ORIGINAL ARTICLE

Pulmonary arterial compliance is a useful predictor of pulmonary vascular disease in congenital heart disease

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Abstract

Histopathological assessment of the pulmonary arteries is crucial to determine the surgical indications in patients with congenital heart disease (CHD) and intractable pulmonary vascular disease (PVD). We aimed to clarify whether pulmonary hemodynamic parameters can predict PVD in patients with CHD and pulmonary arterial hypertension (PAH) We performed histopathological evaluations of lung specimens and cardiac catheterizations in 27 patients with CHD–PAH. We divided these patients into the patients with and without PVD, and compared pulmonary hemodynamic parameters including pulmonary arterial compliance (Cp) between two groups. Age at lung biopsy was 4 (2–7) months. There were 16 patients with trisomy 21. Cardiac diagnosis included ventricular septal defect in 16, atrial septal defect in 5, atrioventricular septal defect in 4, and others in 2. There were 11 patients with histopathologically proven PVD (Heath–Edwards classification grade ≥ 3 in 5; the index of PVD ≥ 1.1 in 3; extremely thickened media in 6; hypoplasia of the pulmonary arteries in 3). Cp in the patients with PVD was significantly lower than that in patients without PVD (0.99 [0.74–1.42] vs 1.56 [1.45–1.88], $p = 0.0047$), although there was no significant difference in the ratio of systemic to pulmonary blood flow, pulmonary arterial pressure, and resistance between two groups. A Cp cutoff value of < 1.22 ml/mmHg m^2 as a predictor of PVD yielded a sensitivity and a specificity of 93% and 64%, respectively. Pulmonary arterial compliance can be a predictor of PVD among patients with CHD–PAH.

Keywords Congenital heart disease · Pulmonary hypertension · Pulmonary vascular disease · Compliance · Histopathology

Introduction

Development of pulmonary vascular disease (PVD) is associated with a poor prognosis in patients with congenital heart disease (CHD) and pulmonary arterial hypertension (PAH) [1]. Histopathological evaluations of pulmonary vasculature is crucial to confirm PVD in these patients [2,3]. PVD often presents with diverse histopathological findings which are classified into three groups: (1) intimal cellular proliferation and fibrous hypertrophy resulting in obstruction of the lumen of small pulmonary arteries (2) extremely thickened media of the small pulmonary arteries (3) hypoplasia of the small pulmonary arteries [4–7]. These pulmonary arterial changes may coexist. The development of intimal proliferative changes or plexogenic pulmonary arteriopathy indicates an irreversible obstructive change, which is a contraindication for surgery. Extremely thickened media and hypoplasia of the small pulmonary arteries are characteristically associated with idiopathic persistent pulmonary hypertension of neonates, which requires a careful consideration prior to selecting patients for surgical intervention [8]. A lung biopsy is often recommended to determine an operative indication when the pulmonary vascular resistance index is higher than 8 Wood unit m^2 in patients with CHD [3]. However, a definitive indication of lung biopsy is required in the management of patients with CHD–PAH.

Regarding with pulmonary circulation, it is important to consider both pulmonary arterial resistance and compliance

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[9]. Pulmonary arterial resistance (Rp), that is the most frequently used parameter, highly depends on the diameter of resistance arterioles and small distal arteries. Pulmonary arterial compliance (Cp) refers to the elasticity and extensibility of vessels. The Windkessel model describes the hemodynamics of pulmonary circulation accounting for the resistance of small distal arteries and the elastic properties of the entire arterial system. There is a hyperbolic relationship between Rp and Cp, and Rp–Cp coupling reflects the condition of the pulmonary vasculature in a patient with CHD–PAH [10]. The product of Rp and Cp, called the resistance-compliance (RC) time, has been shown as being constant during therapy for PAH [11,12]. In patients with CHD, however, RC time is altered by left atrial pressure and the amounts of pulmonary blood flow which are determined by the size of the shunt and the condition of the pulmonary vasculature [10,13]. Therefore, the both assessments of Rp and Cp are necessary to evaluate the accurate condition of the pulmonary vasculature in patients with CHD–PAH. We aimed to clarify whether these pulmonary hemodynamic parameters can predict histopathologically proven PVD in patients with CHD–PAH.

Materials and methods

Patients

This study was approved by the Institutional Ethics Committee of Kyushu Hospital, Japan Community Healthcare Organization (approval number 463). Informed consent was obtained from all patients or their guardians. Between 2000 and 2018, we performed lung biopsies during palliative or corrective cardiac surgery in 27 children diagnosed with CHD–PAH (mean pulmonary arterial pressure > 25 mmHg). We studied the clinical records of a cohort comprising 27 patients, and retrospectively obtained hemodynamic data based on cardiac catheterizations performed before and after surgery. At our hospital, a lung biopsy is indicated in patients demonstrating Rp > 6 Wood units m^2, or when the ratio of pulmonary to systemic flow (Qp/Qs) < 2.0 and mean pulmonary arterial pressure > 40 mmHg. Based on histopathological findings of lung specimens, we speculated the postoperative course and chose therapeutic options including oxygen supplementation, inhalation of nitric oxide, and administration of pulmonary vasodilators as treatment modalities.

Hemodynamic measurements

Cardiac catheterizations were performed approximately a month prior to surgery to evaluate pulmonary hemodynamics. Standard techniques were utilized to measure all catheterization parameters in patients placed in the supine position and using fluoroscopic guidance. Thiamylal sodium was used for sedation. Pressures were measured at end expiration using a Berman angiographic catheter or a Swan-Ganz catheter (Gadelius Medical K.K., Tokyo, Japan). If possible, the left atrial pressure was measured through the foramen ovale, and if not possible, the pulmonary capillary wedge pressure was measured to calculate transpulmonary pressure. Pulmonary blood flow was calculated using the Fick principle. Pulmonary arterial resistance was calculated as the difference between mean pulmonary arterial pressure and left atrial pressure, or pulmonary arterial capillary wedge pressure, divided by the Qp. Pulmonary stroke volume was calculated as Qp divided by heart rate during examination. Pulmonary arterial compliance was calculated as the pulmonary stroke volume divided by pulmonary arterial pulse pressure (the difference between systolic and diastolic pulmonary arterial pressures). The RC time was the product of Rp and Cp as described previously. Acute pulmonary vasodilator tests were also performed using oxygen loading and inhaled nitric oxide. A decrease in the mean pulmonary arterial pressure or resistance > 20% without a decrease in cardiac output is interpreted to be a positive pulmonary vasodilator test, although multiple criteria have been suggested to indicate a positive pulmonary vasodilator test [15].

Histopathological examinations

One block of tissue from each lung was fixed in 10% formalin, and paraffin sections were prepared. In each patient, 30 step-sections at 50 μm intervals were prepared, and Elastica Masson–Goldner staining was performed [14]. We evaluated the small pulmonary arteries in terms of: (1) the severity of intimal lesions resulting in obstruction of the small pulmonary arteries. (2) Thickness of the media in the small pulmonary arteries. (3) Hypoplasia of the small pulmonary arteries. The severity of intimal lesions was determined in each patient using the Heath–Edwards classification and the index of pulmonary vascular disease (IPVD), which has been previously reported by Yamaki et al [4]. In the present study, the significant intimal lesions of small pulmonary arteries were defined as Heath–Edwards classification ≥ grade 3 or the findings of IPVD ≥ 1.1. The thickness of media in the small pulmonary arteries was measured using previously reported morphohistometric methods [4]. Extremely thickened media of small arteries was defined as at least one small pulmonary artery showing a media with a mean thickness greater than the internal diameter of the vessel. This corresponds to the state in which the percent wall thickness is > 33% in a cross-section of a small pulmonary artery. Because the internal and external walls of small pulmonary arteries with extremely thickened media are not usually concentric circles, but oval in shape and are

extremely distorted, the mean percent wall thickness of the major and minor axes was measured [5]. Hypoplasia of the small pulmonary arteries was assessed by comparing the radius of small pulmonary arteries to that of accompanying bronchioles (supernumerary arteries that did not run parallel to the bronchioles were excluded). Hypoplasia of a small pulmonary artery was defined as a condition wherein the radius of a small pulmonary artery was < 60% of the radius of an accompanying bronchiole.

Statistical analysis

Statistical analysis was performed using the analysis toolpack in the Microsoft Office Excel™ add-in software. Values were expressed as the median following the first and third quartiles. We compared variables between patients with and without PVD using the Mann–Whitney U test or chai-square test appropriately, and compared pre- and postoperative variables using the Wilcoxon signed-rank test. Furthermore, the receiver operating characteristic curve was generated by computing sensitivity and specificity at an observed cut-off value for the existence of PVD. For all statistical analyses, a p value < 0.05 was considered statistically significant.

Results

In our study cohort of 27 patients, there were 15 females. Age at the time of a lung biopsy was 4 (2–7) months. Definitive cardiac diagnoses included ventricular septal defect in 16, atrial septal defect in 5, atrioventricular septal defect in 4, and severe tricuspid regurgitation in 1, and tricuspid atresia without pulmonary stenosis in one patient. The most common chromosomal anomaly was trisomy 21 in 16 patients (59%). Other comorbidities included trisomy 18 in 1, Dandy–Walker syndrome in 1, and low birth weight (< 2.5 kg) in 2 patients.

Pulmonary hemodynamic data is shown in Table 1. Systemic oxygen partial pressure (PO_2), mean pulmonary arterial pressure (PAP), Qp/Qs, Rp, Cp, and RC time were 70 (59–75) Torr, 53 (36–60) mmHg, 1.71 (1.24–2.45), 7.47 (3.70–9.59) Wood units m^2, 0.99 (0.74–1.42) mL/mmHg m^2, and 0.45 (0.36–0.51) s, respectively. Acute pulmonary vasodilator tests were performed in 16 patients, which revealed that systemic PO_2, mean PAP, Qp/Qs, Rp, Cp, and the RC time were 241 (151–287) Torr, 38 (32–43) mmHg, 3.40 (2.90–4.78), and 2.48 (2.03–3.17) Wood units m^2, 2.45 (1.72–3.34) mL/mmHg m^2, and 0.40 (0.35–0.47) s, respectively. Positive pulmonary vasodilator tests were observed in 12 patients (75%). There was no significant difference in these parameters between patients who demonstrated positive and negative pulmonary vasodilator tests.

Among the 27 patients studied, 5 patients underwent palliative surgery including 4 pulmonary arterial bandings and one aortopulmonary shunt, and 19 patients underwent primary corrective surgery. One patient diagnosed with ventricular septal defect and pulmonary hypertension was categorized based on the Heath–Edwards classification as grade 3 and IPVD of 1.8, which indicated irreversible pulmonary obstructive vascular disease and a definite contraindication for surgery. Another patient with atrial septal defect and pulmonary hypertension was diagnosed with an extremely thickened media of the small pulmonary arteries despite a lack of intimal proliferative change, which was also considered a definite contraindication for surgery. Postoperative cardiac catheterizations were performed in 19 patients at approximately 1 month after corrective surgery, which showed that systemic PO_2, mean PAP, Qp/Qs, Rp, Cp, and RC time were 80 (68–88) Torr, 20 (18–26) mmHg, 1.00 (1.00–1.00), 3.51 (2.64–5.09) Wood units m^2, 1.61 (1.13–2.01) mL/mmHg m^2, and 0.33 (0.30–0.37) sec, respectively (Table 1). Pulmonary arterial pressure significantly decreased after corrective surgery ($p = 0.0012$), but Rp, Cp, and RC time remained unchanged. At the time of discharge, 15 patients required oxygen supplementation, and

Table 1 Pulmonary hemodynamic data in 27 patients

	Preoperative, $N = 27$	Acute paulmonary vasodilator test, $N = 16$	Postoperative, $N = 19$	P value
PO_2, Torr	70 (59–75)	241 (151–287)	80 (68–88)	0.0143*
Mean PAP, mmHg	53 (36–60)	38 (32–43)	20 (18–26)	0.0012*
Qp/Qs	1.71 (1.24–2.45)	3.40 (2.90–4.78)	1.00 (1.00–1.00)	0.0001*
Rp, Wood unit m^2	7.47 (3.70–9.59)	2.48 (2.03–3.17)	3.51 (2.64–5.09)	0.1779
Cp, ml/mmHg m^2	0.99 (0.74–1.42)	2.45 (1.72–3.34)	1.61 (1.13–2.01)	0.8757
RC-time, s	0.45 (0.36–0.51)	0.40 (0.35–0.47)	0.33 (0.30–0.37)	0.0575

P values are expressed when preoperative and postoperative values are compared

PO_2 partial oxygen pressure, PAP pulmonary arterial pressure, Qp/Qs the ratio of systemic to pulmonary blood flow, Rp pulmonary arterial resistance, Cp pulmonary arterial compliance, RC-time resistance-compliance time

*$P < 0.05$

Table 2 The summary of histopathological findings

Heath–Edwards classification	
Grade 1	19
Grade 2	3
Grade 3	5
IPVD	
1	21
1.5	1
1.6	1
1.8	1
Undetermined	1
Extremely thickened of the media	7
Hypoplastic arterioles	3

IPVD the index of pulmonary vascular disease.

Table 3 Pulmonary hemodynamic parameters between patients with and without abnormal histopathological findings

	PVD (+), $N = 11$	PVD (−), $N = 16$	*p* value
Age, months	4 (3–8)	3 (2–6)	0.1991
Female	4	12	0.1638
PO_2, Torr	70 (59–75)	63 (59–68)	0.6773
Mean PAP, mmHg	53 (36–60)	40 (35–49)	0.2440
Qp/Qs	1.71 (1.24–2.45)	2.17 (1.85–2.90)	0.0906
Rp, Wood unit m^2	7.47 (3.70–9.59)	4.12 (3.51–5.08)	0.0961
Cp, ml/mmHg m^2	0.99 (0.74–1.42)	1.56 (1.45–1.88)	0.0047
RC-time, s	0.45 (0.36–0.51)	0.35 (0.31–0.54)	0.6176

PO₂ partial oxygen pressure, *PAP* pulmonary arterial pressure, *Qp/Qs* the ratio of systemic to pulmonary blood flow, *Rp* pulmonary arterial resistance, *Cp* pulmonary arterial compliance, *RC-time* resistance-compliance time

12 patients were administered oral pulmonary vasodilators including endothelin receptor antagonists or phosphodiesterase inhibitors. We observed 5 deaths (3 perioperative deaths and 2 late postoperative deaths).

The summary of histopathological findings is shown in Table 2. Hisopathologically proven PVD was observed in 11 patients. Based on the Heath–Edwards classification, 19 patients were categorized as grade 1, 3 as grade 2, and 5 as grade 3. The IPVD score was 1.0 in 21 patients, ≥ 1.1 in 3 patients. In one patient, IPVD was not determined because of a decrease in the number and hypoplasia of small pulmonary arteries. Histopathological findings showed extremely thickened media of the small pulmonary arteries in 7 patients, and hypoplasia of the small pulmonary arteries in 3 patients. No patient showed pulmonary venous disease. We observed 3 deaths among 9 patients with histopathologically proven PVD.

Patients were divided into two groups; patients with PVD ($N = 11$), including Heath–Edwards classification ≥ grade 3, IPVD ≥ 1.1, extremely thickened media, or hypoplastic pulmonary arteries, and those without PVD ($N = 16$). When pulmonary hemodynamic parameters were compared between the groups, Cp in patients with PVD was significantly lower than that in patients without PVD (0.99 [0.74–1.42] vs 1.56 [1.45–1.88] mL/mmHg m^2, p = 0.0047) (Table 3). Rp in patients with PVD was tend to be higher than that in patients without PVD, although this difference was not statistically significant (7.47 [3.70–9.59] vs 4.12 [3.51–5.08], $p = 0.0961$). There was no statistically significant difference in systemic PO$_2$, mean PAP, Qp/Qs, and RC time between the groups. Figure 1 shows the histopathological findings in two patients, in whom preoperative cardiac catheterizations revealed similar increases in pulmonary arterial pressure and resistance (data is shown in Table 4). In one patient (A) with Cp of 1.86 mL/mmHg m^2, histopathological findings showed almost normal pulmonary arteries, whereas, in another patient (B) with Cp of 0.99 mL/mmHg m^2, histopathological findings showed an extremely thickened media of the small pulmonary arteries, consistent with idiopathic pulmonary arterial hypertension.

The receiver operating characteristic curve was generated using preoperative Cp values as a predictor of PVD. For prediction of PVD, a Cp cut-off value of < 1.22 mL/mmHg m^2 yielded a sensitivity and a specificity of 93% and 64%, respectively. The area under the curve was 0.784. A Cp < 1.22 mL/mmHg m^2 can be a useful indicator to select patients who require a lung biopsy.

Discussion

Our study demonstrated that a lower Cp is a predictor of PVD in children with CHD–PAH. We recommend that the indications for a lung biopsy should be based on Rp–Cp coupling.

The pulmonary circulation consists of resistance and capacitance vessels, which allows a low-pressure circulatory system with pressure as low as approximately 15 mmHg despite receiving a high blood volume proportional to the entire cardiac output. In a patient with CHD–PAH, a change in the pulmonary blood flow alters Rp–Cp coupling which is affected by capillary recruitment. A reduction in the capacity of the pulmonary vascular bed owing to pulmonary arterial obstruction secondary to intimal proliferation, thickening of media, and/or hypoplasia of the pulmonary arteries leads to a reduction in capillary recruitment, or rarefaction, which can cause increased vascular resistance and decreased vascular compliance. Recent studies have shown that Cp is a more important parameter related to pulmonary hemodynamics than Rp to predict adverse outcomes or the development of late pulmonary arterial hypertension. Cp is the distensibility of pulmonary arterial tree and an important component
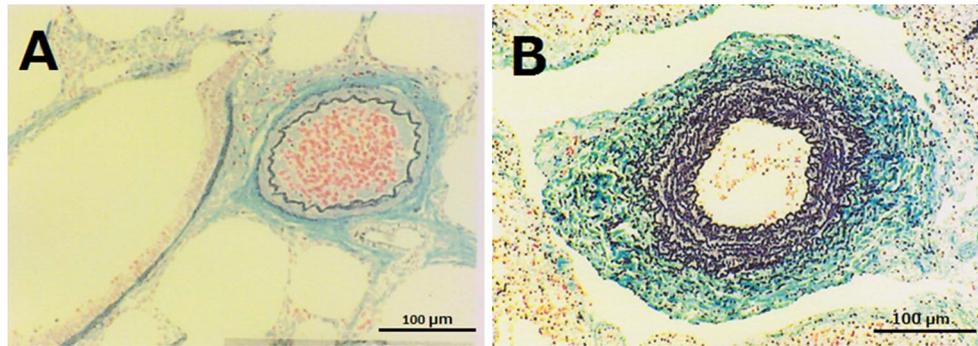
Fig. 1 The histopathological findings in the different patients (see Table 4). Left (**a**) shows mild intimal cellular proliferative change (Heath–Edwards classification grade 2) and IPVD 1.0. There was nei-ther medial thickness nor hypoplasia in **a**. Right (**b**) shows extremely thickened media of the pulmonary arteries, but a lack of an intimal proliferative change

Table 4 Clinical data of patients presented in Fig. 1

	Patient A	Patient B
Age	12 months	4 months
Diagnosis	VSD. PDA. Down syndrome	ASD. Down sydnrome
Qp/Qs	1.38	1.71
PA pressure, mmHg	76/42 (58)	79/29 (53)
O_2 loading test	68/36 (48)	56/18 (34)
Rp, Wood units m^2	9.28	7.47
Cp, ml/mmHg m^2	1.49	0.99
RC time, s	0.82	0.72
Outcome	Alive [postoperative PA pressure 31/8(19) mmHg]	Dead

Fig. 2 When the Rp–Cp coupling curve is shifted downward in patients with PVD, one Rp gives the different Cp

of the right ventricular workload. Therefore, a decrease in Cp is related to the poor morbidity and mortality in patients with different categories of PAH [16–20]. In patients with idiopathic PAH, a reduction in the capacity of the pulmonary vascular bed leads to a decrease in Cp which is associated with disease severity and lower survival rate. Cp is a strong independent prognostic factor and superior to Rp in assessing the right ventricular dysfunction in adults and children with idiopathic PAH [16–18]. In patients with PAH due to the left heart disease, it is known that there are two different hemodynamic subsets: isolated post-capillary PAH and combined post- and pre-capillary PAH [19,20]. Ghio et al. analyzed right heart hemodynamics in a cohort of 295 patients with heart failure and advanced left ventricular systolic dysfunction before and 1 year after heart transplantation. Cp remained lower in patients with combined pre- and post-capillary PAH than in those with isolated post-capillary PAH, although PAP, Rp and cardiac index were normalized after heart transplantation [19]. Previously, we have reported that a low preoperative Cp was related to an increased post-operative pulmonary arterial pressure in infants with CHD
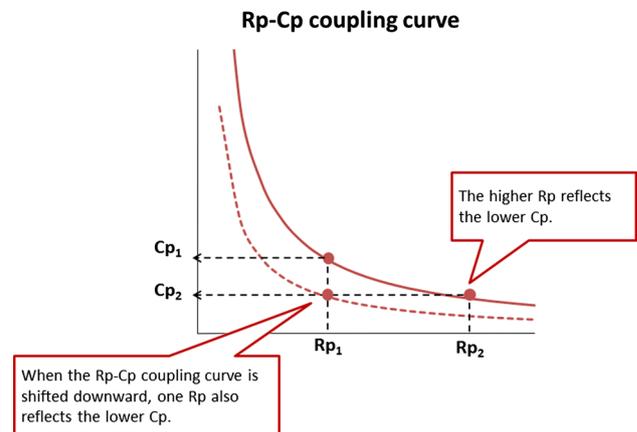
[10]. The present study suggests that a low Cp reflects greater pulmonary arterial rarefaction and a reduced capacity of the effective pulmonary vascular bed secondary to the histopathological changes in the pulmonary arteries.

A low Cp exactly reflects the existence of PVD because there exists an inverse relationship between Rp and Cp——a lower Cp indicates a higher Rp. However, Rp-Cp coupling is altered by the amount of pulmonary blood flow and left atrial pressure in patients with CHD [10,13]. The Rp-Cp coupling curve can be shifted downward when the pulmonary blood flow decreases in patients with PVD, which also leads to a decrease in Cp corresponding to one Rp (Fig. 2). Therefore, a lower Cp effectively reflects PVD in patients with CHD.

The classical Heath–Edwards classification is not sufficient to assess the pulmonary vasculature in the entire lung. Yamaki et al. describe that a high IPVD, which indicates intimal cellular and fibrous proliferative changes, is correlated with pulmonary arterial pressure. Patients

with an IPVD > 2.2 are not considered surgical candidates because that value indicates plexogenic pulmonary arteriopathy, which is a contraindication for surgery [6,8]. Intimal proliferative changes, a thickened media and/or hypoplasia of the pulmonary arteries are important histopathological findings related to adverse outcome in patients with CHD–PAH. Although the thickened media of the small pulmonary arteries is known to regress following reduction of the increased pressure load, patients may not survive postoperatively if adequate recanalization of the occluded portion is not achieved. Therefore, such patients should be classified as non-surgical candidates with an absolute contraindication for surgery. Histopathological changes in the pulmonary arteries in such patients do not differ from those observed in patients diagnosed with plexogenic pulmonary arteriopathy. The severe intimal lesions that occur abruptly at approximately 6 months of age are attributable to the thinning of the hypertrophied media of the small pulmonary arteries [8]. Hypoplasia of the pulmonary arteries is occasionally observed in patients with total anomalous pulmonary venous return with pulmonary venous obstruction or hypoplastic left heart syndrome with intact atrial septum, which is associated with poor outcomes. Our present study demonstrates that a low Cp can detect intimal proliferative changes as well as thickness of the media and/or hypoplasia of the pulmonary arteries, which result in adverse outcomes.

Our study included a limited number of patients, and no patient showed an IPVD score ≥ 2.2 (an absolute contraindication for surgery). Although the present study showed that a low Cp was a predictor of PVD, Rp in patients with PVD tended to be higher than that in patients without PVD. If Rp in patients with PVD is higher than that in patients with PVD, multivariate analysis including both parameters should be performed and further investigation is warranted. Otherwise, two methods are commonly used to calculate Cp in clinical practice: (1) the pulse pressure method, which uses the 2-element Windkessel model with flow waveform and resistance as inputs to estimate the compliance value that best predicts systolic and diastolic pressures. (2) A method derived from the exponential decay of the diastolic pulmonary arterial pressure wave method in vivo. Based on previous studies, the differences observed in the RC time constant can be attributed to the different methods used to calculate compliance. In the present study, we have chosen the pulse pressure method to calculate Cp because ours was a retrospective study, and we used parameters obtained after performing cardiac catheterization.

In conclusions, we demonstrated that Cp is a predictor of PVD in patients with congenital heart disease. We propose a Cp value < 1.22 mL/mmHg m^2 can be viewed as a useful parameter of pulmonary hemodynamic to choose candidates who require a lung biopsy.

Compliance with ethical standards

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