ORIGINAL ARTICLE

Hemodynamic assessment and acute pulmonary vasoreactivity testing in the evaluation of children with pulmonary vascular disease. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK

Christian Apitz,[1] Georg Hansmann,[2] Dietmar Schranz[3]

For numbered affiliations see end of article.

Correspondence to
Prof. Dr. Christian Apitz, Division of Paediatric Cardiology, University Children's Hospital, Ulm, Germany, Eythstr. 24, 89075 Ulm, Germany: Christian.apitz@uniklinik-ulm.de

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ABSTRACT

Invasive assessment of haemodynamics (ventricular, pulmonary) and testing of acute vasoreactivity in the catheterisation laboratory remain the gold standard for the diagnosis of pulmonary hypertension (PH) and pulmonary hypertensive vascular disease. However, these measurements and the interpretation thereof are challenging due to the heterogeneous aetiology of PH in childhood and potentially confounding factors in the catheterisation laboratory. Patients with pulmonary arterial hypertension (PAH) associated with congenital heart disease who have a cardiovascular shunt need to undergo a completely different catheterisation approach than those with idiopathic PAH lacking an anatomical cardiovascular defect. Diagnostic cardiac catheterisation of children with suspected PH usually includes right and left heart catheterisation, particularly for the initial assessment (ie, at the time of diagnosis), and should be performed in experienced centres only. Here, we present graded consensus recommendations for the invasive evaluation of children with PH including those with pulmonary hypertensive vascular disease and/or ventricular dysfunction. Based on the limited published studies and our own experience we suggest a structured catheterisation protocol and two separate definitions of positive acute vasoreactivity testing (AVT): (1) AVT to assess prognosis and indication for specific PH therapy, and (2) AVT to assess operability of PAH associated with congenital heart disease. The protocol and the latter definitions may help in the systematic assessment of these patients and the interpretation of the obtained data. Beyond an accurate diagnosis in the individual patient, such a structured approach may allow systematic decision making for the initiation of a specific treatment and may assist in estimating disease progression and individual prognosis.

INTRODUCTION

Pulmonary Hypertension (PH) is a condition found in several diseases that is frequently associated with high morbidity and mortality.[1] Catheter assessment of cardiovascular haemodynamics and acute vasoreactivity testing (AVT) in the catheterisation laboratory remain the gold standard for the diagnosis and prognostication of PH.[2–4] Invasive assessment of PH follows a non-invasive diagnostic workup and has to be performed in the context of the patient's age, medical history and functional status.[5] A systematic catheterisation protocol is required and has been established in a very standardised manner for the adult population, however, for paediatric PH it usually varies among expert referral centres.[6] Differences include particularly the vasodilative agents used for AVT (nitric oxide (NO)±oxygen (O_2)) versus inhaled iloprost versus other orally or intravenously administered substances (eg, sildenafil, treprostinil),[7–12] the definitions of a positive AVT response, and the mode of anaesthesia (general anaesthesia with mechanical ventilation vs sedation with local anaesthesia). These practice variations make the comparison of testing results difficult between individual centres and might also result in misinterpretation of the results and consecutively misleading decisions on the best therapeutic strategy.[13] However, although basic standardisation of catheterisation protocols is appropriate, the broad spectrum and complexity of childhood pulmonary vascular disease ('syndrome of pulmonary hypertensive vascular disease' (PHVD)) may often require an individualised approach.

METHODS

The recommendations given in table 1 relate to the grading system currently suggested by the European Society of Cardiology and the American Heart Association, and were based on paediatric data only (class, level of evidence). The grading and voting process within the writing group is outlined in the *executive summary*[42] of this online supplement. Computerised searches of the PubMed/MEDLINE bibliographical database from 1990 to January 2015 were conducted. The developer searched using the terms 'paediatric pulmonary hypertension', 'catheterization in pulmonary hypertension', 'vasoreactivity and pulmonary hypertension', 'anesthesia and pulmonary hypertension', 'acute response and paediatric pulmonary hypertension', 'vasoreactivity and children', 'catheterisation and paediatric pulmonary hypertension.'

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Table 1 Recommendations on haemodynamic assessment and acute pulmonary vasoreactivity testing in the evaluation of children with pulmonary vascular disease

Recommendations	COR	LOE
Cardiac catheterisation is indicated in all paediatric patients with pulmonary hypertension (PH) to confirm diagnosis, to evaluate the severity and when PH-specific drug therapy is considered.	I	C
Initial cardiac catheterisation should include right as well as left heart catheterisation to establish the diagnosis (not only RHC), if there is no contraindication.	I	C
Cardiac catheterisation may be omitted in acutely presenting, critically ill patients requiring immediate initiation of therapy.	I	B
Cardiac catheterisation for the diagnosis of PAH should include acute vasoreactivity testing (AVT; see main text), unless there is a reasonable contraindication, such as PH associated with left heart disease (PH Group II).	I	C
AVT to assess prognosis and indication for specific PH therapy: The haemodynamic change that defines a positive response to AVT in PH without shunt (Qp:Qs=1:1) (see main text) for children should be considered as a >20% fall in mean pulmonary arterial pressure (mPAP) and PVRi/SVRi ratio without a decrease in cardiac output.	IIa	C
Haemodynamic indicators of PH severity are PVRi/SVRi ratio and PVRi, rather than per cent fall in mPAP during AVT. Severe PH with high PVRi/SVRi ratio and high PVRi requires advanced and/or combination therapy.	IIa	C
AVT to assess operability of APAH-CHD: The haemodynamic change that defines a positive response to AVT in PH with shunt (Qp:Qs >1.5:1) (see main text) for children should be considered as a >20% fall in PVRi and PVRi/SVRi with respective final values <6 iWU and <0.3	IIa	C
Cardiac catheterisation and AVT should be performed in experienced paediatric heart centres, able to manage potential complications such as PH crisis, potentially requiring extracorporeal membrane oxygenation (depending on disease severity)	I	C
The patient's level of consciousness during cardiac catheterisation should be consistent in subsequent invasive assessments.	I	C
The preferred mode to perform is cardiac catheterisation in a patient with PH/paediatric pulmonary hypertensive vascular disease (PPHVD) who is spontaneously breathing, is either awake or moderately sedated.	I	C
Vasoreactivity testing should be performed using nitric oxide as vasodilator.	I	C
Vasoreactivity testing with the initial combination of nitric oxide and oxygen is reasonable and shortens the AVT study.	IIa	C
The use of calcium channel blocker, intravenous epoprostenol or intravenous adenosine in AVT is not recommended in children, and may cause harm	III harm	C
Repeat cardiac catheterisation should be considered in case of clinical deterioration, for assessment of treatment effect, detection of early disease progression, listing for lung transplant, in children with PH/PPHVD/PAH.	IIa	C
Intervals for repeat catheterisations should be based on clinical judgment but include worsening clinical course, significant change in pharmacotherapy (eg, drug class), or failure to improve during treatment.	I	C
It may be reasonable to have a stable patient with PH/PPHVD on combination therapy (>one medication) undergoing cardiac catheterisation every 12–24 months.	IIb	C

The recommendations relate to the grading system currently suggested by the European Society of Cardiology (ESC) and the American Heart Association (AHA), and were based on paediatric data only (class, level of evidence). The grading and voting process within the writing group is outlined in the *executive summary*[42] of this online supplement.
COR, class of recommendation; LOE, level of evidence; RHC, right heart catheterization; PVRi, indexed pulmonary vascular resistance; SVRi, indexed systemic vascular resistance.

CARDIAC CATHETERISATION IN PAEDIATRIC PAH

Patients with pulmonary arterial hypertension (PAH) associated with congenital heart disease (APAH-CHD) who have an intracardiac shunt need to undergo a completely different catheterisation approach than those with idiopathic PAH (IPAH) lacking an anatomical heart defect. The diagnostic cardiac catheterisation of children with suspected PH usually includes right as well as left heart catheterisation, particularly for the initial assessment (ie, at the time of diagnosis), and should be performed in experienced centres only. Importantly, pulmonary vein stenosis, frequently associated with congenital diaphragmatic hernia, CHD or bronchopulmonary dysplasia, needs to be excluded as a potential cause of PH in these populations.[14 15]

In privileged communities usually all patients with suspected PH (based on clinical symptoms, and/or echocardiographic/MRI data) are referred for invasive haemodynamic assessment in the catheterisation laboratory. Cardiopulmonary haemodynamics need to be analysed in the context of systemic haemodynamics and ventricular systolic and end-diastolic pressures. Importantly, pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR) should be assessed, and the potential cause of the 'condition' PH should be analysed. In the catheterisation laboratory, precapillary PH should be distinguished from postcapillary PH, the severity of the disease should be evaluated, and pulmonary arterial vasoreactivity needs to be assessed for the consideration of the most adequate PH-specific drug therapy. In patients with APAH-CHD with an intracardiac pretricuspid (eg, atrial septal defect) or post-tricuspid shunt (eg, ventricular septal defect), or systemic-to-pulmonary arterial (PA) shunt (patent ductus arteriosus), assessment of operability and data for the estimation of prognosis for the individual patient should be collected.[43 44]

CATHETERISATION PROTOCOL

For invasive assessment of PH, the femoral artery and vein are preferentially accessed. In very sick patients with suprasystemic PH and imminent RV failure, in which an atrial septostomy is indicated, atrial septostomy should be performed before the full cardiopulmonary haemodynamic assessment is commenced due to safety reasons.

Cardiopulmonary haemodynamics are obtained under resting conditions with normal gas exchange (systemic arterial carbon dioxide partial pressure ($paCO_2$) 35–45 mmHg; pH 7.35–7.45). Usually systolic, mean and diastolic systemic arterial, right atrial, RV systolic and end-diastolic pressures, as well as systolic, mean and diastolic PAPs, including bilateral pulmonary arterial wedge pressure (PAWP) are measured. In specific conditions, additional assessment of left atrial pressure and LV end-diastolic pressure is necessary. Simultaneous PAWP and end-diastolic pressure recording can confirm the accuracy of PAWP measurements and the calculated transpulmonary pressure gradients (TPGs). Isolated right heart catheterisation should be avoided—particularly at the initial comprehensive invasive assessment (ie, at diagnosis), but might be sufficient for invasive examinations during the follow-up. The usual catheter positions for the assessment of cardiopulmonary haemodynamics and AVT in a patient with

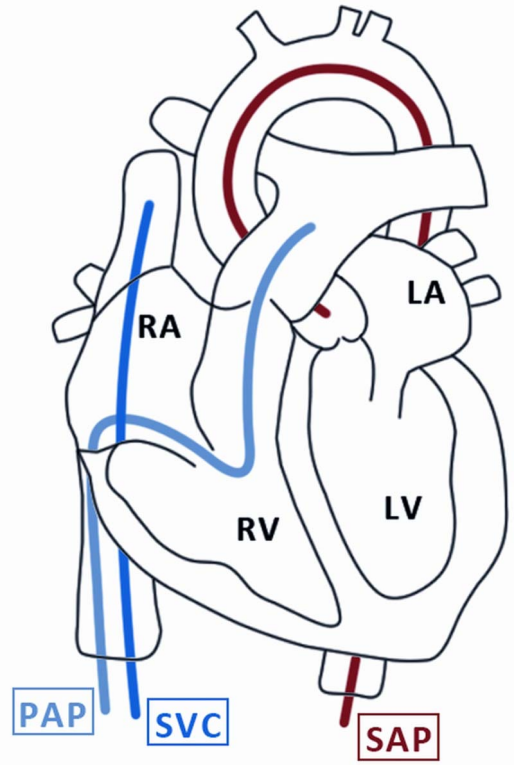

Figure 1 Catheter course and positions for assessment of cardiopulmonary haemodynamics and acute vasoreactivity testing in a patient with suspected or confirmed pulmonary hypertension. PAP, pulmonary arterial pressure; SAP, systemic arterial pressure; SVC, superior vena cava

suspected or confirmed PH is shown in figure 1. To obtain information about oxygen delivery and consumption as well as oxygen extraction ratio, oxygen saturations are measured by co-oximetry after sampling in the superior and inferior caval veins ($SsvcO_2$/$SivcO_2$), pulmonary artery (SvO_2) and if possible in the pulmonary vein ($SpvO_2$). Adequate assessment of the systemic arterial oxygen saturation (SaO_2) is crucial and needs be measured at the upper and lower extremities in certain patients with ductal SO_2 split, such as Eisenmenger syndrome with right-to-left shunting patent ductus arteriosus. Systemic and pulmonary blood flows can be estimated from the Fick equation[16] and systemic resistance and PVR can be calculated from standard equations (mean PAP—mean left atrial pressure divided by pulmonary flow). Blood flow and vascular resistances are usually indexed to body surface area. Oxygen consumption (VO_2) under resting conditions ranges between 180 mL/min×m^2 and 130 mL/min×m^2 in infants, children and young adults, respectively.[16] Estimates of VO_2 from historic data tables may be inadequate, for example, VO_2 may be severely decreased in critically ill patients with severe PAH due to low cardiac output. The most precise calculation of blood flow using the Fick equation includes direct measurement of VO_2. This can be done by respiratory mass spectroscopy or by the breath-by-breath method of measuring VO_2 which however requires intubation during cardiac catheterisation.[17] In a non-cardiac shunt patient thermodilution is also an accurate method of assessing cardiac index and eliminates all the hassle of estimating/measuring oxygen consumption.

Moreover, while interpreting haemodynamic data one must recognise the broad paediatric spectrum of PH, and the differences between systolic PAP and diastolic PAP (dPAP). In contrast to the systolic and mean arterial pressures, the dPAP is a variable that is rather independent of RV stroke volume and cardiac output. If significant pulmonary valve regurgitation is absent, dPAP reflects a direct view on the vascular resistance.[18] Therefore, systolic, diastolic and mean PAPs always have to be interpreted in the context of the simultaneously recorded systemic arterial pressures (SAPs), and should be presented as ratio of PAP/SAP or percentage of SAP. In addition, the TPG, using the mean PAP (mTPG=mPAP—mLAP (or alternatively PAWP)) as well as dPAP (dTPG or synonymously diastolic pressure difference (DPD)=dPAP—mLAP (or alternatively PAWP)) should be calculated, respectively. A DPD of less than 3 mm Hg is usually considered normal.

Based on the limited published clinical studies and our own experience, we suggest a structured catheterisation protocol and two separate definitions of positive AVT: (1) AVT to assess prognosis and indication for specific PH therapy, and (2) AVT to assess operability of APAH-CHD. The protocol and the latter definitions may help in the systematic assessment of these patients and in the interpretation of the obtained data.

We suggest the following *protocol* for testing of the acute vasodilator response in patients with assumed or already diagnosed precapillary PH (PH with or without elevated PVR), or patients with an additional precapillary component in the setting of postcapillary PH (ie, PHVD and left heart disease (LHD) with elevated left atrial pressure (LAP) and pulmonary venous pressures):

If at all possible, the child with PH undergoing cardiac catheterisation should be only moderately sedated and spontaneously breathing, allowing normal gas exchange, and adequate systemic vascular resistance (SVR) and blood pressure (SAP). Haemodynamic and oxygen transport measurements are made at stable baseline conditions (at 'usual' FiO_2) and then the vasoreactivity is tested as the effects of inhaled nitric oxide (NO) at 20–40 ppm, for 10 min on mean and diastolic PAP, SAP and PVR/SVR ratio. Thereafter, the effects of the additional application of oxygen with fractional inspired oxygen (FiO_2) ~0.8 (if possible) is assessed in patients with IPAH, but not in APAH-CHD with an intracardiac shunt (see below). During close observation for possible rebound-phenomena, NO+O_2 should be discontinued and new baseline haemodynamic parameters should be obtained after 10 min. Subsequently, the effects of aerosolised iloprost (0.3–0.5 μg/kg) administered by a specific applicator should be assessed; thereafter, if not contraindicated, NO+O_2 should be inhaled again to define the haemodynamic effects of combined cyclic AMP, cyclic guanosine monophosphate and oxygen-dependent pulmonary vasodilator effects. As an additional vasoreactivity test, the pulmonary flow reserve as a marker of the pulmonary endothelial function can be measured with a flow wire catheter by local pulmonary arterial application of acetylcholine (10^{-6} to 10^{-5} M), that is, a substance that induces the NO release from the endothelium and—potentially—subsequent relaxation of the muscularised pulmonary arterioles. This optional measurement may add additional information regarding the aetiology and stage of PHVD, best treatment strategy and prognosis in children with PAH.[19 20]

ACUTE VASODILATOR RESPONSE AND OTHER CRITERIA OF INVASIVE ASSESSMENT OF PH

Data on acute vasodilator response (AVR) are derived predominantly from studies in patients with IPAH and hereditary PAH (HPAH). Although AVR (=positive AVT) has important clinical consequences, its definition still remains controversial. Three

criteria are generally used: the criteria according to Barst, Rich and Sitbon.[21–23]

1. Barst criteria, 1986: decrease in mPAP of ≥20%, unchanged or increased cardiac index, and decreased or unchanged PVR to SVR ratio (PVR/SVR);
2. Rich criteria, 1992: decrease in mPAP and PVR of ≥20%;
3. Sitbon criteria, 2005: decrease in mPAP of ≥10 mm Hg reaching an mPAP value of ≤40 mm Hg, and an increased or unchanged cardiac output.

The Rich criteria were the first commonly used criteria for adults. In 2005, Sitbon *et al* suggested revised criteria for adult IPAH, based on a retrospective evaluation of an adult patient cohort with IPAH. These Sitbon criteria are currently recommended in international guidelines for adult patients with PAH, but not for children. In children, the Barst criteria are frequently used. In IPAH, the proportion of patients with an AVR (ie, a positive AVT) has been reported to be much higher in children (up to 50%) than in adults (10–15%).[22–24] However, these paediatric studies used different response criteria, which make it difficult to directly compare the relationship between some degree of AVR and outcome among these studies.[13]

Considering the specific characteristics of paediatric PH, we suggest a modification of the Barst criteria, and *two definitions* of AVR (=positive AVT) depending on the clinical scenario: (A) AVT to assess prognosis and indication for specific PH therapy, and (B) AVT to assess operability of APAH-CHD.[43 44]

4. Modified 'Barst criteria' of the European Paediatric pulmonary vascular disease (PVD) Network, 2016 (see also table 1):

In patients with IPAH/HPAH, the haemodynamic change that defines a positive response to AVT in PH without shunt (ratio of pulmonary to systemic flow (Qp:Qs)=1:1) for children should be considered as a >20% fall in mean PAP *and* indexed pulmonary vascular resistance (PVRi)/indexed systemic vascular resistance (SVRi) ratio without a decrease in cardiac output ('AVR in IPAH/HPAH'). In the presence of a positive AVR, a fall of the ratio of PVRi/SVRi (or as the authors suggest alternatively, the ratio of the diastolic PAP/SAP) below 0.4 due to the AVT might be an indication for calcium-channel blocker therapy.[25] A positive AVR can fade over time, and this may have consequences on the PH-specific pharmacotherapy. Therefore, especially patients on oral calcium channel blocker therapy need repeated AVT, for example, annual cardiac catheterisations, unless a highly significant clinical and haemodynamic improvement could be achieved.

In patients with APAH-CHD and shunt, AVT is used to assess operability. Therefore, the above mentioned criteria need some modification due to different underlying pathophysiology. The haemodynamic change that defines a positive response to AVT in PAH associated with a shunt defect (Qp:Qs >1.5:1; APAH-CHD-shunt) for children should be considered as a >20% fall in PVRi and PVRi/SVRi with respective final values <6 indexed Wood units (iWU) and <0.3.[43 44] Nevertheless, operative safety in APAH-CHD with a shunt cannot be guaranteed (grey zone is PVR 6–8 iWU, and PVR/SVR ratio 0.3–0.5) and an element of clinical subjectivity is inevitable. Further investigation is warranted in selected populations, such as the growing number of children with CHD complicated by chronic lung disease of prematurity[45] and in the developing world where patients are more likely to present late with advanced pulmonary vascular disease and often shunt reversal (right-to-left, ie, Eisenmenger syndrome) (tables 2 and 3).

We suggest that the evaluation of AVR in APAH-CHD should focus on the alteration of the diastolic pulmonary pressures, diastolic TPG (DPD, or synonymously dTPG), and the diastolic pulmonary to SAP ratio, in addition to the PVR and the ratio of PVR to SVR.

It should be noted, that blood flow to the pulmonary and systemic circulation, and any change in shunting, may affect PAP response to vasodilators. It also has to be considered that no fall in PAP does not necessarily mean no fall in PVR. Patients could respond to pulmonary vasodilator agents with decrease of PVR and increase of Qp without significant change of the mean pulmonary pressure. It is recommended by our group, that especially in the assessment of operability in patients with APAH-CHD, the use of pure oxygen as an agent to test AVR should be avoided, if other pulmonary vasodilators are available. Use of pure oxygen for AVT in APAH-CHD may result in a potential source of error due to the presence of dissolved oxygen. With the increased concentration of inspired oxygen the partial pressure of oxygen in pulmonary alveoli and in pulmonary capillary and pulmonary venous blood will rise to supernormal levels. This will result in quite significant amounts of oxygen being transported dissolved in plasma, in addition to

Table 2 Invasive measures and clinical implications

Measure	Abnormality	Clinical implications
mPAP (mm Hg)	mPAP ≥25mmHg	Definition of group 1–5 (2013 World Symposium on Pulmonary Hypertension (WSPH) classification)
mPAP/mSAP	mPAP/mSAP >0.3	Adjunct criterion for definition of group 1–5
	mPAP/mSAP >0.75	Higher mortality
PCWP (mm Hg)	PCWP >15 mm Hg	Postcapillary PH, group 2
Mean RAP	Mean RAP >15 mm Hg	RV failure, higher mortality
	Mean RAP >20 mm Hg	Contraindication for balloon atrioseptostomy
PVRI, Wood units×m^2	PVRI >3 WU×m^2	Group 1–5
	PVRI >8 WU×m^2	Inoperability in APAH-CHD
	PVRI >15 WU×m^2	Higher mortality
Fick or thermodilution CI, L/min×m^2	CI <2.5 L/min×m^2	Low cardiac output, higher mortality
SVO_2, %	SVO_2 <55%	Low cardiac output, higher mortality

APAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; CI, cardiac index; mPAP, mean pulmonary arterial pressure; mSAP, mean systemic arterial pressure; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVRI, Pulmonary vascular resistance index; RAP, right atrial pressure.

Table 3 Haemodynamic definitions of PH (modified from Galie[24])

Definition	Invasive measures	PH-group
PH	mPAP ≥25mmHg	1–5
	CI normal or reduced	
Precapillary PH	mPAP ≥25mmHg	1,3,4,5
	PVRi >3 iWU	
	PCWP <15mmHg	
	CI normal or reduced	
Postcapillary PH	mPAP ≥25mmHg	2
	PCWP ≥15mmHg	
	CI normal or reduced	
Passive	DPD <7 mm Hg (adults)	
Reactive (formerly: 'out of proportion')	DPD ≥7mmHg (adults)	

CI, cardiac index; DPD, diastolic pressure difference; mPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVRi, pulmonary vascular resistance index.

that which is bound to haemoglobin. If the calculations do not take this into account the oxygen content difference between pulmonary venous blood and pulmonary arterial blood will be underestimated. The estimated pulmonary blood flow will then be overestimated and pulmonary resistance will appear to be lower than is really the case. If higher concentrations of oxygen (50% or greater) are to be used then the calculation of pulmonary blood flow (and Qp:Qs ratio) should involve measurement of pO_2 on at least the pulmonary vein sample (preferably also the pulmonary artery sample). This allows inclusion of dissolved oxygen in the calculation. However, if the measured saturation is less the 100%, dissolved pO_2 does not need to be included in the Fick calculation (i.e. if the blood is not hyperoxygenated). Then the blood gas in the PA for dissolved oxygen would not be necessary. Ideally, any blood gas taken in a shunt patient should be proximal to the shunt with the pulmonary vein being the best location. If it is absolutely necessary and there is no atrial defect, transseptal puncture is appropriate.

In patients with PH due to LHD (PH-LHD) (defined as mPAP ≥25 mm Hg and PAWP ≥15 mm Hg), the DPD (DPD=dTPG=dPAP—PAWP) should be considered to rule out any additional precapillary PAH-component,[18 26 27] instead of the mean TPG (mTPG=mPAP—PAWP). The mTPG is influenced by all determinants of mPAP, including flow, resistance and left heart-filling pressure. In contrast, diastolic PAP, when compared with systolic and mean PAPs, is less influenced by cardiac output, which might be explained by a lower sensitivity to vessel distensibility.[18 27] Therefore, dTPG (DPD) seems to provide the most reliable characteristics to determine pulmonary vascular disease and PVR. In healthy subjects, dTPG (DPD) values range between 1 mm Hg and 5 mm Hg, in adults a dTPG (DPD) of less than 3 mm Hg is normal. In patients evaluated for cardiac disease (except for shunts), the dTPG (DPD) usually remains less than 7 mm Hg.[18] A dTPG (DPD) of ≥7 mm Hg has been identified to predict worse outcome in adult patients with PH due to LHD,[26] however in a very recent study this association could not be confirmed.[28] At the fifth World Symposium on PH in Nice 2013, the expert panel released a definition on postcapillary PH with additional precapillary PAH (formerly known as 'out- of-proportion' PH) as a TPG ≥15mmHg and a DPD ≥7 mm Hg.[27] Whether these normal values are also appropriate for the paediatric population cannot reliably be stated as at this date, since corresponding specific paediatric data are needed. According to our own clinical experience, young children with PH-LHD may show reversibility of their precapillary component more likely than adults, even in dTPG (DPD) values markedly above 7 mm Hg (tables 2 and 3).

In patients with a functional single ventricle, there is growing evidence that mPAP of >15 mm Hg may be associated with early and late mortalities after the Fontan operation. In single ventricle physiology after Fontan completion (total cavopulmonary anastomosis, syn. total cavopulmonary connection, without a subpulmonary ventricle), The Pulmonary Vascular Research Institute Panama classification defines PHVD to present, when as dTPG is >6 mm Hg or PVR >3 iWU, even if the mPAP is <25 mm Hg.[29] In Fontan patients, a PVR of less than 2.5 iWU belongs to criteria of low risk, resistance values between 2.5 iWU and 4 iWU have an intermediate risk, PVR above 4 iWU usually is considered unsuitable for a Fontan circulation.[30] However, the relationship of preoperative pulmonary haemodynamics with early and late morbidities remains to be defined. Therefore, patients with Fontan circulation (characterised by non-pulsatile pulmonary blood flow) need to be carefully assessed, that is, differentiation between a precapillary (mTPG >6 mm Hg) and postcapillary (mTPG ≤6 mm Hg) PH, or determination that a combination of both components is evident. There is an uneasily determined degree of preoperative pulmonary vascular disease and/or PHVD (defined by Pulmonary Vascular Research Institute Panama 2011[29]) that puts an individual patient at increased risk for severe cyanosis or death after a total cavopulmonary anastomosis (Fontan completion). Of note, the Fontan circulation is characterised by a higher infradiaphragmatic oxygen extraction ratio, reflected by a lower oxygen saturation in the inferior caval vein compared with the superior caval vein. The difficulties in obtaining an accurate assessment of pulmonary vascular disease and PHVD in the complex single ventricle have been frequently discussed and need further evaluation.

VASODILATIVE AGENTS FOR TESTING THE PULMONARY ARTERIAL VASOREACTIVITY

The ideal vasodilatory agent for AVT should be (1) selective for the pulmonary circulation (with little effects on ventricular performance and SVR) and (2) short-acting (short biological half-life). Inhaled NO (iNO 20–80 ppm) and oxygen (FiO_2 1.0) act in seconds, and aerosolised prostanoids (iloprost (0.3–0.5 µg/kg inhal. for 15 min.), treprostinil (three to six breaths (18–36 µg)) within minutes of inhalation, thus fulfil the aforementioned criteria and are usually recommended for AVT in children. However, careful monitoring is recommended particularly during the weaning of iNO, since paradox or rebound PH has been reported in a few cases.[31] If inhaled NO is not available (ie, in many developing countries) and oxygen is regarded as unfavourable (ie, for the assessment of operability in patients with APAH-CHD and shunt), oral application of the phosphodiesterase-5 inhibitor sildenafil can be used alternatively to perform AVT.[11 12] In special conditions, epoprostenol (2–10 ng/kg/min; increments 2 ng/kg/min intravenous for 10 min; half-life 3 min) or iloprost (0.5–2 ng/kg/min) test infusion might be indicated, that is, for testing the individual patient's dosage threshold value (until the systemic pressure begins to drop).[32] Adenosine is nowadays not used in children (although still recommended in adults), because its side effects are not predictable and might be dangerous due to induction of bradycardia and potentially systemic hypotension; adenosine also may be associated with a paradox pulmonary vasoconstriction particularly if pulmonary endothelial function is severely impaired.[33 34]

GENERAL ANAESTHESIA VERSUS CONSCIOUS SEDATION IN CHILDREN WITH PH DURING CARDIAC CATHETERISATION AND AVT

General anaesthesia has a confounding impact on haemodynamic assessment due to its cardiodepressive effects and vasodilatory actions in the systemic and pulmonary circulation. Nevertheless, anaesthesia is frequently used in paediatric patients with PH. Intubation and mechanical ventilation in association with volatile or intravenous anaesthetic drugs may have such a significant influence on vascular resistance and ventricular performance that haemodynamic assessment of patients with IPAH or single ventricle physiology (Fontan) becomes unreliable.[35] Considering a 10% physiological change of PAP during spontaneous breathing, a >20% difference might be induced by mechanical ventilation and anaesthetic drugs before any specific AVT drug is administered. Therefore, different baseline values, and even lower potency and efficacy of PA-selective drugs might be observed using a cardiac catheterisation and AVT protocol with general anaesthesia. In addition, induction and—in particular—weaning from general anaesthesia has to be considered a

problematic and potentially life-threatening scenario.[36] Therefore, it may be useful to perform invasive AVR testing in children and adults, and even in infants with PH in light to moderate conscious sedation. We suggest the use of low dose intravenous propofol infusion (1–2 mg/kg/h), if not contraindicated, or repetitive single low doses of diazepam (0.1 mg/kg/dose intravenous) or midazolam (0.1 mg/kg/dose intravenous)—without mechanical ventilation and general anaesthesia. However, a resuscitation protocol, prepared syringes containing emergency medications (eg, epinephrine, atropine, sodium bicarbonate) on the sterile table and on the side of the catheterisation table, appropriate ventilatory equipment for bag-and-mask ventilation and endotracheal intubation must be available for all cardiac catheterisation procedures with or without invasive AVR testing, in children with PH.

SAFETY OF CARDIAC CATHETERISATION

Importantly, the risk of catheterisation procedure is increased in patients with PH (compared with non-PH patients), with the highest risk in patients with IPAH.[36–40] A report of the TOPP registry (Tracking Outcomes and Practice in Paediatric Pulmonary Hypertension) on the safety of invasive haemodynamic assessment in children with PH found that 7% (37/554) of patients at diagnosis had significant complications within 24 h after heart catheterisation, including new inotropic support (3%; 14/554), pulmonary hypertensive crisis (10/554; 2%) and cardiac arrest (0.9%; 5/554).[6] For the total number of heart catheterisations (n=908) performed at diagnosis (n=554) and follow-up (n=354), complications including pulmonary hypertensive crises, need for inotropic support, cardiac arrest, arrhythmias and pulmonary haemorrhage were reported in 5.9% of cases; and there were five cases of procedure-related deaths.[6] The complication rate for cardiac catheterisation with or without anaesthesia is apparently higher in children than in adults,[41] reminding us that we must weigh the risks and benefits of invasive procedures in this fragile patient population, and that the care of children with PH should be performed in experienced centres only.

Author affiliations
[1]Division of Pediatric Cardiology, University Children's Hospital, Ulm, Germany
[2]Department of Pediatric Cardiology and Critical Care, Hannover Medical School, Hannover, Germany
[3]Pediatric Heart Centre, Justus-Liebig-University, Giessen, Germany

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REFERENCES

1 Berger RM, Beghetti M, Humpl T, *et al*. Clinical features of paediatric pulmonary hypertension: a registry study. *Lancet* 2012;379:537–46.
2 Ivy DD, Abman SH, Barst RJ, *et al*. Paediatric pulmonary hypertension. *J Am Coll Cardiol* 2013;62:D117–26.
3 Galiè N, Corris PA, Frost A, *et al*. Updated treatment algorithm of pulmonary arterial hypertension. *J Am Coll Cardiol* 2013;62:D60–72.
4 Hill KD, Lim DS, Everett AD, *et al*. Assessment of pulmonary hypertension in the paediatric catheterization laboratory: current insights from the Magic registry. *Catheter Cardiovasc Interv* 2010;76:865–73.
5 Lopes AA, Barst RJ, Haworth SG, *et al*. Repair of congenital heart disease with associated pulmonary hypertension in children: what are the minimal investigative procedures? Consensus statement from the congenital heart disease and paediatric task force, pulmonary vascular research institute (PVRI). *Pulm Circ* 2014;4:330–41.
6 Beghetti M, Berger RM, Schulze-Neick I, *et al*., TOPP Registry Investigators. Diagnostic evaluation of paediatric pulmonary hypertension in current clinical practice. *Eur Respir J* 2013;42:689–700.
7 Atz AM, Adatia I, Lock JE, *et al*. Combined effects of nitric oxide and oxygen during acute pulmonary vasodilator testing. *J Am Coll Cardiol* 1999;33:813–19.
8 Limsuwan A, Khositthseth A, Wanichkul S, *et al*. Aerosolized iloprost for pulmonary vasoreactivity testing in children with long-standing pulmonary hypertension related to congenital heart disease. *Catheter Cardiovasc Interv* 2009;73:98–104.
9 Ivy DD, Doran AK, Smith KJ, *et al*. Short- and long-term effects of inhaled iloprost therapy in children with pulmonary arterial hypertension. *J Am Coll Cardiol* 2008;51:161–9.
10 Takatsuki S, Parker DK, Doran AK, *et al*. Acute pulmonary vasodilator testing with inhaled treprostinil in children with pulmonary arterialhypertension. *Pediatr Cardiol* 2013;34:1006–12.
11 Apitz C, Reyes JT, Holtby H, *et al*. Pharmacokinetic and hemodynamic responses to oral Sildenafil during invasive testing in children with pulmonary hypertension. *J Am Coll Cardiol* 2010;55:1456–62.
12 Ajami GH, Borzoee M, Radvar M, *et al*. Comparison of the effectiveness of oral sildenafil versus oxygen administration as a test for feasibility of operation for patients with secondary pulmonary arterial hypertension. *Pediatr Cardiol* 2008;29:552–5.
13 Douwes JM, van Loon RL, Hoendermis ES, *et al*. Acute pulmonary vasodilator response in paediatric and adult pulmonary arterial hypertension: occurrence and prognostic value when comparing three response criteria. *Eur Heart J* 2011;32:3137–46.
14 Cerro MJ, Sabaté Rotés A, Cartón A, *et al*. Pulmonary hypertension in bronchopulmonary dysplasia: clinical findings, cardiovascular anomalies and outcomes. *Pediatr Pulmonol* 2014;49:49–59.
15 Drossner DM, Kim DW, Maher KO, *et al*. Pulmonary vein stenosis: prematurity and associated conditions. *Paediatrics* 2008;122:e656–61.
16 Wilkinson JL. Haemodynamic calculations in the catheter laboratory. *Heart* 2001;85:113–20.
17 Guo L, Cui Y, Pharis S, *et al*. Measurement of oxygen consumption in children undergoing cardiac catheterization: comparison between mass spectrometry and the breath-by-breath method. *Pediatr Cardiol* 2014;35:798–802.
18 Naeije R, Vachiery JL, Yerly P, *et al*. Transpulmonary pressure gradient for the diagnosis of pulmonary vascular disease. *Eur Respir J* 2013;41:217–23.
19 Apitz C, Zimmermann R, Kreuder J, *et al*. Assessment of pulmonary endothelial function during invasive testing in children and adolescents with idiopathic pulmonary arterial hypertension. *J Am Coll Cardiol* 2012;60:157–64.
20 Apitz C, Latus H, Schranz D. Subpulmonary right ventricle in congenital heart disease. In: Voelkel NF, Schranz D, eds. *The right ventricle in health and disease*. New York, Springer, 2015:79–101.
21 Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992;327:76–81.
22 Barst RJ. Pharmacologically induced pulmonary vasodilatation in children and young adults with primary pulmonary hypertension. *Chest* 1986;89:497–503.
23 Sitbon O, Humbert M, Jais X, *et al*. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation* 2005;111:3105–11.
24 Galiè N, Hoeper MM, Humbert M, *et al*., ESC Committee for Practice Guidelines (CPG). Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009;30:2493–537.
25 Barst RJ, Agnoletti G, Fraisse A, *et al*., NO Diagnostic Study Group. Vasodilator testing with nitric oxide and/or oxygen in paediatric pulmonary hypertension. *Pediatr Cardiol* 2010;31:598–606.
26 Gerges C, Gerges M, Lang MB, *et al*. Diastolic pulmonary vascular pressure gradient: a predictor of prognosis in "out-of-proportion" pulmonary hypertension. *Chest* 2013;143:758–66.
27 Vachiéry JL, Adir Y, Barberà JA, *et al*. Pulmonary hypertension due to left heart diseases. *J Am Coll Cardiol* 2013;62:D100–8.

28 Tampakakis E, Leary PJ, Selby VN, *et al*. The diastolic pulmonary gradient does not predict survival in patients with pulmonary hypertension due to left heart disease. *JACC Heart Fail* 2015;3:9–16.
29 Cerro MJ, Abman S, Diaz G, *et al*. A consensus approach to the classification of paediatric pulmonary hypertensive vascular disease: Report from the PVRI Paediatric Taskforce, Panama 2011. *Pulm Circ* 2011;1:286–98.
30 Gewillig M. The Fontan circulation. *Heart* 2005;91:839–46.
31 Atz AM, Adatia I, Wessel DL. Rebound pulmonary hypertension after inhalation of nitric oxide. *Ann Thorac Surg* 1996;62:1759–64.
32 Maron BA, Bhatt DL, Nykiel M, *et al*. Protocol for vasoreactivity testing with epoprostenol in pulmonary hypertension. *Crit Pathw Cardiol* 2012;11:40–2.
33 Zhang DZ, Zhu XY, Meng J, *et al*. Acute hemodynamic responses to adenosine and iloprost in patients with congenital heart defects and severe pulmonary arterial hypertension. *Int J Cardiol* 2011;147:433–7.
34 Oliveira EC, Ribeiro AL, Amaral CF. Adenosine for vasoreactivity testing in pulmonary hypertension: a head-to-head comparison with inhaled nitric oxide. *Respir Med* 2010;104:606–11.
35 Shekerdemian LS, Bush A, Shore DF, *et al*. Cardiopulmonary interactions after Fontan operations. *Circulation* 1997;96:3934–42.
36 Taylor CJ, Derrick G, McEwan A, *et al*. Risk of cardiac catheterization under anaesthesia in children with pulmonary hypertension. *Br J Anaesth* 2007;98:657–61.
37 Taylor K, Holtby H. Emergency interventional lung assist for pulmonary hypertension. *Anesth Analg* 2009;109:382–5.
38 Zuckerman WA, Turner ME, Kerstein J, *et al*. Safety of cardiac catheterization at a center specializing in the care of patients with pulmonary arterial hypertension. *Pulm Circ* 2013;3:831–9.
39 Williams GD, Maan H, Ramamoorthy C, *et al*. Perioperative complications in children with pulmonary hypertension undergoing general anesthesia with ketamine. *Paediatr Anaesth* 2010;20:28–37.
40 Bobhate P, Guo L, Jain S, *et al*. Cardiac catheterization in children with pulmonary hypertensive vascular disease. *Pediatr Cardiol* 2015;36:873–9.
41 Hoeper MM, Lee SH, Voswinckel R, *et al*. Complications of right heart catheterization procedures in patients with pulmonary hypertension in experienced centers. *J Am Coll Cardiol* 2006;48:2546–52.
42 Hansmann G, Apitz C, Abdul-Khaliq H, *et al*. Expert Consensus Statement on the Diagnosis and Treatment of Paediatric Pulmonary Hypertension. Executive Summary. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart* 2016;102:ii86–100.
43 Hansmann G, Apitz C. Treatment of Children with Pulmonary Hypertension. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart* 2016;102:ii67–85.
44 Kozlik-Feldmann R, Hansmann G, Bonnet D, *et al*. Pulmonary Hypertension in Children with Congenital Heart Disease (PAH-CHD, PPHVD-CHD). Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart* 2016;102:ii42–8.
45 Hilgendorff A, Apitz C, Bonnet D, Hansmann G. Pulmonary hypertension associated with acute or chronic lung diseases in the preterm and term neonate and infant. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart* 2016;102:ii49–56.