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Biomarker and shear stress in secondary pediatric pulmonary hypertension

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Background/aim: Endothelial dysfunction, tissue damage, inflammation, and microthrombosis are involved in the pathogenesis of pulmonary hypertension (PH), which may be present as a complication of congenital heart diseases. This study aims to identify how indicators of endothelial dysfunction (shear stress), tissue damage (brain natriuretic peptide and troponin T), inflammation (C-reactive protein (CRP)), and microthrombosis (D-dimer and von Willebrand factor) are altered in children with congenital left-to-right shunting.

Materials and methods: This is a review of 25 children who developed PH due to congenital left-to-right shunting, 40 children who underwent corrective surgery for congenital left-to-right shunting, and 40 healthy children.

Results: Serum brain natriuretic peptide (BNP), CRP, and CA-125 levels were significantly increased and shear stress was significantly decreased in children with PH (P = 0.001, P = 0.044, P = 0.012, and P = 0.011). A BNP level of >225 pg/mL had a sensitivity of 95.3% and specificity of 92.4%, whereas a CRP level of >2.2 IU/L had a sensitivity and specificity of 87.5%, and a CA-125 level of >35 IU/mL had a sensitivity of 92.2% and a specificity of 90.4% for PH. Shear stress of <2.5 dyn/cm^2 had a sensitivity of 84.8% and specificity of 92.9%.

Conclusions: A combination of BNP, CRP, CA-125, and shear stress might be used to predict the development of PH during follow-up of children with congenital left-to-right shunting.

Key words: Biomarkers, child, congenital heart defects, pulmonary hypertension, shear strength

1. Introduction

Pulmonary hypertension (PH) is a chronic disease that is characterized by progressive elevation in pulmonary artery pressure. This disease may be present as an adverse outcome of congenital heart diseases. The pathogenesis of PH is primarily based on endothelial dysfunction within pulmonary vasculature, which eventually leads to medial thickening, intimal fibrosis, inflammation, and microthrombosis. Tissue damage, inflammation, and microthrombi formation are also involved in the pathogenesis of PH (1–4).

Endothelial dysfunction within systemic circulation occurs as a result of reduced wall shear stress. Wall shear stress is a frictional force caused by a viscous drag along the inner wall of the artery. This force modulates endothelial function and, if altered, exerts a detrimental effect on cardiovascular health. However, little is known about the endothelium-specific response to wall shear stress within the pulmonary vasculature and its role in the pathogenesis and progression of pulmonary vascular diseases (5,6).

Like shear stress, certain biomarkers can be used to track the course of PH in children. For instance, brain natriuretic peptide (BNP) and troponin T are indicators of myocardial damage in the right ventricle, and they both have diagnostic and prognostic value for children who have PH. Similarly, C-reactive protein (CRP) is an indicator of inflammation that might be used in the follow-up of children with PH. On the other hand, D-dimer and von Willebrand factor (vWF) might indicate the formation of microthrombi in affected children. CA-125 might also be considered as a potential biomarker for pediatric PH because serum CA-125 levels correlate significantly with pulmonary artery pressures (7–10).

This study aims to identify how these indicators of endothelial dysfunction (shear stress), tissue damage (BNP and troponin T), inflammation (CRP), and microembolization (D-dimer and vWF) are altered in children who have congenital heart diseases with left-to-right shunting. The present study also aims to determine whether these indicators can be used to predict the development of PH in children with congenital left-to-right shunting.

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2. Materials and methods

This study has been approved by the Institutional Review Board and the Ethical Committee of the Gazi University Medical Faculty in Ankara, Turkey.

2.1. Study design

This is a cross-sectional study of 105 children (55 males, 50 females) who consecutively underwent consultation in the Department of Pediatric Cardiology at Gazi University Hospital between January 2012 and December 2013. The study cohort consisted of three groups. Group I included 25 children who were diagnosed with secondary PH (in relation to congenital heart diseases) according to the catheter angiography findings. These children represented neglected cases of congenital heart diseases with left-to-right shunting eventually diagnosed as Eisenmenger syndrome. Group II consisted of 40 children who underwent corrective surgery for congenital heart defects with left-to-right shunting with no findings of PH based on preoperative cardiac catheterization findings. Group III was made up of 40 healthy children who had innocent murmurs.

Children with acute or chronic bacterial and viral infections, diabetes mellitus, systemic hypertension, hypercholesterolemia, cardiomyopathies, valvular heart diseases, coagulation disorders, hepatic dysfunction, and renal failure were excluded.

2.2. Echocardiography examination

All patients were examined by a single experienced echocardiographer who was blinded to the results of the rheological measurements and who used two-dimensional, pulse-wave Doppler echocardiography with a 2.5-MHz transducer (Vivid 7, GE Vingmed Ultrasound, Horten, Norway). The main pulmonary artery and the left and right pulmonary artery branch diameters were measured from the parasternal short axis at the level of pulmonary artery bifurcation. Measurements were made in the lateral–medial plane at end diastole.

2.3. Cardiac catheterization

Groups I and II consisted of 80 children who had congenital heart diseases. These children underwent routine cardiac catheterization and hemodynamic studies that were performed with intravenous midazolam sedation. Pressure measurements were recorded using fluid-filled catheters connected to pressure transducers. Oxygen consumption was estimated based on age, sex, and heart rate, according to the LaFarge–Miettinen formula (11). Pulmonary (Qp) and systemic (Qs) blood flow levels were calculated using the Fick equation and indexed for body surface area. The ratio of Qp/Qs blood flow, pulmonary (Rp) and systemic (Rs) vascular resistance, and the Rp/Rs ratio were calculated according to the standard formulas (12).

2.4. Rheological measurements

Rheological measurements were made by a single experienced physiologist who was blinded to the clinical and echocardiographic findings. Plasma viscosity was determined in ethylenediaminetetraacetic acid plasma by using a viscometer of the capillary type at 25 °C (Processer Viscosity System 1, Lauda, Germany). Whole blood viscosity was measured in ethylenediaminetetraacetic acid plasma using a rotational viscometer (Contraves LS 30, Contraves, Switzerland) at a high shear rate (94.5/s) at 37 °C (13). Peak and mean wall shear stress (dyn/cm^2) were calculated as previously described (13): shear stress = 4 × blood viscosity (P) × blood velocity (cm/s)/internal diameter of the main pulmonary artery (cm).

2.5. Laboratory studies

Serum concentrations of BNP, troponin T, D-dimer, and CA-125 were measured by electrochemiluminescence immunoassay (Elecsys 2010 Analyzer, Roche Diagnostics, Mannheim, Germany). Serum uric acid level was determined with radioimmunoassay (L X 20-Pro Analyzer, Beckman Coulter, Woerden, the Netherlands). Serum concentrations of CRP were measured by enzyme-linked immunosorbent assay (Sigma-RAB0096 ELISA kit, Sigma-Aldrich Corporation, Berlin, Germany). vWF serum concentration was defined by latex immunoassay (STA-Liatest vWF, Triolab AB, Gothenburg, Sweden). Intraassay coefficients of variation were 5.3%, 3.8%, 7.8%, 6.2%, 5.0%, 5.0%, and 6.2% whereas interassay coefficients of variation were 1.8%, 1.5%, 10.0%, 5.7%, 4.1%, 4.0%, and 5.7% for BNP, uric acid, troponin T, CRP, D-dimer, vWF, and CA-125, respectively.

2.6. Statistical analysis

Collected data were analyzed with SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Data were expressed as either mean ± standard deviation (range: minimum–maximum) or numbers or percentages when appropriate. A Smirnov–Kolmogorov test was used to test the distribution of data. One-way ANOVA, Kruskal–Wallis, and Mann–Whitney U tests were used for comparisons. A Bonferroni adjustment was applied for all possible group comparisons, controlling for type I errors. Probable relationships were evaluated with a Pearson correlation test. The cutoff levels for inflammatory biomarkers were determined using a receiver operating characteristic (ROC) analysis. Two-tailed P-values less than 0.05 were accepted to be statistically significant. Since secondary pediatric PH is a relatively rare disease, all of the children who were diagnosed with this disease were enrolled in this study. The sizes of the other two subgroups were based on the size of the PH group. Therefore, a retrospective post hoc analysis was carried out and it was determined that a cohort size of 105 children (40 healthy controls, 40 children with congenital heart defects, and 25 children with secondary

PH) had 58.6% power to detect a difference at the 0.05 significance level.

3. Results

Table 1 summarizes the demographic and clinical characteristics of the study cohort. Mean age was significantly lower (P = 0.001), body weight was significantly lower (P = 0.001), body height was significantly shorter (P = 0.001), and body mass index was significantly lower (P = 0.001) in Group I than in Group II. When compared with Group II, serum BNP, troponin T, CRP, and CA-125 levels were significantly higher in Group I (P = 0.001, P = 0.042, P = 0.044, and P = 0.001, respectively). Moreover, vascular diameter was significantly larger, blood flow velocity was significantly higher, and shear stress was significantly lower in Group I (P = 0.032, P = 0.044, and P = 0.001, respectively).

Table 2 lists the echocardiography and catheter angiography findings of the reviewed children. Tricuspid regurgitation velocity was significantly higher (P = 0.001), tricuspid annular plane systolic excursion was significantly lower (P = 0.001), and aortic annulus and pulmonary artery diameters were significantly larger in the PH group (P = 0.004 and P = 0.001, respectively). Systolic right-ventricle pressure, diastolic left-ventricle pressure, and systolic, diastolic, and mean pulmonary artery pressures were also significantly higher in these children (P = 0.001, P = 0.018, P = 0.001, P = 0.003, and P = 0.001, respectively). On the contrary, Qp and Qp/Qs were significantly lower and Rp and Rp/Rs were significantly higher (P = 0.005, P = 0.022, P = 0.026, and P = 0.001, respectively).

The Figure shows the receiver operating characteristic curves for BNP, CRP, and CA-125. The cutoff values for BNP, uric acid, troponin T, CRP, D-dimer, vWF, CA-125, and shear stress were assigned as 305 pg/mL, 4.2 mg/dL, 0.025 ng/mL, 2.2 IU/L, 150 ng/mL, 160 IU/dL, 35 IU/mL, and 2.5 dyn/cm^2, respectively (Table 3).

Serum BNP levels significantly correlated with systolic right-ventricle pressure (r = 0.411, P = 0.003), diastolic right-ventricle pressure (r = 0.316, P = 0.005), and tricuspid annular plane systolic excursion (r = –0.592, P = 0.001). Serum CRP levels significantly correlated with ejection fraction (r = –0.625, P = 0.001) and fractional shortening (r = –0.466, P = 0.003). Serum CA-125 levels correlated significantly with tricuspid annular plane systolic excursion (r = –0.347, P = 0.003). Shear stress values correlated significantly with ejection fraction (r = –0.572, P = 0.001) and fractional shortening (r = –0.495, P = 0.001).

Table 1. Demographic and clinical characteristics of the study cohort.

	Group I (n = 25)	Group II (n = 40)	Group III (n = 40)	P
Age (years)	7.5 ± 5.7	11.0 ± 0.6	10.9 ± 0.9	0.001†*
Sex (male/ female)	12/13 (48.0%/52.0%)	20/20 (50%/50%)	23/17 (57.5%/42.5%)	0.703
Body height (cm)	110.8 ± 38.0	134.2 ± 30.7	145.4 ± 24.6	0.001†*
Body weight (kg)	22.4 ± 16.8	37.2 ± 10.5	41.9 ± 17.8	0.001†*
Body mass index (kg/m^2)	14.6 ± 4.1	20.7 ± 2.8	19.9 ± 3.6	0.001†*
Congenital heart defects				
Ventricular septal defect	11 (44.0%)	21 (52.5%)		0.321
Patent ductus arteriosus	7 (28.0%)	12 (30.0%)		
Atrioventricular septal defect	7 (28.0%)	5 (12.5%)		
Atrial septal defect	-	2 (5.0%)		
Biochemical measurements				
Brain natriuretic peptide (pg/mL)	870.1 ± 75.7	316.7 ± 18.4	12.5 ± 19.1	0.001†*
Troponin T (ng/mL)	0.044 ± 0.022	0.026 ± 0.001	0.017 ± 0.007	0.042†*
C-reactive protein (IU/L)	3.2 ± 0.8	1.9 ± 0.2	1.8 ± 0.2	0.044†*
D-dimer (ng/mL)	111.4 ± 42.7	148.2 ± 21.6	137.5 ± 24.1	0.642
von Willebrand factor (IU/dL)	189.3 ± 18.4	167.4 ± 19.2	132.5 ± 14.3	0.610
CA-125 (IU/mL)	68.5 ± 2.3	32.5 ± 1.5	13.8 ± 0.7	0.001†*
Rheological measurements				
Vascular diameter (cm)	2.6 ± 1.1	1.8 ± 0.5	1.5 ± 0.4	0.032†*
Blood flow velocity (c/s)	1.8 ± 0.7	1.6 ± 0.5	1.2 ± 0.2	0.044†*
Shear stress (dyn/cm^2)	2.8 ± 1.2	5.4 ± 0.6	7.1 ± 3.1	0.001†*

*P < 0.05 was accepted to be statistically significant.
†Statistical significance is detected between Group I and Group II.

Table 2. Echocardiography and catheter angiography findings of the study cohort.

	Group I (n = 25)	Group II (n = 40)	Group III (n = 40)	P
Echocardiography findings				
Ejection fraction (%)	65.7 ± 11.5	77.9 ± 8.0		0.656
Fractional shortening (%)	35.6 ± 7.8	38.9 ± 7.6		0.377
Tricuspid regurgitation velocity	3.4 ± 1.0	2.6 ± 0.6		0.001†*
Tricuspid annular plane systolic excursion	2.6 ± 0.4	2.8 ± 0.6		0.001†*
Aortic annulus diameter (mm)	22.1 ± 3.8	20.0 ± 4.2		0.004‡*
Pulmonary artery annulus diameter (mm)	24.3 ± 3.5	21.8 ± 4.0		0.001†*
Right pulmonary artery diameter (mm)	14.8 ± 3.4	13.0 ± 2.8		0.174
Left pulmonary artery diameter (mm)	15.7 ± 3.5	13.5 ± 3.0		0.096
Catheter angiography findings			77.7 ± 5.6	
Systolic pulmonary artery pressure (mmHg)	95.4 ± 23.3	31.0 ± 7.4	42.6 ± 7.8	0.001*
Diastolic pulmonary artery pressure (mmHg)	47.5 ± 19.3	16.8 ± 13.5	2.0 ± 0.5	0.003*
Mean pulmonary artery pressure (mmHg)	69.4 ± 20.0	17.9 ± 6.8	3.3 ± 0.6	0.001*
Right atrium pressure (mmHg)	5.2 ± 2.7	8.8 ± 8.2	19.3 ± 4.1	0.591
Systolic right-ventricle pressure (mmHg)	100.0 ± 20.9	40.2 ± 11.5	20.2 ± 4.2	0.001*
Diastolic right-ventricle pressure (mmHg)	4.6 ± 3.7	3.0 ± 1.8	12.8 ± 2.3	0.031
Systolic left-ventricle pressure (mmHg)	104.1 ± 21.5	103.5 ± 23.3	13.2 ± 3.1	0.595
Diastolic left-ventricle pressure (mmHg)	6.7 ± 5.1	4.0 ± 2.8		0.018*
Pulmonary capillary wedge pressure (mmHg)	14.7 ± 4.5	7.0 ± 4.2		0.064
Pulmonary flow (m/s)	5.1 ± 3.7	12.6 ± 6.2		0.005*
Systemic flow (m/s)	3.7 ± 0.7	4.8 ± 1.5		0.078
Pulmonary/systemic flow	1.5 ± 1.2	2.6 ± 0.6		0.022*
Pulmonary vascular resistance (U/m^2)	15.7 ± 10.3	6.4 ± 0.9		0.026*
Systemic vascular resistance (U/m^2)	21.8 ± 9.6	14.7 ± 5.5		0.087
Pulmonary/systemic vascular resistance	0.8 ± 0.6	0.1 ± 0.1		0.001*

*P < 0.05 was accepted to be statistically significant.
†Statistical significance is detected between Group I and Group III.
‡Statistical significance is detected between Group II and Group III.

4. Discussion

A biomarker can be defined as a parameter that is objectively measured and evaluated as an indicator of a normal biologic mechanism, pathogenic process, or pharmacologic response. A variety of biomarkers associated with inflammation, coagulation, and myocardial stretching can be used to specify the progression of this disease. Although several biomarkers are utilized to assess and follow adults with PH, these markers have not been validated in pediatric PH (9,10,14).

BNP has been addressed as the most frequently studied biomarker in adults and children with PH (15,16). A systematic review of 14 studies conducted on children with PH showed that BNP had good prognostic value and significantly correlated with mortality (17). It has also been clarified that BNP levels differ significantly in children with primary and secondary PH, but that BNP values remain constant in the primary and secondary PH groups (18).

In this study, serum BNP concentrations of the healthy children and children with congenital heart diseases were significantly lower than those of children with Eisenmenger syndrome. Moreover, it was specified that BNP values correlated significantly with systolic right-ventricle pressure, diastolic right-ventricle pressure, and tricuspid annular plane systolic excursion. These findings imply that an increase in BNP reflects myocardial strain in the right ventricles of children with congenital left-to-right shunting.

CRP is an inflammatory marker that has been identified as a prognostic marker in adults with Eisenmenger syndrome. Elevated levels of CRP can be used to distinguish individuals with increased cardiovascular morbidity and mortality among apparently healthy subjects, patients with coronary artery disease, or those with atherosclerosis (19–21). It was found that serum concentrations of highly sensitive CRP positively correlated with pulmonary artery pressures in children with cystic fibrosis (22). Similarly, a

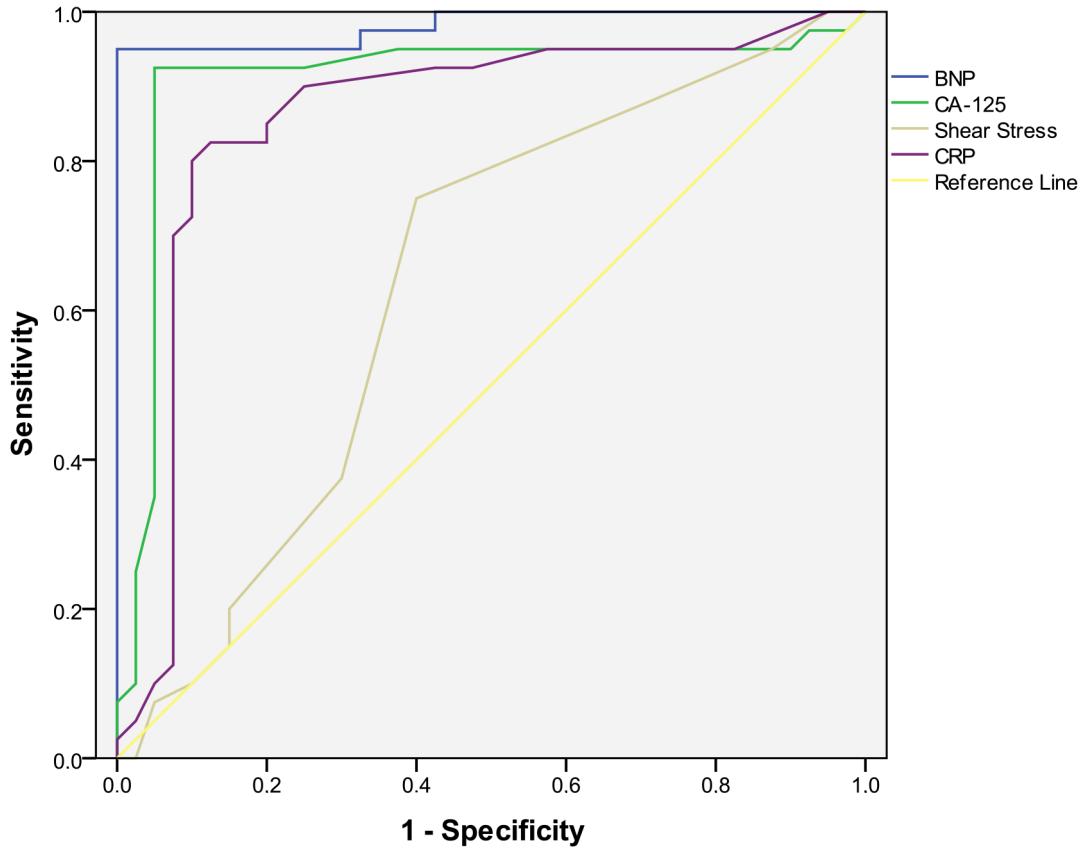

Figure. ROC curves for BNP, CRP, CA-125, and shear stress show the predictive power of these parameters when their cutoff values were assigned as 255 pg/mL, 2.2 IU/L, 35 IU/mL, and 2.5 dyn/cm^2, respectively.

Table 3. Predictive power of biomarkers and shear stress.

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	χ^2	P
Brain natriuretic peptide	96.1%	93.2%	82.8%	87.1%	62,596	0.001*
Troponin T	70.2%	28.3%	49.1%	46.2%	146,460	0.330
C-reactive protein	88.0%	88.1%	81.7%	82.1%	73,380	0.001*
D-dimer	33.8%	59.6%	54.3%	51.5%	137,030	0.225
von Willebrand factor	51.5%	68.5%	68.5%	56.0%	166,455	0.318
CA-25	92.2%	90.4%	86.7%	84.5%	55,132	0.001*
Shear stress	84.8%	82.9%	85.3%	82.4%	37,040	0.001*

*P < 0.05 was accepted to be statistically significant.

Turkish study found that that highly sensitive CRP levels were significantly higher in children with secondary PH when compared to healthy children (23).

This study was also able to detect a significant increase in the serum CRP levels of children who were diagnosed with Eisenmenger syndrome. In addition, CRP values correlated significantly with ejection fraction and fractional shortening values. These findings suggest that increased CRP might reflect the inflammatory changes that proceed within the myocardial tissues of children with congenital left-to-right shunting.

Serum CA-125 concentrations are markedly elevated during myocardial infarction, and this increase correlates significantly with systolic and mean pulmonary artery

pressures. Patients with chronic obstructive pulmonary disease also have high CA-125 levels, which significantly correlate with systolic pulmonary artery pressure, right-ventricular myocardial performance index, and fractional area change. It has been reported that CA-125 is a valuable biomarker in evaluating the efficiency of short-term treatment for right heart failure, but the combination of CA-125 and BNP might even be more valuable (24–26).

This study demonstrated a significant increase in serum CA-125 levels of children with secondary PH. Additionally, CA-125 values were found to correlate significantly with right-ventricle functional area change and tricuspid annular plane systolic excursion values. These findings could be interpreted as a body of evidence for observing increased CA-125 as an indicator of myocardial damage in the right ventricles of children with congenital left-to-right shunting. Therefore, a combination of increased BNP, CRP, and CA-125 concentrations could be used to predict the development of PH during the clinical course of congenital heart diseases with left-to-right shunting in children.

The pathogenesis of PH is associated with a remodeling process that increases vascular diameter, causes vascular thickening, and induces vascular stiffness within pulmonary tissues. It has been noted that patients with PH have significantly reduced vascular distensibility and blood flow in pulmonary vasculature (27). Truong et al. were the first to report on the significant reduction in shear stress in children and adolescents with PH (28). Schäfer et al. later concluded that shear stress throughout the main pulmonary artery is decreased in PH, and that this decrease is significantly associated with catheter angiography findings (29). High oscillatory shear index and low wall shear stress measured with three-dimensional magnetic resonance imaging were considered potential markers that could be used to predict increased pulmonary artery pressure in patients with a high index of suspicion for PH (30).

This work also reports that shear stress is significantly reduced in the pulmonary vasculature of children with secondary PH. The major reasons for this significant reduction are an increase in vascular size and decrease in vascular distensibility. This attenuation in shear stress induces endothelial proliferation and medial hypertrophy, eventually leading to right-ventricular failure. Accordingly, decreased shear stress may be used to predict the emergence of PH in association with congenital left-to-right shunting.

In conclusion, it has been well established that BNP, CRP, and shear stress have prognostic value in adults with Eisenmenger syndrome, whereas CA-125 reflects cardiac functions in adults with heart failure. This study points out that BNP, CRP, and CA-125 are significantly increased while shear stress is significantly decreased in children with Eisenmenger syndrome. Therefore, the combination of BNP, CRP, CA-125, and shear stress can be used to predict the development of PH during follow-up of children with congenital left-to-right shunting. However, the findings of the present study should be carefully interpreted as their significance is limited by the small cohort size, absence of longitudinal data, and inability to use cardiac magnetic resonance imaging. Another limiting factor was the fact that the adoption of the La Farge formula for oxygen consumption in the assessment of pulmonary blood flow (and vascular resistance) was assessed by an indirect Fick method. This may represent an important source of error, particularly in patients younger than 2 years old (31). Further research is needed to clarify the role of biomarkers and shear stress in the development of PH during the clinical course of congenital heart diseases.

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