Introduction

In congenital heart defects with left to right shunting, the increased pulmonary blood flow and pulmonary hypertension leads to structural and functional changes in the pulmonary vasculature. These changes, known as pulmonary plexogenic arteriopathy, include increased muscularization, altered vasoconstrictive and impaired vasodilatatory responses in the arterial tree, and extensive extracellular matrix modulation (including increased collagen deposition and gradual occlusion of the small pulmonary arteries by intimal proliferation and fibrosis). These alterations will result in decreased compliance by the pulmonary vessels and, thus, a stiffening of the arterial wall. In plexogenic pulmonary arteriopathy, characteristic vascular lesions emerge in the course of the disease process; these include concentric laminar intimal fibrosis, fibrinoid necrosis and plexiform lesions. The term plexogenic arteriopathy does not imply the presence of plexiform lesions, but the potential to form this characteristic lesion in the course of the disease. The combined vascular changes will lead to an increase in both the steady and pulsatile hydraulic loads of the subpulmonary ventricle. Depending on the progression of the process and the type of surgical procedure, these vascular changes may jeopardize surgical correction of the heart defect, or seriously affect the patient’s prognosis.

Key Words: Pulmonary hypertension, pulmonary vascular disease, haemodynamics, angiography, histology, congenital heart disease.

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Plexogenic arteriopathy is a specific type of pulmonary arteriopathy that occurs most frequently in congenital heart diseases with increased pulmonary blood flow. However, it may also occur in other conditions, for instance, unexplained pulmonary hypertension. Pulmonary plexogenic arteriopathy differs from other types of pulmonary arteriopathy, such as hypoxic arteriopathy or pulmonary congestive arteriopathy, not only by the characteristic vascular lesions in the advanced stage of the disease, but also by the progress of the disease. In plexogenic pulmonary arteriopathy, the early vascular changes are reversible after the underlying heart defect has been corrected. However, if untreated, plexogenic pulmonary arteriopathy advances to a certain ‘point of no return’ at which the disease process is not only irreversible, but progresses even when the underlying heart defect is corrected. In patients with congenital heart disease, the state of the pulmonary vasculature is, thus, an important determinant of management, clinical course and prognosis.

In congenital heart disease, pulmonary circulation problems are not restricted to those of pulmonary over-flow, but may also concern aspects of pulmonary under-development, such as in pulmonary hypoperfusion where there is insufficient growth of vessels, or in patients with pulmonary atresia, ventricular septal defect and aortopulmonary collateral arteries, where there is abnormal pulmonary development. However, in this review we will focus on the evaluation of the effects of increased blood flow, on the pulmonary vasculature in congenital heart defects, with or without concomitant pulmonary hypertension, and, thus, on the assessment of progression of pulmonary vascular disease. Various diagnostic techniques can be used to evaluate the progression of pulmonary vascular disease in the clinical setting. However, although all these techniques have indisputable value, they all have specific drawbacks and intrinsic limitations. This paper discusses these diagnostic techniques.
Non-invasive techniques to evaluate the pulmonary vasculature

Clinical examination, chest X-ray and electrocardiographic evaluation may suggest the presence of pulmonary hypertension; however, sensitivity is very low[12,13]. Echocardiography using tricuspid or pulmonary regurgitation velocity measurements[14–16] with pulsed Doppler is more reliable in determining the presence of pulmonary hypertension. However, although these techniques are invaluable in the diagnosis and management of patients with congenital heart disease, the presence of pulmonary hypertension in congenital heart disease provides limited information on the state of the pulmonary vascular bed and, in general, the progression of pulmonary vascular disease cannot be assessed with these diagnostic tools.

Estimation of left-to-right intracardiac shunting and in vivo evaluation of pulmonary blood flow patterns using velocity-encoded, phase-difference magnetic resonance imaging has been recently reported[17–21]. This technique may hold a promise for the future; however its value in the evaluation of pulmonary vascular disease remains to be investigated.

Haemodynamic evaluation of the pulmonary vasculature

The technique most frequently used to evaluate the pulmonary vascular bed in congenital heart disease is cardiac catheterization[22–24]. In this procedure, the pulmonary artery pressures and pulmonary wedge pressure or left atrium pressure are measured, shunt size and pulmonary blood flow are determined and, subsequently, pulmonary vascular resistance is calculated by dividing the pressure gradient across the lungs by the pulmonary blood flow. The pulmonary vascular resistance constitutes a key parameter in the pre-operative evaluation of the pulmonary vasculature[25]. It is regarded as a measure of the functional state of the vascular bed, and its reaction to vasodilators as a measure of the reversibility of the disease process. Although haemodynamic evaluation of the pulmonary vascular bed has proven to be extremely valuable in clinical practice, it has both conceptual and practical limitations[25].

Practical considerations

As with any other invasive technique, cardiac catheterization has certain risks, especially in patients with pulmonary vascular disease[26,27]. However, with the currently available techniques and material, including non-ionic contrast media, the risks of paediatric cardiac catheterization are relatively low[28,29]. The conditions under which the haemodynamic measurements are performed, such as the position of the patient and level of agitation, may influence the results of the measurements[30]. Conditions should be standardized throughout the procedure to ensure reliable and comparable haemodynamic data. To calculate the pulmonary vascular resistance, the pressure difference over the pulmonary bed and pulmonary blood flow measurements are required. A serious drawback of haemodynamic evaluation, however, is the difficulty in accurately determining blood flow in the clinical setting. Various methods exist to quantify cardiac output and intracardiac shunting. These are based on the Fick principle: a known amount of a specific indicator is added to a volume of fluid. If the concentration of the indicator in the blood before and after this addition is known, the volume of fluid can be calculated[27,31,32].

The Fick method uses the physiological uptake of oxygen as an indicator. Pulmonary blood flow can be calculated by dividing oxygen consumption by the difference in oxygen content between the pulmonary artery and the veins. The oxygen content of the blood is calculated using measured oxygen saturation, haemoglobin concentration, oxygen binding capacity and dissolved oxygen. Oxygen saturation, i.e. the oxygen attached to haemoglobin, must be measured instead of calculated in order to avoid the influence of multiple factors, such as temperature, pH, pCO2 and amount of fetal haemoglobin. In room air, dissolved oxygen, i.e. oxygen dissolved in the serum, is a small percentage of the amount attached to haemoglobin and can usually be ignored. However, when the patient is breathing oxygen this factor substantially increases and must be considered. The advantages of oximetry are that it is easy to perform, results are available immediately and it allows the site and magnitude of the shunt to be ascertained. A drawback of oximetry is the difficulty in defining mixed venous blood in patients with left to right shunting, especially in those whose shunts are at the level of the atrium. Different methods are used to determine the mixed venous blood oxygen content, but usually these are various combinations of superior and inferior caval vein blood samples[33]. However, in patients without intracardiac shunts, the oxygen content may gradually increase in the caval veins, right atrium, right ventricle and pulmonary artery[34–37]. Using multiple samples for oximetry, Dexter et al. defined criteria for normal right-sided oxygen step-ups, which resulted in a normal oxygen content difference of maximal 1·9 ml·dl−1 between the superior caval vein and the right atrium, 0·9 ml·dl−1 between the right atrium and right ventricle and 0·5 mg·dl−1 between the right ventricle and pulmonary artery[34]. This means that the minimal ratio of pulmonary-to-systemic flow (Qp/Qs) that can be reliably detected by oximetry is 1·5–1·9 at the atrial level, 1·3–1·5 at the ventricular level and 1·3 at the level of the great arteries[27,38]. Measuring oxygen saturations nowadays can be performed relatively easily, within an accuracy of approximately 2%, using paramagnetic oxygen sensors[39]. However, in heart defects with large left-to-right shunts, the pulmonary arterial oxygen saturation is high, and variations of 2% in oxygen saturations
may result in a 25% or more\cite{27} change in calculated blood flow.

Measurement of the patients’ oxygen consumption is another potential source of error. In the past, cumbersome methods, such as the Douglas bag, have been used for this purpose. However, procedural complexity prohibited its widespread use in routine catheterization laboratories. In recent years, more practical instrumentation has become available, that can be used routinely.\cite{40} However, measuring oxygen consumption is based on measuring the difference in oxygen content between inspired and expired air. In contrast to metabolic studies, determination of cardiac output requires an absolute value for oxygen consumption. This, in turn, requires precise, absolute measurements of respiratory gas volumes, so that leakage of respiratory gases has to be precluded. This is cumbersome in most paediatric patients, but is virtually impossible in small, intubated children. For this reason, many routine catheterization laboratories continue to use assumed oxygen consumption, based on body weight or surface area, derived from predictive tables, like that of LaFarge and Miettinen\cite{41}. This is a serious limitation, since these figures may not be reliable, specifically in patients with congenital heart disease, whose oxygen consumption may be influenced by intracardiac shunts\cite{27,42,43}. Finally, when 100% oxygen inhalation is used to test pulmonary vasoreactivity, measuring oxygen consumption, as described, is not possible because the Haldane equation cannot be applied\cite{44}.

The dye dilution technique, first described by Stewart, is often regarded as the gold standard for measuring blood flow in patients\cite{31}. A bolus of dye, most frequently indocyanine green, is injected into one part of the circulation (e.g. pulmonary artery) and sampled at another site (e.g. femoral artery) by continuous withdrawal through a densitometer cuvette, leading to a concentration-time curve, characterized by a primary peak and a recirculation peak (Fig. 1)\cite{31,32}. In left-to-right shunts, the curve demonstrates prominent early recirculation\cite{45}. The area of the primary curve is proportional to \(Q_p\), whereas the area of the early recirculation curve is proportional to shunt flow. Both can be calculated by different mathematical techniques\cite{36,37,38,39}. These techniques require a complex analysis of the inscribed curve, a process that may be especially difficult in the setting of very large or small shunts. The method developed by Carter et al. is much simpler but restricts itself to quantitating the intracardiac shunt\cite{50}. To detect a left-to-right shunt using the direct mathematical analysis of the indocyanine green curve, the \(Q_p/Q_s\) ratio has to be at least 1.15\cite{51}, whereas the method of Carter can reliably detect left-to-right shunts only when \(Q_p/Q_s\geq 1.35\)\cite{52,53}. Limitations of the indocyanine green dilution technique include (1) the complexity and time-consuming nature of the procedure, (2) the need for temporary withdrawal of fairly large volumes of blood from the systemic circulation, which may constitute a potential hazard in infants, (3) problems in cuvette sterilization and (4) very important in patients with congenital heart disease: the rapid recirculation in large left-to-right shunts may hamper the description of the primary circulation curve, influencing the accuracy of the calculation\cite{27,38,54}.

The thermodilution technique, which uses temperature difference after injection of a bolus of a cold

\[A = \int c(t) \, dt\]

\[A_x, A_n, A_y\]

\[\text{Time}\]

\[\text{Concentration}\]

\[\text{Concentration}\]

\[\text{Time}\]

\[c(t)\]

\[A\]

\[A = \int c(t) \, dt\]

\[A_x, A_n, A_y\]

\[\text{Time}\]

\[\text{Concentration}\]

\[\text{Concentration}\]

\[\text{Time}\]

\[c(t)\]

\[A\]

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\[\text{Figure 1}\]

(a) Relationship between time and dye concentration in the femoral artery of a normal subject, after injection of a bolus of dye into the pulmonary artery. (b) Relationship between time and dye concentration in the femoral artery after injection of dye into the right heart. A pre-normal x-peak is due to a right-to-left shunt. A post-normal y-peak is due to a left-to-right shunt.
solution as an indicator, is found to be reliable in patients without shunts, but is not accurate in the presence of left-to-right shunts. The difficulties in quantitative determination of blood flow are illustrated by the limited correlations between the different methods. When reviewing the intrinsic limitations of the various techniques, it has to be acknowledged that the determination of shunt size and pulmonary blood flow, and thus pulmonary vascular resistance, are at best estimations.

Conceptual considerations

The equation used to calculate pulmonary vascular resistance, analogous to Ohm’s law in electrical resistance, assumes a constant, steady flow. The Poiseuille–Hagen equation, derived from a rigid tube, indicates the importance of the vessel radius, or cross-sectional area of the vascular bed, to steady flow resistance:

\[ PVR = \frac{\text{mean}PAP - \text{mean}LAP}{\text{Qp}} \times \frac{8L}{\pi r^4 \eta} \]

in which: \( PVR \) = pulmonary vascular resistance, \( PAP \) = pulmonary artery pressure, \( LAP \) = left atrial pressure, \( Qp \) = pulmonary blood flow, \( L \) = length of tube, \( r \) radius and \( \eta \) = viscosity. The differences between the steady flow of water through a long, straight, glass tube on the one hand, and the pulmonary circulation on the other, were clearly outlined by Hoffman in 1972. Several considerations have to be taken into account when interpreting pulmonary vascular resistance in children with congenital heart disease: (1) the total cross-sectional area of the pulmonary vascular bed may be diminished for reasons other than vasoconstriction or structural vascular changes occurring in the pulmonary vascular disease. For instance, vascular underdevelopment in congenital diaphragmatic hernia, or pulmonary thrombi may cause a decrease in the total cross-sectional area. The increased pulmonary vascular resistance in these conditions is not the result of decreased vascular hindrance due to vascular disease, but to a reduced number of vessels. Narrowing of arteries may be the result of extrinsic pressure, for instance in cases of perivascular oedema fluid. (2) Blood viscosity, a factor in the equation that applies to clinical conditions, may be increased due to polycythemia in children with cyanotic heart disease or pulmonary vascular disease, and may raise pulmonary vascular resistance, independent of pulmonary vascular changes. (3) A third factor to take into account is the critical closing pressure, resulting from the forces which tend to collapse a vessel. In the lung, these may originate from the alveoli or from the vessel itself, in the latter case due to its elastic or muscular recoil. In physiological conditions, left atrial pressure exceeds the critical closing pressure. However, when critical closure pressure exceeds left atrial pressure, as may occur in pathological conditions, such as emphysema or pulmonary hypertension, the usual calculation of pulmonary vascular resistance becomes misleading because left atrial pressure is no longer the appropriate downstream pressure. Finally, a conceptual limitation of pulmonary vascular resistance, that represents resistance of the pulmonary vasculature to steady flow, is that it fails to take account of the pulsatile nature of the pulmonary circulation. In this context, it has to be realized that in normal conditions approximately 30% of the workload of the right ventricle consists of pulsatile load. In pulmonary hypertension this load increases, because of the decreased distensibility of the pulmonary arteries and increased amplitude and velocity of reflected pulse waves. These aspects cannot be evaluated using pulmonary vascular resistance. The acute response of the vascular bed to vasodilators during cardiac catheterization is regarded as a measure of the reversibility of the disease process. This is based on the concept that changes in pulmonary vascular disease consist of a vasoconstrictive component and a structural component. Many studies focus on which pharmacological substance produces the most powerful and selective pulmonary vasodilation. However, it has to be acknowledged that the predictive value of acute testing of pulmonary vasoreactivity, with regard to the operability of the cardiac defect, the likelihood of a peri-operative pulmonary hypertensive crises, and persistent pulmonary hypertension following repair, has never been convincingly demonstrated in children with congenital heart disease. Furthermore, recent observations in patients with advanced primary pulmonary hypertension, who did not respond to acute vasodilator testing, showed that long-term continuous epoprostenol therapy improved the clinical status and haemodynamic data. These observations seriously challenge the concept of reversibility and irreversibility of pulmonary vascular disease.

Histological evaluation of lung biopsy

Although the value of this diagnostic technique is also defined by its ability to determine the type of pulmonary arteriopathy and the morphological substrate for clinically unexplained pulmonary hypertension, we will focus in this review on its use in assessing plexogenic pulmonary arteriopathy in congenital heart defects. From a histological point of view, the most prominent vascular changes are localized in the small, muscular pulmonary arteries (Fig. 2). In 1958, Heath and Edwards described six grades of progressive structural change in the small pulmonary arteries of congenital cardiac defects: grade I=medial hypertrophy of arteries and arterioles, but no intimal changes; grade II=the above plus cellular intima proliferation; grade III=intimal fibrosis, in addition to medial hypertrophy; grade IV=progressive generalized vascular dilatation and plexiform lesions; grade V=the presence of other dilatation lesions, including vein-like branches and
Figure 2 (a) Normal muscular pulmonary artery with a thin media, bounded by internal and external lamina elastica, accompanying a bronchus. (Elastica-van Gieson stain, x 40). (b) Medial hypertrophy of a muscular pulmonary artery in the presence of pulmonary hypertension (Elastica-van Gieson stain, x 40). (c) Plexiform lesion at the origin of a supernumerary artery, branching from a muscular pulmonary artery. The distal part of the supernumerary artery is very dilated and thin-walled. Intimal fibrosis is present in the parent artery (Elastica-van Gieson, x 100).
angiomatoid lesions; grade VI=the stage in which necrotizing arteritis occurred. This grading system has been widely used in assessing the severity of hypertensive pulmonary vascular disease. However, as awareness of the complexity of the vascular lesions has increased there has been debate about the sequence of the vascular changes in the course of the disease process and their biological meaning[67]. Wagenvoort et al. advocated abandoning the grading principle, because the degree and extent of the various lesions, the different types of intimal fibrosis and additional features should all be assessed, not only in arteries but also in other vessels[67–69]. Careful consideration and weighing of all these features are necessary in order to form an opinion on reversibility and prognosis of pulmonary vascular disease. In general, severe concentric laminar intimal fibrosis, angiomatoid dilated lesions, fibrinoid necrosis and plexiform lesions are considered advanced vascular muscularized. They also quantified medial thickening and used the alveolar–artery ratio[71] to assess the number of small arteries.

The tendency of the various vascular changes to progress or regress has been assessed in patients with shunts at the ventricular level, who had first undergone pulmonary artery banding and subsequent surgical repair of their cardiac anomalies[70]. However, systematic studies of long-term follow-up of patients evaluated by any method are scarce[69,72,73].

Practical considerations

To assess pulmonary vascular disease, a lung biopsy of adequate size requires an open lung biopsy and, thus, a thoracotomy. The amount of lung tissue obtained by transbronchial biopsies or transthoracic needle biopsies is small and the vessels are often severely damaged, precluding adequate evaluation[69]. Inadequate lung biopsy size, which may be the result of removing too little tissue or pleural thickening, leaves the patient subjected to the risks of the procedure without benefit[69]. An open lung biopsy as an isolated procedure carries a certain risk, that substantially increases in patients with pulmonary vascular disease. In patients with high pulmonary vascular resistance, morbidity rate, including pulmonary hypertensive crises, arrhythmias and haemorrhage, have been reported in up to 13%, and mortality in up to 20%[74]. The processing of biopsy specimens is important for reliable evaluation. For example, handling by the surgeon or the pathologist may easily result in collapse of tissue, whereas intravascular injection of fixative may lead to unpredictable dilatation of vessels, both leading to qualitative and quantitative misinterpretation of the pulmonary blood vessels. Fixation of lung tissue under vacuum has been widely used in assessing the severity of hypertensive pulmonary vascular disease. However, as awareness of the complexity of the vascular lesions has increased there has been debate about the sequence of the vascular changes in the course of the disease process and their biological meaning[67]. Wagenvoort et al. advocated abandoning the grading principle, because the degree and extent of the various lesions, the different types of intimal fibrosis and additional features should all be assessed, not only in arteries but also in other vessels[67–69]. Careful consideration and weighing of all these features are necessary in order to form an opinion on reversibility and prognosis of pulmonary vascular disease. In general, severe concentric laminar intimal fibrosis, angiomatoid dilated lesions, fibrinoid necrosis and plexiform lesions are considered advanced vascular muscularized. They also quantified medial thickening and used the alveolar–artery ratio[71] to assess the number of small arteries.

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Practical considerations

Histological examination of lung biopsy yields a static description of morphological changes in the vascular bed and does not take into account the functional activity of the vascular endothelium and smooth muscle cells[75–77]. Controversy exists as to the predictive value of lung biopsy evaluation, since it has been suggested that the vascular changes in pulmonary vascular disease, especially the advanced lesions, may be distributed unequally in the lung and thus may be missed in a lung biopsy[71,78]. Also, the presence of such advanced lesions is unusual in the first 2 years of life, even in the presence of severely elevated, non-responsive pulmonary vascular resistance[71]. This possible drawback may be overcome by the classification of Rabinovitch et al., which looked at features that are distributed uniformly through the lung. This classification, however, is based on the concept that small arteries become reduced in size and number in the course of pulmonary vascular disease[71,79,80]. A concept that has been seriously challenged[81,82].

Pulmonary wedge angiography

The pulmonary wedge angiogram provides angio graphic visualization of pulmonary arteries as small as 100 μm and allows definition of tapering and tortuosity of muscular arteries, supernumerary arteries and of the background capillary blush, representing the perfusion of intraacinar vessels (Fig. 3)[83–86]. These variables can be described qualitatively and quantitatively and have been demonstrated to correlate with both haemodynamic data and structural findings in lung biopsies[84–86]. It has been suggested that the presence of obstructive, irreversible pulmonary vascular disease can be determined by wedge angiography[84]. Two techniques of pulmonary wedge angiography have been described. In the first, an end-hole catheter is placed in wedge position and 0.5–3 ml contrast medium is injected slowly by hand until most of the small arteries and some of the interlobular veins are seen. Then 5–10 ml solution is flushed through the catheter until the major pulmonary veins fill and the lobular capillary blush disappears[84]. In the second method, a balloon-tipped, end-hole catheter is used. The catheter is placed in a segment artery and after the artery is occluded by inflation of the balloon, 0.3 ml kg−1 contrast medium (with a minimum of 2 ml) is injected at a flow rate of approximately 5 ml s−1. After the injection, the balloon is deflated and the venophase can be examined separately[85].

Practical considerations

The procedure carries risks: lung parenchymal damage, pulmonary infarction and haemoptysis after injection of contrast medium at a peripheral localization, and
further general risks of pulmonary angiography in patients with pulmonary vascular resistance\textsuperscript{26,83}. However, with the currently available materials, such as non-ionic contrast fluids, and with the techniques described, these risks are low\textsuperscript{84–86}. A limitation of the method is that features, such as abrupt termination of vessels, tortuosity, arborization and background flush are largely qualitative and subjective. These factors have been accommodated partly by Rabinovitch \textit{et al.}, who provided quantitative variables, such as tapering rate and circulation time\textsuperscript{85}. High resolution angiography facilities are required in the catheterization laboratory.

\textbf{Conceptual considerations}

A decrease in the tapering rate of a vessel may have various causes, such as a dilatation of the proximal part of the artery, as is the case in high flow states, or narrowing of the distal part of the artery, as occurs in obstructive
disease, or vasoconstriction of the distal part of the artery or, finally, by a combination of these phenomena. These cannot be distinguished by angiography. Circulation time may reflect a structurally reduced pulmonary vascular bed, due to partially or completely obstructed vessels. However, circulation time may be also directly related to flow, and consequently may only reflect pulmonary blood flow. Indeed, circulation time appeared to be decreased in patients with pulmonary stenosis[85].

Evaluation of pulmonary vascular compliance

In the concept of pulsatile flow, the total forces opposing the blood flow consist of a vascular resistance component, a vascular elasticity component and a blood volume related inertia component[87]. In normal humans, blood flows through the pulmonary and systemic vasculature are approximately equal, whereas the pulmonary pressure wave is more rounded and of lower amplitude. This means that the compliance of the pulmonary arteries is substantially higher than that of its systemic counterparts[87]. In the normal pulmonary vasculature, elastic arteries extend to arteries of approximately 1 mm in size and have much thinner walls than systemic arteries[89]. In pulmonary vascular disease, the compliance of the elastic pulmonary arteries decreases, probably because of structural changes in the arterial wall and, when pulmonary hypertension is present, because the artery operates on a steeper part of its pressure-volume relationship. Consequently, forces opposing the pulsatile flow, such as arterial compliance and reflected pulse waves, which have little importance in the normal pulmonary circulation, become major components of the right ventricular load in pulmonary vascular disease[59].

Using harmonic analysis of pressure and flow waves, pulmonary vascular impedance can be studied. However, until now its use has been restricted to animals and experimental model[88–90]. In systemic arteries, vascular compliance has been studied using pulse wave velocity; however, this has not been feasible in pulmonary arteries. Recently, pulsatility and distensibility of pulmonary arteries have been studied, using intravascular ultrasound or magnetic resonance techniques[91,93]. These data, however, remain to be validated and interpreted in the clinical context.

Discussion

The techniques described all evaluate different properties of the pulmonary vasculature. As outlined, haemodynamic evaluation describes functional aspects of the pulmonary vascular bed associated with the total cross-sectional area of that bed, whereas lung biopsy describes morphological, structural changes of the small pulmonary arteries. Pulmonary wedge angiography describes changes in the course, the luminal diameter and the perfusion of peripheral pulmonary arteries. Pulmonary arterial wall distensibility describes the functional behaviour and properties of the larger pulmonary arteries and its consequences for the pulsatile circulation. Although all these different aspects of the pulmonary vasculature are subject to changes in the course of pulmonary vascular disease, the information obtained by the various techniques is far from identical. Therefore, it is not surprising that, although the results of the different techniques are correlated, these correlations are limited and results may appear conflicting in individual patients[58,60,71,84,85,93].

No doubt haemodynamic evaluation, lung biopsy and pulmonary wedge angiography have contributed greatly to our knowledge of pulmonary vascular disease and to the management of children with congenital heart disease at risk for this disease. However, with the different aspects that are evaluated by each technique and their intrinsic limitations, we are still not confident on how to explain or how to handle discrepancies between the different technique results in individual patients. Clinicians have developed their own preferences and strategies for evaluating the pulmonary vasculature in children with congenital heart disease, frequently dictated by institutional experience and facilities. A three-pronged approach has been suggested to determine surgical risk and outcome[14]. In our institution, we use haemodynamic evaluation, including determination of pulmonary vascular resistance, as a key parameter in the assessment of the severity of pulmonary plexogenic arteriopathy in patients with congenital heart defects. An adequately determined indexed pulmonary vascular resistance of 6–8 WU . m² or lower is, in general, indicative of reversibility of the vascular disease, and thus for eligibility of biventricular repair, especially if an acute pulmonary response to vasodilatory agents, such as prostacyclin, inhaled oxygen or nitric oxide, can be achieved. In these cases, evaluation of the structural state of the pulmonary vascular bed, by wedge angiography or lung biopsy, usually provide no additional information. If pulmonary vascular resistance is higher than 8 WU . m², no acute vasodilatory response can be demonstrated and the findings on wedge angiography agree with advanced and irreversible disease, then further assessment by lung biopsy will mostly only confirm these findings and, in our opinion, is not indicated for diagnostic purposes. However, in selected cases, when data appear discrepant, data are difficult to interpret or in borderline cases, diagnostic open lung biopsy may be considered. In such cases it is important to acknowledge that the presence of advanced vascular lesions is indicative of irreversibility of the disease, whereas reversibility may not be concluded in the absence of these lesions[9,60,72].

Bearing in mind that no technique is perfect, it may be clear that these recommendations are, at best, rough guidelines and that the findings always have to be interpreted in the complete context of clinical data, such as the age of the patient, the anatomical diagnosis of the
cardiac malformation and, very important, the type of the arteriopathy. However, although in use for over 30 years now, reliable data on the predictive values of the different techniques, with regard to reversibility and long-term prognosis are scarce[5,6,7,25,73,94]. This is especially the case when the disease process is in the ‘grey zone’ between reversible and irreversible disease. Moreover, in the current era, in which univentricular heart repairs, such as Fontan and Norwood procedures, are performed with increasing frequency, evaluation of the pulmonary vasculature faces higher demands, for instance, on the pathological functional activity of the pulmonary arteries in the early stages of pulmonary vascular disease. Until new diagnostic tools have been developed, evaluation of the pulmonary vascular bed, in potential candidates for univentricular heart repair, is still based on modifications of the three pulmonary criteria of Choussat and colleagues, which seem to be still valid[95]; a mean pulmonary artery pressure of less than 15–25 mmHg, an indexed pulmonary vascular disease of less than 4 Woods units . m² and adequate size of the pulmonary arteries. The latter item has been debated in recent years and, from a physiological point of view, one may wonder what additional, independent information pulmonary artery size might add to pulmonary vascular resistance. It has been suggested that pulmonary artery size may represent a measure of pulmonary arterial wall compliance[96]. This might explain its relationship with outcome in the Fontan circulation. Effort should be made to develop new clinical, diagnostic tools, that provide additional information on the state of the pulmonary vasculature, with special attention to aspects of the pulsatile nature of the pulmonary circulation and the effects of the absence of this pulsatile component.

Our limited capability of a refined assessment of the pulmonary vasculature in pulmonary vascular disease may be because the pathophysiology of this characteristic vascular disease process is still largely unknown. In the last decade, due to emerging research in vascular cell biology, significant progress has been made on insights into mechanisms at the cellular and molecular level that appear to be involved in pulmonary vascular disease[5,6,7,25,73,94]. The vascular disease process is characterized by excessive cell proliferation, changes in cellular phenotype and extracellular matrix modulation, directed by various vasoactive modulators and growth factors. The unravelling of these mechanisms may not only provide insight on the progression and functional consequences of the disease process, but may also lead to novel therapeutic strategies directed to prevent or reverse the vascular disease[6,65,76].

In conclusion, each of the diagnostic techniques for evaluating pulmonary vascular disease in patients with congenital heart disease, describes specific aspects of the pulmonary vasculature and each has its specific practical and conceptual limitations. Data on the predictive value of the techniques regarding reversibility and long-term outcome are scarce. The value of the information obtained has to be weighed against the risks of the diagnostic procedure. The results of the different techniques may provide discrepancies in individual patients, hampering the interpretation of the findings. Research focused on the pathophysiology of pulmonary vascular disease in congenital heart disease will increase our understanding of these patients and may aid the clinician in ascertaining optimal management and its timing.

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