects PAP and *CO*, rapid onset and rapid washout	Systemic hypotension, bradycardia
Nitric oxide	Inhaled	5–20 ppm for 10 min	Affects PAP alone, rapid onset and washout	Rebound pulmonary hypertension in few cases
Iloprost	Inhaled	2.5–5.0 μg per inhaled dose	Affects PAP selectively with minimal effects on *CO*, can be used as chronic therapy	Potential dosing variabilities depending on investigator experience, inhalation device and breathing pattern of the patient

CO, cardiac output; PAP, pulmonary artery pressure. Data from Ghofrani *et al.* [19••].

the total 147 patients, 42 (29%) were acute responders to iNO, whereas 23 (16%) were BMPR2 mutation positive. Those BMPR2 mutants were less likely to have positive acute vasodilator testing response than BMPR2-negative patients (4 vs. 33%, $P < 0.03$). Subgroup analysis for 78 IPAH/FPAH children demonstrated that the BMPR2 mutation-positive children also appeared less likely to respond to acute vasodilator testing than mutation-negative children (13 vs. 44%).

Natural history and outcome of responders

In general, young children with PAH appear to have a more reactive pulmonary vascular bed relative to both active pulmonary vasodilatation and pulmonary vasoconstriction, with severe acute pulmonary hypertensive crisis more than older children or adults [28]. These findings are correlated with the pathological evidence of medial hypertrophy, which is a prominent feature in lung specimen in patients younger than 15 years of age and the only usual change seen in infants [29].

In children with IPAH, the probability of having a positive response to the pulmonary vasoreactivity test appears to be age dependent, with the youngest having the greatest likelihood of pulmonary vasodilation; the percentage of responders in children is 30–40% compared with 10–15% in adults [30]. Haworth and Hislop [2•] have recently shown the 80% predicted survival of 5 years in IPAH children treated with CCB, whereas the retrospective analysis of vasoreactivity testing in adults with IPAH demonstrated that only 54% of patients showed acute pulmonary vasoreactivity response and experienced long-term improvement with CCB [18].

In contrast, our study could not demonstrate that age is a predictor for the positive response to pulmonary vasodilator testing in children with longstanding PAH related to CHD [23•]. Budts *et al*. [31] reported the residual pulmonary vasoreactivity to iNO in adult patients with Eisenmenger's syndrome. The follow-up study by Post *et al*. [32] demonstrated a better mid-term survival in these Eisenmenger's patients who had responsiveness to the iNO; survival rate at 76 months of follow-up was 100% in responders but only 63.6% in nonresponders.

Conclusion

Pulmonary vasoreactivity testing remains an important assessment of the pulmonary vascular bed in children with PAH, guiding towards the best treatment option to be adopted. Various pulmonary vasodilator agents are now currently available with some limited supporting documents in pediatric experience. However, it is important to emphasize that precise definition of positive pulmonary vasoreactivity response is still controversial. It needs to be cautious in interpretation and comparing the result of pulmonary vasoreactivity reports. Further controlled and well designed studies with prognostic follow-up are necessary to assess the actual impact criteria for responder in long-term outcome of children with PAH.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 683).

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