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Factors associated with the uncorrectable congenital heart disease in children with pulmonary arterial hypertension

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ABSTRACT

BACKGROUND Pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) is a common complication of uncorrected left-to-right shunt defects in acyanotic CHD and a frequent type of pulmonary hypertension in youth. The standards for operability in left-to-right shunts with increased pulmonary vascular resistance are not universally agreed upon. This study aimed to identify variables associated with uncorrectable lesion in children with PAH-CHD.

METHODS This retrospective study used a database of all children who underwent cardiac catheterization at Sanglah Hospital, Bali, from May 2009 to April 2021. Pulmonary hypertension was defined as pulmonary artery pressure of >25 mmHg, while correctability was a fall of >20% in the pulmonary arterial resistance index (PARI) with final value of <6 WU/m^2 when doing an acute vasoreactivity test using 100% oxygen. The analyses were carried out using SPSS software version 22.0 (IBM Corp., USA).

RESULTS A total of 104 children were included. Cardiac catheterization showed that the uncorrectable group had a higher PARI (14.4 [8.88] WU/m^2 *versus* 8.43 [3.85] WU/m^2) and lower flow ratio (1.27 [0.83] *versus* 1.47 [0.77]) at baseline. In terms of correctability, pre-tricuspid lesions (OR = 0.05; 95% CI = 0.01–0.47; p = 0.01) and younger age group (OR = 0.32; 95% CI = 0.12–0.85; p = 0.01) were protective variables, whilst high baseline PARI (OR = 4.54; 95% CI = 1.64–12.57; p = 0.01) was unfavorable.

CONCLUSIONS High baseline PARI was the most significant variable in predicting uncorrectable left-to-right shunt defects in PAH-CHD.

KEYWORDS children, congenital heart disease, heart septal defects, pulmonary hypertension

Patients with uncorrected congenital heart disease (CHD) are more likely to develop pulmonary arterial hypertension (PAH), which is diagnosed as pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) and typically results from a significant systemic-to-pulmonary shunt that is present from infancy.[1] The remodeling of the pulmonary vascular system leads to increased pulmonary arterial pressure (PAPs). PAH-CHD accounts for over 40% of all PAH cases and is the second most prevalent form among children. This form is also prevalent in developing and impoverished regions.[2] PAH-CHD has a significant negative impact on health-related quality of life across several physical and mental domains, including physical functioning, symptoms at rest and during physical activity, and social functioning. Other impacts of PAH-CHD are adverse effects from medication, uncertainty about prognosis, anxiety, and depression in patients and caregivers.[3]

Patients with uncorrected PAH-CHD may not have undergone corrective surgery or transcatheter device closure. Moreover, late repair of CHD with

intra- or extracardiac shunt is an important etiology of pulmonary hypertension. Therefore, prompt repair of such pathology is crucial since, in most cases, early shunt closure can halt the progression of pulmonary hypertension in the future.[4] However, procedures to fix the defect might increase morbidity in certain circumstances.

Cardiac catheterization is required to plan a surgical repair when an intervention to close a cardiac defect during catheterization is impossible. Cardiac catheterization can capture information such as pressure measurements, blood oxygen saturation, estimated cardiac output, and pulmonary vascular resistance (PVR), as well as angiographic images using fluoroscopic imaging during contrast injection. The integrated cardiac center at Sanglah Hospital, Bali, Indonesia, a tertiary healthcare facility that receives regional referrals from Bali, Nusa Tenggara, and some parts of the East Java province, has performed cardiac catheterizations and cardiac surgeries since 2009. In Sanglah Hospital, correctability in CHD is defined during an acute vasoreactivity test (AVT) using 100% oxygen.[5] However, there is currently no consensus on the criteria for correctability in left-to-right shunts with elevated PVR. The practical definition of correctability may also vary between centers. Therefore, this study aimed to determine the variables predicting uncorrectable lesion in children with PAH-CHD.

METHODS

This retrospective study used a database comprising the medical data of all children who underwent cardiac catheterization at Sanglah Hospital, Bali, Indonesia, from May 2009 to April 2021. Variables regarding age, sex, anthropometric measurements, related to clinical condition and hemoglobin (Hb) level, as well as anatomy and hemodynamic status from cardiac catheterization of all children aged 3 months and above were extracted from the database. The Research Ethics Committee of the Faculty of Medicine Universitas Udayana, Bali, Indonesia approved this study (Approval No: 2230/UN14.2.2.VII.14/LT/2021). The need for informed consent was waived by the ethics committee.

During cardiac catheterization, anatomical defects were identified, and intracardiac pressures were measured before and after an AVT using 100% oxygen. Defect size was classified according to the type of defect. Ventricular septal defects (VSDs) were considered small if they had a diameter <5 mm, moderate VSD had a diameter ≥5 and <10 mm; while large VSD had a diameter ≥10 mm.[6] Small atrial septal defects (ASDs) in infancy had a diameter >3 mm to ≤5 mm, moderate defects measured >5 mm to 9 mm, and large defects were ≥10 mm. After infancy, the ASD size was interpreted as follows: <10 mm as small, 10–20 mm as moderate, and >20 mm as large.[7] Patent ductus arteriosus (PDA) was considered small at 1.5 to 3 mm, moderate between 3 and 5 mm, and large if it exceeded 5 mm.[8] Mean pulmonary arterial pressure (mPAP) was the pressure in the pulmonary artery measured during a catheterization procedure. Mean systemic arterial pressure was defined as the aortic pressure measured during the catheterization procedure. Pulmonary arterial resistance index (PARI) was defined as the absolute value of pulmonary artery resistance against the patient's body surface area, representing body size's effect on blood flow. The flow ratio was the total pulmonary blood flow to the total systemic blood flow. Pulmonary hypertension was defined as PAP greater than 25 mmHg, as determined by cardiac catheterization. Correctability as a dependent variable was defined as a fall in the PARI of >20% with final values of <6 WU/m^2 during the AVT using 100% oxygen. These values were the basis for classifying PAH-CHD as correctable or uncorrectable.

Data were analyzed using SPSS software for Windows version 22.0 (IBM Corp., USA). Descriptive data are summarized as means and percentages. The data in this study were not normally distributed. For the univariate analysis, the chi-square test was used to analyze the association between independent and dependent variables. Post-hoc analysis using the logistic regression test was conducted to determine the most significant predictors of uncorrectable PAH-CHD. The results are reported as odds ratios (ORs) and 95% confidence intervals. *p*-values lower than 0.05 were deemed statistically significant.

RESULTS

A total of 104 pediatric patients with PAH-CHD identified during cardiac catheterization were included in this study. They were divided into three age groups: infants (3–11 months 29 days old), children (1–12 years 11 months old), and adolescents (13–18 years old). Most of the participants in the uncorrectable group were

Table 1. Variables associated with uncorrectable CHD in children with PAH (N = 104)

Variables	Uncorrectable (N = 26)	Correctable (N = 78)	Univariate analysis*		Multivariate analysis†	
			OR (95% CI)	*p*	OR (95% CI)	*p*
Age (months), n, mean (SD)			-	-	-	-
Infants	11, 6.91 (3.21)	15, 6.4 (2.41)				
Children	9, 81.1 (43.89)	56, 52.7 (41.89)				
Adolescents	6, 187.33 (23.56)	7, 189.86 (24.59)				
Infant, n (%)	11 (42)	15 (19)	0.32 (0.12–0.85)	**0.01**‡	0.25 (0.07–0.89)	**0.03**‡
Male sex, n (%)	9 (35)	31 (40)	1.25 (0.49–3.15)	0.64	1.39 (0.42–4.61)	0.58
Height (cm), mean (SD)			-	-	-	-
Infants	61.18 (8.39)	57.8 (4.83)				
Children	105.1 (18.16)	93.52 (23.16)				
Adolescents	156.5 (3.73)	148.57 (12.83)				
Weight (kg), mean (SD)			-	-	-	-
Infants	5.09 (1.55)	4.88 (0.96)				
Children	17.02 (6.98)	13.04 (8.25)				
Adolescents	41.58 (6.89)	38.86 (8.91)				
Pneumonia, n (%)	6 (23)	8 (10)	-	-	-	-
Clinical Down syndrome, n (%)	4 (15)	8 (10)	1.59 (0.44–5.79)	0.48	1.14 (0.21–6.29)	0.88
Hb (g/dl), mean (SD)	13.79 (2.07)	12.27 (1.61)				
Defect types						
Simple defect, n				**0.01**‡		**0.01**‡
Pre-tricuspid shunt	5	1	0.05 (0.01–0.47)		0.04 (0.0–0.41)	
Post-tricuspid shunt	19	74	1.00		1.00	
Combined defects, n			-	-	-	-
VSD + PDA	2	3				
Defect size, n				0.28		0.35
Small to moderate	11	24	0.61 (0.24–1.5)		0.55 (0.16–1.9)	
Large	15	54	1.00		1.00	
Hemodynamic status at baseline, mean (SD)			-	-	-	-
mPAP (mmHg)	47.92 (14.69)	46.1 (14.34)				
mSAP (mmHg)	64.44 (14.73)	66.58 (12.81)				
PARI (WU/m^2)	14.4 (8.88)	8.43 (3.85)				
FR	1.27 (0.83)	1.47 (0.77)				
PARI of >8, n (%)	20 (77)	33 (42)	4.54 (1.64–12.57)	**0.01**‡	3.76 (1.08–13.14)	**0.04**‡
FR of <1.5, n (%)	20 (77)	49 (63)	1.97 (0.71–5.48)	0.19	0.79 (0.21–2.96)	0.72
Hemodynamic status after AVT, mean (SD)			-	-	-	-
PARI, WU/m^2	8.95 (5.67)	1.69 (1.09)				
FR	1.67 (1.23)	6.27 (9.29)				

AVT=acute vasoreactivity test; CHD=congenital heart disease; CI=confidence interval; FR=flow ratio; Hb=hemoglobin; mPAP=mean pulmonary arterial pressure; mSAP=mean systemic arterial pressure; PAH=pulmonary arterial hypertension; PARI=pulmonary arterial resistance index; OR=odds ratio; PDA=patent ductus arteriosus; SD=standard deviation; VSD=ventricular septal defect

*Chi-square test; †logistic regression test; ‡significant if $p<0.05$

infants (42%), and most in the correctable group were children (72%). Both groups had a female predominance with a male-to-female ratio of 1:1.8. The uncorrectable group had a higher proportion of patients with Down syndrome and pneumonia and higher Hb levels. From the baseline pressure measurement during cardiac catheterization, the correctable group had lower mPAP, lower PARI, and higher flow ratio (Table 1).

The most frequent anatomical cardiovascular disorders were VSD (48 of 102) and PDA (42 of 102), with the most frequent defect size being large (69 of 102). Hemodynamic status was measured before and after the AVT using 100% oxygen. A baseline PARI of >8 WU/m^2 was found in 42% of patients in the correctable group (33 of 78) compared with 77% in the uncorrectable group (20 of 26).

Variables hypothesized to correlate with the uncorrectable PAH-CHD were analyzed. Post-hoc analysis showed that a type of CHD, age group, and baseline PARI were independent variables associated with uncorrectable defects. Furthermore, a baseline PARI of >8 WU/m^2 had the highest OR for predicting uncorrectable defects in children with PAH-CHD (Table 1).

DISCUSSION

This study found that age at presentation were correlated with the correctability of pulmonary hypertension. Infants had more severe pulmonary hypertension than older children. The most common defect in the uncorrectable group was a large PDA, in which Eisenmenger's physiology usually develops in early infancy. These results are similar to those of a study by Chinawa et al[9] who reported that infants with PDA were more likely to have pulmonary hypertension than older children.

The female predominance in the present study is similar to that in a study by the Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension registry, which involved 456 children aged 3 months to 18 years. Females were more prevalent in populations with pulmonary hypertension due to any cause (59%) and in those with PAH-CHD (62%).[10]

Pulmonary hypertension is a complication of CHD in individuals with Down syndrome. According to Bush et al,[11] children with Down syndrome and CHD are 5 times more likely to be diagnosed with pulmonary hypertension than those with Down syndrome only. They also have a higher prevalence of pulmonary hypertension than patients with non-syndromic CHD.[12] Various studies have reported that patients with Down syndrome and CHD tended to develop pulmonary hypertension faster than patients without Down syndrome. The pathophysiology of Down syndrome is thought to be influenced by genetic expression, which leads to poor lung vascular development and signaling.[13] In this study, the uncorrectable group, which was associated with a more severe form of pulmonary hypertension, had a higher proportion of patients with Down syndrome.

Children with CHD are prone to recurrent pneumonia and are more likely to develop severe pneumonia, including respiratory failure. In this study, pneumonia was more common in the uncorrectable group; however, a single-center retrospective cohort study by Inrianto et al[14] reported that pneumonia was not associated with pulmonary hypertension.

Hb, a protein in red blood cells, contains iron and is responsible for carrying oxygen. In this study, the uncorrectable group had a higher Hb level. This result is consistent with a Taiwanese cohort study that found that children with Eisenmenger syndrome who had high Hb levels also had worse outcomes.[15]

In this study, the most common cardiac defects identified in patients with pulmonary hypertension were VSD and PDA, with mostly large defect sizes. The blood in each ventricle of a person with a VSD has two alternative systolic routes: it can exit through the normal ventricular outflow tract or escape through the VSD and exit through the other ventricular outflow tract. The volume and direction of systolic flow over the defect are both determined by the relative resistance of each conduit. The sum of resistance from the left ventricle to the pulmonary artery, for instance, is very low compared with the resistance of flow to the systemic circulation, resulting in a large left-to-right systolic flow across the defect in the presence of normal PVR and a large, nonrestrictive VSD. Small VSDs have higher resistance at the defect site, restricting the left-to-right shunt.[16]

The clinical histories of VSD and PDA are identical. The patient mostly shows signs of congestive heart failure in infancy if the PDA is large. If the abnormality is not fixed, this condition frequently advances into Eisenmenger's physiology. At the PDA, a right-to-left shunt forms as PVR increases.[17] The PDA cannot be closed because of the same physiological reasons as

those because of which patients with Eisenmenger syndrome cannot tolerate VSD repair.

From the baseline pressure measurement, the correctable group had lower mPAP, lower PARI, and higher flow ratio. These findings are consistent with the pathophysiology of shunt through a defect in CHD. The left ventricular volume and pressure spread to the pulmonary vascular bed in patients with moderate-to-large defects. If the problem is not treated, Eisenmenger's physiology develops. In this process, the medial layer of the pulmonary arterioles hypertrophies in response to the stimulus of the left ventricle's volume and pressure. PVR starts to increase as pulmonary artery lumens are reduced. The tiny vessels eventually become utterly obliterated as the hypertrophy advances. Resistant levels in the lungs increase until they surpass systemic resistance. At this point, the patient's blood flow is reversed into a right-to-left shunt, which makes the patient cyanotic. Since this process is irreversible, the severity of the clinical symptoms corresponds with the PAP readings. Any procedure performed to repair the defect at this point would result in abrupt right ventricle failure, venous stasis, reduced cardiac output, and lower life expectancy than if left open.

PAP, shunting, and AVT are performed during cardiac catheterization to assess the impact of short-acting pulmonary vasodilators on PVR. Although the AVT remains the gold standard for diagnosing and prognosticating pulmonary hypertension,[18,19] no standardized guideline for the pediatric population with pulmonary hypertension has been established, and referral facilities typically follow different practices.[20] The differences include the vasodilators (nitric oxide ± oxygen *versus* inhaled iloprost *versus* other orally or intravenously administered substances [sildenafil and treprostinil]),[21–26] definition of a positive AVT response, and mode of anesthesia (general anesthesia with mechanical ventilation *versus* local anesthesia). These differences make it challenging to compare test results, and they may lead to misunderstandings and, eventually, incorrect decisions concerning the most appropriate intervention.[27]

The definition of a positive acute vasodilator test remains controversial. In children with PAH-CHD, an acute vasodilator test is used to assess operability. A favorable response to the acute vasodilator test should be defined as a >20% decrease in PARI with a final value of <6 WU/m^2.[28,29] Nevertheless, surgical safety cannot be ensured (the gray zone is defined as a PARI of 6–8 WU/m^2). In this study, both groups showed a decrease of >20% in PARI after the acute vasodilator test, but the PARI in the uncorrectable group remained >6 WU/m^2. This result is consistent with a diagnostic study by Day,[30] who found that a PARI of <8 WU/m^2 had a sensitivity of 100% and specificity of 35% in predicting correctability, with a 46% accuracy. Adding 100% oxygen to the acute vasodilator test increases specificity to 88% and accuracy to 88%.[30] A cohort study by Jarutach et al[31] of patients with completely repaired CHD found a decreased 10-year survival rate from 98.6 ± 0.8% in patients with a PARI of <4 WU/m^2 to 76.5 ± 11.2% in patients with a PARI of >8 WU/m^2.

Age at which the surgery is performed, in addition to the type or size of the lesion and concomitant syndromes, is one of the most crucial variables for long-term survival in a child with PAH-CHD. The American Heart Association and American Thoracic Society recommend cardiac catheterization to evaluate the PARI and flow ratio if the repair had not been performed by the age of 2 years.[2] In that case, repair should be considered if the PARI is <6 WU/m^2 or the AVT reveals reversibility when the PARI is ≥6 WU/m^2. However, the European Pediatric Pulmonary Vascular Disease Network suggested that there is a gray zone group whose PARI is between 6 and 8 WU/m^2. In this group, individual patient evaluation is necessary, and clinical subjectivity is inevitable.[29] In contrast, Saudi guidelines suggested repair when the PARI is between 4 and 8 WU/m^2.[32] Despite the variation, all guidelines do not recommend repair if the PARI value exceeds 8 WU/m^2. Measurement of PARI is emphasized as an important predictor to determine correctability in children with PAH-CHD.

This study had several limitations. This was a single-center study in which the patient's sociodemographic characteristics might differ from those in other centers. There was also a difference in sample size and proportion between groups, which might affect the results. Moreover, the patients were not observed following the cardiac catheterization procedure. A multicenter cohort study is needed to confirm the results of this study.

In conclusion, pre-tricuspid lesions, young age, and high baseline PARI were significant predictors of uncorrectable defects in children with PAH-CHD. A baseline PARI of >8 WU/m^2 had the highest OR as the

predictor of uncorrectable defects in children with PAH-CHD. This study not only provides the clinical relevance of PARI measurement in assessing operability, but also additionally supplies clinical data regarding children with PAH-CHD in Indonesia.

Conflict of interest

The authors affirm no conflict of interest in this study.

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