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Original Article

Measurement, interpretation and use of hemodynamic parameters

Antonio A. Lopes,[1] Patrick W. O'Leary[2]

[1]*Department of Pediatric Cardiology and Adult Congenital Heart Disease, Heart Institute, University of São Paulo Medical School, São Paulo, SP, Brazil and* [2]*Division of Pediatric Cardiology, Mayo Clinic, Rochester, Minnesota, United States of America*

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In pulmonary arterial hypertension, assessment of pulmonary hemodynamics by means of cardiac catheterization is crucial to confirm diagnosis and establish vasodilator therapy. In the specific setting of pulmonary hypertension associated with congenital cardiac disease, the rationale for obtaining hemodynamic parameters goes far beyond choosing and evaluating the effects of drugs, encompassing the need for defining operability and deciding between correction, palliation, and combination of surgical and medical treatments. The scenario is therefore considerably different.

In terms of defining operability, the frequency with which cardiac catheterization is needed tends to decrease in developed countries. Surgical correction of anomalies associated with significant left-to-right shunting in early infancy avoids damage to the pulmonary circulation from increased blood flow and pressure. Nevertheless, some patients present with clinical features suggestive of markedly elevated pulmonary vascular resistance early in life, therefore representing a challenge to assessment by non-invasive methods alone. This is seen more frequently with certain anomalies such as transposition of the great arteries, truncus arteriosus and atrioventricular septal defects. However, even in the setting of simple malformations, some infants and young children can display elevated pulmonary vascular resistance (no history of pulmonary congestion or failure to thrive) with moderately sized or large defects very early in life. On the other hand, in developing countries, patients with large shunts frequently seek medical care after reaching two years of age. In these instances, definition of operability based on noninvasive evaluation is unrealistic.

In the presence of shunts, pulmonary and systemic blood flow and vascular resistance cannot be assessed by thermodilution, and are generally measured using the Fick principle. This involves a number of methodological problems and sources of errors.[1,2] Furthermore, pulmonary circulation needs to be challenged by vasodilators for a full understanding of the functional component of vascular resistance, a major determinant of operability. In small infants and children, the whole procedure is carried out under general anesthesia, and anesthetic drugs are known to induce undesirable changes in pulmonary and systemic hemodynamics. In these situations, appropriate selection of anesthetic protocol plays an important role in obtaining accurate hemodynamic data (see the section discussing anesthesia protocols below).

The aim of the present session is to provide literature-based information potentially useful for adequately assessing hemodynamics in congenital cardiac disease associated with pulmonary hypertension, particularly in the setting of preoperative evaluation. Besides the literature, expert opinion was obtained from geographically representative reference centers, by means of quick surveys.

Correspondence to: Antonio A. Lopes, M.D., Director, Dept. Pediatric Cardiology and Adult Congenital Heart Disease, The Heart Institute (InCor) – HC.FMUSP, Av. Dr. Eneas de Carvalho Aguiar, 44, 05403-000 – São Paulo – Brazil. Tel: 55-11-3069-5350; Fax: 55-11-3069-5409; E-mail: aablopes@usp.br

Which patients should undergo cardiac catheterization?

There are no controlled studies on this subject, and specialist opinion is not totally uniform. The less conservative pediatric cardiologists would rely on noninvasive evaluation to determine operability for most of their patients. They would not catheterize young patients (e.g. in the first year of life) with simple anomalies, in particular "if pulmonary hypertension is felt to improve significantly following operation". To the other side of the range, more conservative specialists would catheterize all patients who do not present with a history of overt congestion and clear evidence of left-to-right shunting.

There are points of convergence. Most specialists would agree that decision to catheterize must be based on a careful analysis of the full clinical picture and echocardiographic findings. Catheterization is unnecessary in the presence of overt pulmonary congestion associated with left-to-right shunting, in particular below the age of six months. Infants with truncus arteriosus, atrioventricular septal defects or transposition of the great arteries associated with a ventricular septal defect are very unlikely to need invasive hemodynamic evaluation if correction is considered before three months of age. Patients presenting with these anomalies above the age of 12 months should undergo cardiac catheterization. Catheter evaluation may also be needed in select patients between six and 12 months of age, when there is clinical concern about irreversible elevation of pulmonary vascular resistance. Also, most pediatric cardiologists would catheterize patients with functionally univentricular physiology who are candidates to direct anastomoses between the systemic veins and pulmonary arteries (so-called bidirectional Glenn and Fontan operations), since even mild elevations of pulmonary vascular resistance in these patients might cause significant hemodynamic disturbances postoperatively.

For patients living at high altitude, catheterization may be necessary even below the age of three to six months, as some of them may be inoperable. Alternatively, these patients could be relocated to the sea level, with assessment of hemodynamic parameters one to three months later to determine operability. Additional infants that are at a greater risk of inoperability are those with omphalocele. Catheterization early in life is warranted for this group, as it is for all infants without a clear cut history of congestive cardiac failure and/or failure to thrive.

Anesthesia protocols

All anesthetic agents have potential hemodynamic effects on the pulmonary and systemic circulation.

Cardiac catheterization should be considered for all patients with congenital heart disease and pulmonary hypertension without clinical evidence of left-to-right shunting causing pulmonary congestion, and those presenting with transposition of the great arteries, truncus arteriosus or atrioventricular septal defect above the age of 12 months, as well as select patients between six and 12 months of age. Patients with complex anomalies and single ventricular physiology who are candidates to the Fontan operation should undergo catheterization as well.

Class: IIa. *Level of evidence: C.*

Although anesthesia is necessary to catheterize infants and children, use of these agents can be problematic when obtaining of accurate measures is critical. Furthermore, combinations of more than two drugs are often a routine in many centers, leading to unpredictable results. We attempted to examine the available literature and expert opinion to decide if it is possible to suggest protocols that include two drugs at most.

It is generally accepted that catheterization aimed at obtaining accurate hemodynamic measures must be planned in a different way as compared with routine procedures for other purposes (angiography, electrophysiological studies and interventions). Pediatric cardiologists must work in close association with anesthesiologists and a discussion of the specific goals of the catheterization is often helpful. Although there is no consensus about intubation, specialists agree that patients should be adequately ventilated during the entire procedure, with PCO_2 maintained at normal levels or slightly decreased, and a peripheral oxygen saturation close to the pre-catheterization level. It should be noted that relative to non-cyanotic patients, those who are cyanotic require a much larger volume of ventilation per minute to maintain a normal PCO_2 and the minute volumes of the ventilator must be adjusted accordingly. It is useful to obtain an arterial blood gas analysis prior to the formal hemodynamic evaluation to ensure adequate tidal volume/minute volume settings in cyanotic patients. Administration of oxygen at high concentrations throughout the exam is neither necessary nor recommended, and may influence hemodynamic measurements (see pulmonary vasoreactivity test). Concentrations in the range of 21% to 30% are adequate for most patients and should be maintained at a consistent level for at least 10 minutes prior to the first hemodynamic measurement and until the assessment is completed.

There has been a variety of drug protocols for anesthesia in children. A major difficulty is that in many publications, hemodynamic data are not available. Most specialists would agree that inhaled drugs should be avoided in view of their myocardial

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depressant effects.[3] Of the drugs that have been used intravenously, fentanyl, ketamine, midazolan and propofol deserve consideration. There is no general agreement about the use of premedication, but if this is the case, the same drugs can serve the purpose, with no need for additional ones. Continuous rather than bolus administration is recommended to avoid undesirable hemodynamic oscillations.

Propofol given as a single drug seems to decrease systemic vascular resistance, making calculations of shunts unreliable.[4,5] Also, there is controversial information that ketamine may increase pulmonary vascular resistance, in particular when given as boluses.[6] In one prospective randomized study, continuously administered ketamine did not affect pulmonary vascular resistance significantly.[5] In low-dose protocols, ketamine has been used in association with either midazolan[7] or propofol.[8] Finally, fentanyl has been attempted in association with midazolan.[3] Alternatively, remifentanyl might be considered as a better option in view of its short action.

In pediatric patients undergoing cardiac catheterization for hemodynamic measurements, sedation and analgesia can be achieved by combining midazolan with fentanyl, or by using low-dose ketamine in association with either midazolan or low-dose propofol. Continuous intravenous administration is preferable. Multi-drug cocktails, inhaled agents, propofol as single drug and bolus administration of any drugs should be avoided.

Class: IIa. *Level of evidence: B.*

Assessment of pulmonary and systemic blood flow and vascular resistance

Calculation of pulmonary and systemic blood flow and vascular resistance using the Fick principle requires attention to several possible sources of errors. Inappropriate hemodynamic and respiratory conditions, and inadequate blood sampling and processing for gas analyses are among the most important and avoidable ones. Inappropriate assumptions and approximations may also lead to unpredictable deviations. In this way, there are special recommendations regarding the values of mixed venous and pulmonary venous oxygen saturation to be used in the formulas. Also, in patients breathing 80%–100% oxygen (see pulmonary vasoreactivity test), oxygen content in blood samples must be calculated taking into account not only the hemoglobin-bound but also the dissolved fraction. A complete review including all the needed formulas and important technical advice is available.[2]

The value of oxygen consumption to be used in the formulas for calculation of pulmonary and systemic flow is a matter of concern. Although direct measurement is preferable (mass spectrometry, indirect calorimetry) and indirect prediction (tables, nomograms or regression models) is notoriously unreliable, measurements are not routinely performed in many institutions for several reasons. Adequate measurement of oxygen consumption is difficult in intubated (non-cuffed) patients, and not possible during inhalation of oxygen at high concentrations. Reviewing 241 publications under "pulmonary vascular resistance in congenital cardiac disease" between 1997 and 2007, we identified 57 studies involving calculations of pulmonary vascular resistance and pulmonary to systemic resistance ratio. Eight of them were multicentric and the remaining ones represented 36 institutions in 16 countries. Of these 57 studies, oxygen consumption was measured in 13, assumed in 20, either measured or assumed in 3, and not specified in 21. Expert opinion is also variable. Those who are against the use of assumed values would rely on pulmonary to systemic resistance ratio (where oxygen consumption is not required) for decision making.

If assumption is considered, more than one value should be obtained,[2] and several methods are available for this purpose.[9–12] Although the formula proposed by LaFarge and Miettinen[9] has been largely used, it must be acknowledged that in young patients (infants), it tends to provide higher oxygen consumption values as compared with the methods of Lindhal[10] and Lundell et al.,[12] thereby resulting in optimistic results (lower values) in terms of pulmonary vascular resistance. Calculations based on assumed oxygen consumption may be a real problem in cyanotic patients (measured values are far greater than the assumed ones), and candidates to the Fontan operation, for whom very accurate results are necessary.[13]

In view of the difficulties with flow calculations using the Fick principle, other techniques have been considered. In this way, flow measurement using dye dilution techniques has been proposed as an alternative.[1,11]

1. *In patients with congenital heart disease associated with pulmonary hypertension, pulmonary and systemic blood flow and vascular resistance should be calculated preferably using measured oxygen consumption, with attention to all other potential sources of error.*

Class: IIa. *Level of evidence: B.*

2. *If measured values of oxygen consumption cannot be obtained, calculations should be performed assuming alternative values at the upper and lower limits of the likely range for that given patient, and results expressed as intervals. If the likely range is too wide and a narrow one is required for decision-making, assumed values should not be used at all.*

Class: IIb. *Level of evidence: B.*

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Acute pulmonary vasoreactivity test and operability

Attempts to validate an index for precisely selecting patients with congenital cardiac shunts who will be free of significant pulmonary hemodynamic disturbances postoperatively have not been successful. Thus, operability has been largely defined on the basis of the likelihood of a favourable versus unfavourable outcome, taking into account a substantial amount of clinical, echocardiographic and sometimes hemodynamic information. In terms of hemodynamics, in practice, both pulmonary vascular resistance and pulmonary to systemic resistance ratio, and the way they change during an acute vasodilator challenge have been taken into consideration.[14,15]

From the strict hemodynamic point of view, a baseline pulmonary vascular resistance index of <6 Wood units $\cdot m^2$ associated with a resistance ratio of <0.3 has been interpreted as indicative of favourable outcome following operations resulting in biventricular circulations, with no need for a vasoreactivity test. The acute vasodilator challenge has been strongly encouraged if baseline pulmonary vascular resistance index is between 6 and 9 Wood units $\cdot m^2$ in the presence of a resistance ratio of ~ 0.3 to ~ 0.5. Although the magnitude of response to be considered as significant is controversial, it is generally accepted that patients can be assigned to operation if *all* of the following criteria are met: 1) $\geqslant 20\%$ decrease in pulmonary vascular resistance index; 2) $\geqslant 20\%$ decrease in pulmonary to systemic vascular resistance ratio; 3) final pulmonary vascular resistance index of <6 Wood units $\cdot m^2$; 4) final resistance ratio of <0.3. Interpreting other responses as positive or taking into account some but not all of the mentioned criteria to define operability is controversial. Finally, in some centers, patients with baseline pulmonary vascular resistance index of $\geqslant 8$–9 Wood units $\cdot m^2$ and a resistance ratio of $\geqslant 0.5$ are assigned to corrective operation depending on the overall picture. However, the risk of serious postoperative complications and/or persistent pulmonary hypertension is considerable in this group.[16] In this case, defining operability on the basis of less stringent criteria is unacceptable.

These criteria are not applicable to candidates for the Fontan operation or other single ventricular palliations using venous sources for pulmonary blood flow. In these patients pulmonary vascular resistance should ideally be much lower; usually <3 Wood units $\cdot m^2$.[13,17] In many cases, one must consider not only the absolute value of pulmonary vascular resistance, but also the amount of pulmonary blood flow and ventricular compliance in assessing these patients. In the setting of significant pulmonary "overcirculation" (large left-to-right shunts), a somewhat greater level of pulmonary vascular resistance can be accepted, particularly if the planned palliation will eliminate or significantly reduce the shunt volume. A combined index including pulmonary vascular resistance, the sum of pulmonary and systemic flow and ventricular end-diastolic pressure, can be helpful in estimating the risks/results of Fontan completion in these complex hemodynamic situations.[18]

Despite the general opinion that oxygen and nitric oxide are the most appropriate and selective agents for testing pulmonary vasoreactivity in patients with congenital cardiac disease and pulmonary hypertension, controversy remains about the relative concentrations to be used in practice. A maximal stimulation can be achieved in the absence of any significant toxic effects, with a 10 minute administration of a mixture containing $\geqslant 90\%$ oxygen and 80 ppm nitric oxide.[15,19] Although a positive response could be helpful for planning long-term vasodilator therapy, assignment to operation based on response obtained only at maximal stimulation has been a matter of debate. In this way, some would prefer to use 20 ppm nitric oxide with or without increased oxygen concentration.[20,21] Intermediate protocols of 21%–30% oxygen with 80 ppm nitric oxide[15,19] or $\sim 100\%$ oxygen with 40 ppm nitric oxide[22] have been used as well. Starting at low concentrations with gradual increases until response is a possible strategy, but delayed procedure and excessive blood sampling are important limitations in young patients at high risk for cardiac catheterization. Also, at high oxygen concentrations, determination of arterial PO_2 is necessary and measurement of oxygen consumption is not possible.

1. *In patients with congenital heart disease and pulmonary hypertension, there are no simple ways to predict outcomes following correction of the cardiac defects. Therefore, operability (which does not imply a warranty of favourable outcome without any residual elevation of pulmonary pressures) should be defined on an individual basis, taking into account a substantial amount of clinical data as well as information derived from noninvasive and sometimes invasive evaluation.*

Class: I. *Level of evidence: C.*

2. *In patients with biventricular circulations and baseline elevation of pulmonary vascular resistance $\geqslant 6$ Wood units $\cdot m^2$ and a pulmonary to systemic resistance ratio of $\geqslant 0.3$, a $\geqslant 20\%$ decrease in both parameters during inhalation of low concentrations of nitric oxide, with respective final values of <6 Wood units $\cdot m^2$ and <0.3 indicates that vasoconstriction plays a role, and suggests that from the hemodynamic point of view, correction of the defect may be considered as a reasonable approach.*

Class: I. *Level of evidence: B.*

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Conclusion

For the majority of patients with congenital cardiac defects associated with left-to-right shunts, correction can be safely carried out early in life based on data obtained from noninvasive evaluation. There are specific conditions, however, where detailed analysis of the pulmonary circulation and how it responds to an acute vasodilator challenge are crucial for decision making, particularly in view of future possibilities of combining surgical and medical therapies. Importantly, although with improvement of peri-operative care many children can now survive surgical correction, this is not necessarily the best treatment for some of them on a long-term basis.

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