Progress in Pediatric Cardiology 34 (2012) 123–127

Contents lists available at SciVerse ScienceDirect

Progress in Pediatric Cardiology

journal homepage: www.elsevier.com/locate/ppedcard

Why all pulmonary hypertensive patients need a heart catheter study?

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ARTICLE INFO

Keywords:
Cardiac shunt
Cardiac catheterization
Pulmonary hypertension
Vasoreactivity

ABSTRACT

Pulmonary arterial hypertension (PAH) constitutes a progressive and limiting disease. This condition requires an accurate diagnostic and right cardiac catheterization (RHC) is considered the gold standard. It is also useful to assess the severity of the hemodynamic impairment and test the vasoreactivity of the pulmonary circulation providing essential information to evaluate the patient prognosis and to guide the clinical care.

1. Introduction

Pulmonary arterial hypertension (PAH) constitutes a progressive and limiting disease characterized by multiple changes in pulmonary circulation including arterial vasoconstriction, smooth-muscle cell and endothelial-cell proliferation, and vascular thrombosis [1].

Patients with PAH require an accurate diagnosis in order to clarify the origin, classify the defect, stratify the prognosis, tailor a proper treatment and follow-up the response to the therapy. Currently, right cardiac catheterization (RHC) is considered the gold standard to confirm the diagnosis of PAH, assess the severity of the hemodynamic impairment and test the vasoreactivity of the pulmonary circulation. Cardiac catheterization not only allows a precise initial diagnosis but also provides essential information to evaluate the patient prognosis and to guide the clinical care.

The present paper focuses on the contemporary role of cardiac catheterization in evaluating and treating patients with PAH with congenital heart disease (CHD).

2. Cardiac catheterization measurements

Firstly, it is important to point out that accurate measurements can be more optimally achieved in baseline conditions without general anesthesia. The parameters that are required to confirm the diagnosis of pulmonary hypertension (PH) are: 1) PA pressures (systolic, diastolic and mean), 2) mean capillary wedge or left atrial pressure, and 3) cardiac output (CO). Nonetheless, a more complete assessment including right atrial (RA) and right ventricle (RV) pressures as well as pulmonary vascular resistance (PVR) evaluation is typically recommended [2]. Cardiac output can be assessed by angiographic, thermodilution or Fick methods. In case of shunt, the Fick is the accepted method for measuring the CO. A left-to-right cardiac shunt should generally be ruled out, typically by excluding a significant blood oxygen saturation step-up between the vena cavas and the right atrium ($\geq$7%) or between the other cardiac chambers ($\geq$5%). In addition to the right heart chambers, blood oxygen saturations from the aorta and the pulmonary vein (if possible) are necessary to evaluate the severity of the shunt (Fig. 1). Vascular resistances (pulmonary, systemic and the ratio between the two) can be measured directly by cardiac catheterization using a formula integrating the PA pressure and the CO (Fig. 1).

In patients with CHD, invasive cardiac catheterization is not always easy but it is particularly valuable as it might provide anatomical information to complement the diagnosis (in combination with other imaging modalities) and might help the physician to understand the hemodynamic behavior of the defect. Additionally, a left heart catheterization including a coronary angiogram should be performed if coronary artery disease is suspected or routinely before cardiac surgery in men > 40 years of age and postmenopausal women [3].

3. Cardiac catheterization to confirm and categorize pulmonary hypertension

RHC is mandatory to confirm the diagnosis of PH as the accepted definition requires the existence of an elevated mean PA pressure of > 25 mm Hg at rest assessed by invasive catheterization [2]. The presence of a PA pressure > 30 mm Hg on exercise was proposed but then removed from the criteria as healthy subjects can reach much higher values [4].

According to the World Health Organization (WHO), PH is classified in 5 groups based on the pathophysiology (Table 1). Pre-capillary PH includes groups 1, 3, 4 and 5 and post-capillary PH just only group 2. PAH is defined, like all other pre-capillary forms, by a mean PA pressure > 25 mm Hg at rest with a mean capillary wedge pressure ≤ 15 mm Hg and a normal or decreased cardiac output [2].

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1058-9813/$ – see front matter © 2012 Published by Elsevier Ireland Ltd.
http://dx.doi.org/10.1016/j.ppedcard.2012.08.012

$$QP/QS^{1} = \frac{Sat\ (aorta) - Sat\ (mixed\ venous^{2})}{Sat\ (pulmonary\ vein^{3}) - Sat\ (pulmonary\ artery)}$$

$$PVR^{4} = \frac{Mean\ PAP - Mean\ CWP}{Cardiac\ Output}$$

Fig. 1. Pulmonary to systemic blood flow ratio equation (QP/QS) and pulmonary vascular resistance (PVR) formula. Footnote: Sat, saturation; PAP, pulmonary artery pressure; CWP, capillary wedge pressure. [1] This equation can be used to determine the relative blood flow between the body and the lungs. The normal value for this ratio is close to 1, so there is equal blood flow to the lungs and body. [2] Ideally it should be measured as [Sat (superior vein cava) 3 + Sat (inferior vein cava)/4]. If not possible, right atrium saturation can be taken as the value as it is where superior and inferior cava vein blood gets mixed. [3]As we usually cannot measure this value, capillary wedge saturation can be taken or we can assume that, with healthy lungs the blood will be fully oxygenated (100%). [4]Measurements in Wood Units. Normal values are from 0.7 to 1.1 Wood Units.

PAH prevalence is estimated in around 15-20 subjects per million population in Europe [5]. Idiopathic-PAH constitutes the most frequent form of PAH accounting for 40–50% of cases [5,6]. CHD is also a common cause of PAH. Approximately, 5% to 10% of patients with CHD will develop PAH of variable severity [7–9]. The diagnosis of PH in adults with CHD is associated with more than 2-fold higher risk of mortality compared to patients without PH [10]. The classification of PAH secondary to CHD is very challenging due to the dynamic nature of the disease and the different individual response to similar underlying lesions [11,12]. For this reason, the classification has been recently updated in order to provide a more accurate individual definition based on clinical (Table 2) and anatomical–pathophysiological information (Table 3) [13].

4. Cardiac catheterization to evaluate vasoreactivity

Vasoreactivity assessment is recommended in patients with PAH (group 1) after confirming the diagnosis with RHC as a part of the initial evaluation [2]. In general, a positive test identifies the patients that might benefit from long term therapy with calcium channel blockers (CCB). Although acute vasoreactivity testing is recommended for all types of PAH, its predictive value for long-term CCB responsiveness seems to be superior in idiopathic-PAH [14]. Significant vasoreactivity is uncommon in PAH associated with CHD but has also a prognostic value in patients with Eisenmenger's physiology [15]. In patients with other types of PH (groups 2, 3, 4 and 5), acute vasoreactivity testing to evaluate the long-term response to CCB is not recommended [2].

The definition of a positive response is a reduction of at least 10 mm Hg in mean PA pressure to reach an absolute value of less than 40 mm Hg with an increased or unchanged CO [14]. The agents that are utilized for vasoreactivity have usually short-acting and limited systemic effects. Although several different drugs have been proposed to test reactivity in the past, currently, the most accepted drug is inhaled nitric oxide (IIa indication) followed by intravenous epoprostenol (IIb indication) and intravenous adenosine (IIb indication) [2] (Table 4). The use of oral or intravenous CCB is not recommended due to potential severe side effects, and the role of new generation drugs like oral sildenafil or inhaled iloprost has not been well established yet.

The presence of vasoreactivity constitutes one of the most important factors to guide medical treatment. In case of a positive response, CCB at high doses are recommended and must be continued long-term if there

Table 1
Updated clinical classification of pulmonary hypertension [24].

Group 1—Pulmonary Arterial Hypertension (PAH)
1.1 Idiopathic-PAH
1.2 Heritable
1.3 Drug and toxin induced
1.4 Associates with
1.4.1 Connective tissue disease
1.4.2 Human immunodeficiency virus (HIV) infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.4.6 Chronic hemolytic anemia
Group 2—Pulmonary hypertension due to left heart disease
Group 3—Pulmonary hypertension due to lung disease and/or hypoxia
Group 4—Chronic thromboembolic pulmonary hypertension
Group 5—Pulmonary hypertension due to unclear multifactorial mechanisms

Table 2
Clinical classification of congenital, systemic-to-pulmonary shunts associated with pulmonary arterial hypertension.

A. Eisenmenger's syndrome
Eisenmenger's syndrome includes all systemic-to-pulmonary shunts due to large defects leading to a severe increase in PVR and resulting in a reversed (pulmonary-to-systemic) or bidirectional shunt. Cyanosis, erythrocytosis, and multiple organ involvement are present.
B. Pulmonary arterial hypertension associated with systemic-to-pulmonary shunts
In these patients with moderate to large defects, the increase in PVR is mild to moderate, systemic-to-pulmonary shunt is still largely present, and no cyanosis is present at rest.
C. Pulmonary arterial hypertension with small defects (sizes for adults)
In cases with small defects (usually ventricular septal defects <1 cm and atrial septal defects <2 cm of effective diameter assessed by echocardiography) the clinical picture is very similar to idiopathic PAH.
D. Pulmonary arterial hypertension after corrective cardiac surgery
In these cases, congenital heart disease has been corrected but PAH is either still present immediately after surgery or has recurred several months or years after surgery in the absence of significant post-operative residual congenital lesions or defects that originate as a sequela to previous surgery.

Table 3
Anatomical-pathophysiological classification of congenital systemic-to-pulmonary shunts associated with PAH (modified from Venice 2003).

1—Type of defect
1.1 Simple pre-tricuspid shunts
1.1.1. Atrial septal defect (ASD)
1.1.1.1. Ostium secundum
1.1.1.2. Sinus venosus
1.1.1.3. Ostium primum
1.1.2. Total or partial unobstructed anomalous pulmonary venous return
1.2. Simple post-tricuspid shunts
1.2.1. Ventricular septal defects (VSD)
1.2.2. Patent ductus arteriosus (PDA)
1.3. Combined shunts : Described combination and define predominant defect
1.4. Complex congenital heart disease
1.4.1 Complete atrioventricular septal defect
1.4.2. Truncus arteriosus
1.4.3. Single ventricle physiology with unobstructed pulmonary blood flow
1.4.4. Transposition of the great arteries with VSD (without pulmonary stenosis) and/or PDA
1.4.5. Other
2—Dimension (specify for each defect if more than one congenital heart defect exists)
2.1. Hemodynamic (specify QP/QS)
2.1.1. Restrictive (pressure gradient across the defect)
2.1.2. Non-restrictive
2.2. Anatomic
2.2.1. Small to moderate (ASD ≤2 cm and VSD ≤1 cm)
2.2.2. Large (ASD >2 cm and VSD>1 cm)
3—Direction of the shunt
3.1. Predominantly systemic-to-pulmonary
3.2. Predominantly pulmonary-to-systemic
3.3. Bidirectional
4—Associated cardiac and extracardiac abnormalities
5—Repair status
5.1. Unoperated
5.2. Palliated (specify type of surgery and age of surgery)
5.3. Repaired (specify type of operation and age of surgery).