Original Article

Survival of Patients with High-Risk Pulmonary Arterial Hypertension Associated with Congenital Heart Disease

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Background: Pulmonary arterial hypertension (PAH) is a common complication of congenital heart disease (CHD) with uncorrected left-to-right shunts. Currently, no consensus guideline exists on the management of PAH-CHD in children, especially those who do not meet operability criteria.

Objective: To compare survival between three groups of high-risk PAH-CHD, group 1: total correction including both surgical and percutaneous intervention, group 2: palliative treatment, and group 3: conservative with medical treatment group.

Materials and Methods: All pediatric patients with PAH-CHD that underwent cardiac catheterization between January 1, 2008 and December 31, 2017 were retrospectively reviewed. Inclusion criteria were high risk PAH-CHD patients who had pulmonary vascular resistance (PVR) greater than 6 Wood unit·m^2 and PVR-to-SVR ratio greater than 0.3 evaluated in room air. Exclusion criteria were younger than three months of age, severe left side heart disease with pulmonary capillary wedge pressure greater than 15 mmHg, obstructive total pulmonary venous return, and single ventricle physiology. The Kaplan-Meier analysis was performed from the date of PAH diagnosis to the date of all-cause mortality or to censored date at last follow-up.

Results: Seventy-six patients with a median age at diagnosis of 27.5 months (IQR 14.5 to 69.0 months) were included in this study. The patients were divided into three subgroups and included 38 patients (50.0%) in group 1, six patients (7.9%) in group 2, and 32 patients (42.1%) in group 3. The median follow-up time was 554 days (IQR 103 to 2,133 days). The overall mortality was 21.7%. One-year survival in patients with simple lesion in group 1 and 3 were 79.5% and 87.5% and patients with complex lesions in group 1, 2, and 3 were 93.8%, 83.3%, and 73.1%, respectively. The results showed that most mortalities occurred in the first year. There were no statistically significant differences in survival among difference types of treatment (log rank test, p=0.522).

Conclusion: The mortality of high-risk PAH-CHD patients were not different among those who underwent corrective surgery, palliative, or conservative treatment. The mortality was high in the first year after PAH diagnosis and remain stable afterward. Management decision for an individual with high-risk PAH-CHD patients requires comprehensive clinical assessment to balance the risks and benefits before making individualized clinical judgment.

Keywords: Pulmonary hypertension; Congenital heart disease; High-risk patients

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Pulmonary arterial hypertension (PAH) is a common co-morbidity in patients with congenital heart disease (CHD). The prevalence of PAH has been estimated to be 1.6 to 12.5 cases per million adults, which may be underestimated[1]. Congenital heart defects occur in 0.8% to 1% of live births[2], and PAH is a major complication in children with left-to-right or systemic-to-pulmonary shunt. PAH in cardiac defects with left-to-right shunt is a result of increases in shear stress secondary to increased pulmonary blood flow. The endothelial dysfunctions are induced by hemodynamic forces within pulmonary vessels[3] that finally cause vascular smooth muscle hypertrophy and proliferation[3]. The vascular remodeling results in a progressive increase in pulmonary vascular resistance (PVR). Around 5% of adults with CHD develop PAH[4], 25% to 50% of whom exhibiting the most serious form, Eisenmenger syndrome[1].

In developed countries, neonatal and infant cardiac surgeries can be safety performed before the development of PAH and pulmonary vascular disease (PVD). The prognosis of postoperative PAH-CHD is mainly based upon the timing of shunt closure[5]. Nonetheless, un-operated or late operated

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patients may develop irreversible PAH with worse outcome[6,7]. PAH associated with CHD remains a problem in developing countries in which the majority of patients were undiagnosed until late childhood or even adulthood[8]. Those patients with high PVR at the time of diagnosis are high risk for surgery and decisions for their treatment become challenging.

At the present time, there are several guidelines for operability in adults with CHD and pulmonary hypertension, however, no consensus exists on the management of PAH in children with CHD, especially those who do not to meet operability criteria.

Objective

The present study aimed to compare survival of high-risk patients diagnosed with pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) among three groups, group 1, patients that underwent total correction including both surgical and percutaneous intervention, group 2, patients that underwent palliative treatment such as balloon atrial septostomy or balloon branch pulmonary artery, and group 3, patients who were conservative with mainly medical treatment.

Materials and Methods

Study population and data collections

Following the approval from the Institutional Ethic Committee, Faculty of Medicine Chulalongkorn University (IRB No. 663/60), the medical records of all patients underwent cardiac catheterization to assess their hemodynamic data and/or transcatheter closure of the defects at the Department of Pediatrics, King Chulalongkorn Memorial Hospital between January 1, 2008 and December 31, 2017 were retrospectively reviewed. Inclusion criteria were high risk patients with PAH, defined by mean pulmonary arterial pressure (mPAP) of more than 20 mmHg and PVR of more than 6 Wood unit·m² and PVR-to-systemic vascular resistance (SVR) ratio greater than 0.3[9]. Exclusion criteria were 1, patients who were younger than three months of age because they might possess persistent high pulmonary pressure due to their normal physiology, 2, severe left side heart disease which was diagnosed when left atrial pressure or pulmonary capillary wedge pressure (PCWP) greater than 15 mmHg because of their post-capillary pulmonary hypertension physiology, 3, obstructive total anomalous pulmonary venous return (TAPVR) that is an emergency condition for surgery and possess post-capillary pulmonary hypertension physiology, and 4, patients with single ventricle physiology.

Seventy-six patients were classified as high-risk patients with a PVR greater than 6 Wood unit·m² and a PVR-to-SVR ratio greater than 0.3. Demographic information including date of birth, gender, age at catheterization, hemoglobin (%), cardiac catheterization hemodynamic data including Qp:Qs, PVR and PVRi at baseline in room air and following acute vasodilator testing (AVT) were obtained.

Definition and diagnosis

PAH was diagnosed when mPAP from cardiac catheterization greater than 20 mmHg, based on the definition of PAH derived from the Sixth World Symposium on Pulmonary Hypertension (WSPH)[10].

According to the assessment of operability for shunt lesions in patients with CHD and pulmonary hypertension from the American Heart Association and the American Thoracic Society Guideline 2015[9], high-risk patients were classified when PVR greater than 6 Wood unit·m² and a PVR-to-SVR ratio greater than 0.3.

AVT was performed after inhalation of 100% oxygen for 10 minutes to assess reversibility of PAH in patients with PAH-CHD. Potential operable patients were defined by positive AVT of at least a 20% decrease in PVRi and a PVR/SVR ratio from baseline with respective final values of less than 6 Wood unit·m² and less than 0.3, respectively[11].

Severe cases were classified when the patients exhibit at least one of these factors, intensive care unit (ICU) stay before or after cardiac catheterization, intubation, inotropic drug used during the admission, and cases who presented with emergency conditions.

Pulmonary hypertensive crisis was diagnosed when the patient had an acute rise in pulmonary pressure, measured or presumed, to the point where it exceeded systemic pressure due to rapid increase in PVR, causing pressure overload of right ventricle, decrease pulmonary blood flow, hypoxia, and decrease cardiac output due to leftward displacement of the interventricular septum[12].

Follow-up

The primary endpoint of the study was all-cause mortality. Time of survival was calculated from the date of diagnostic cardiac catheterization to the survival endpoint, which was taken either as the date of mortality or at the last day of follow-up.

Statistical analysis

The patients' baseline characteristics and

Table 1. The clinical characteristics and hemodynamic data (n=76)

Total (n=76)	No. of subject	Subgroup by final treatment			
		Total correction (n=38)	Palliative treatment (n=6)	Medical treatment (n=32)	p-value
Male†	41 (53.9)	21 (55.3)	3 (50.0)	17 (53.1)	0.964
Simple lesions†	31 (40.8)	19 (50.0)	0 (0.0)	12 (37.5)	0.060
Syndrome†	26 (34.2)	11 (28.9)	0 (0.0)	15 (46.9)	0.053
Severe case†	10 (13.2)	5 (13.2)	1 (16.7)	4 (12.5)	0.962
Age at cath (months)‡	27.5 (14.5 to 69.0)	27.0 (11.0 to 63.0)	33.0 (24.0 to 64.0)	28.5 (15.0 to 73.5)	0.689
Hb (g/dL)‡	13.5 (12.0 to 15.3)	13.0 (11.8 to 14.0)	14.3 (12.2 to 15.0)	14.3 (12.5 to 16.1)	0.126
Aortic saturation (%)§	83.8±7.2	85.9±8.0	76.9±16.7	80.2±11.6	0.033*
mPAP (mmHg)§	55.4±16.8	55.0±16.0	42.0±15.0	57±17.0	0.118
Qp:Qs§	1.0±0.5	1.1±0.5	0.7±0.4	0.9±0.5	0.170
Rpi (Wood unit·m^2)‡	9.1 (7.7 to 12.1)	9.1 (8.0 to 10.9)	8.7 (7.4 to 9.7)	9.1 (7.0 to 13.8)	0.966
Rp:Rs‡	0.53 (1.1 to 3.7)	0.77 (0.61 to 1.02)	0.79 (0.58 to 1.44)	0.75 (0.50 to 1.11)	0.981

Hb=hemoglobin; mPAP=mean pulmonary artery pressure; Qp:Qs=pulmonary blood flow to systemic blood flow ratio; Rpi=pulmonary vascular resistance index; Rp:Rs=pulmonary to systemic vascular resistance ratio; IQR=interquartile range; SD=standard deviation

* Statistical significance level of <0.05

† Data were analyzed with chi-square test, presented as n (% of groups); ‡ Data were analyzed with Kruskal-Wallis test, presented as median (IQR); § Data were analyzed with one-way ANOVA, presented as mean±SD

outcomes were summarized using descriptive statistics. Normally distributed data were presented as mean ± standard deviation (SD), and median with interquartile range (IQR) when the distribution was not normal. Categorical data were represented as number and percentage (%). Differences in the categorical data were assessed using chi-square. The one-way analysis of variance with Bonferroni's correction was used to determine differences between continuous variables of more than two groups, when the distribution was normal. The Kruskal-Wallis test was used to determine differences between continuous variables of more than two groups when the distribution was not normal. Cumulative survival from date of diagnosis to the endpoint was calculated using the Kaplan-Meier method. A p-value of less than 0.05 was considered to be statistically significant. The statistical analyses were performed with IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

Of the 391 patients with PAH-CHD, 76 high-risk patients were included in the present study. Median age at cardiac catheterization was 27.5 months old (IQR 14.5 to 69.0 months), half of the patients were male (41 patients, 53.9%). One-third were syndromic patients (26 patients, 34.2%), of which the most common were Down syndrome (16 patients) and DiGeorge syndrome (3 patients). Forty percent of patients (31 patients) had simple cardiac lesion such as ventricular septal defect (VSD), patent ductus arteriosus (PDA), or atrioventricular septal defect (AVSD). Sixty percent of the patients (45 patients) had complex lesions such as PDA with coarctation of aorta, double outlet right ventricle, pulmonary atresia with VSD with major aortopulmonary collateral arteries (MAPCAs), transposition of great arteries with VSD, and hemitruncus arteriosus.

The patients were divided into three subgroups according to their final treatment. Group 1 had both surgical and transcatheter intervention (38 patients, 50.0%), group 2 had palliative treatment (6 patients, 7.9%), and group 3 had medical treatment (32 patients, 42.1%). The patients' characteristics in each group are shown in Table 1. In the 31 patients with simple lesion, none of them were in group 2.

Twenty-eight patients (36.8%) underwent total surgical repair. Sixteen patients (21.1%) underwent transcatheter intervention in which 10 of 16 procedures were transcatheter closure of cardiac defect and classified into total correction group. Six patients had palliative transcatheter treatment such as balloon atrial septostomy or balloon branch pulmonary artery. Thirty-two patients (42%) were conservative with medical treatment.

AVT were performed in one-third of the patients (26 patients, 34.2%) which 19 of 26 patients (73.1%) had negative result (non-responsive). Ten patients

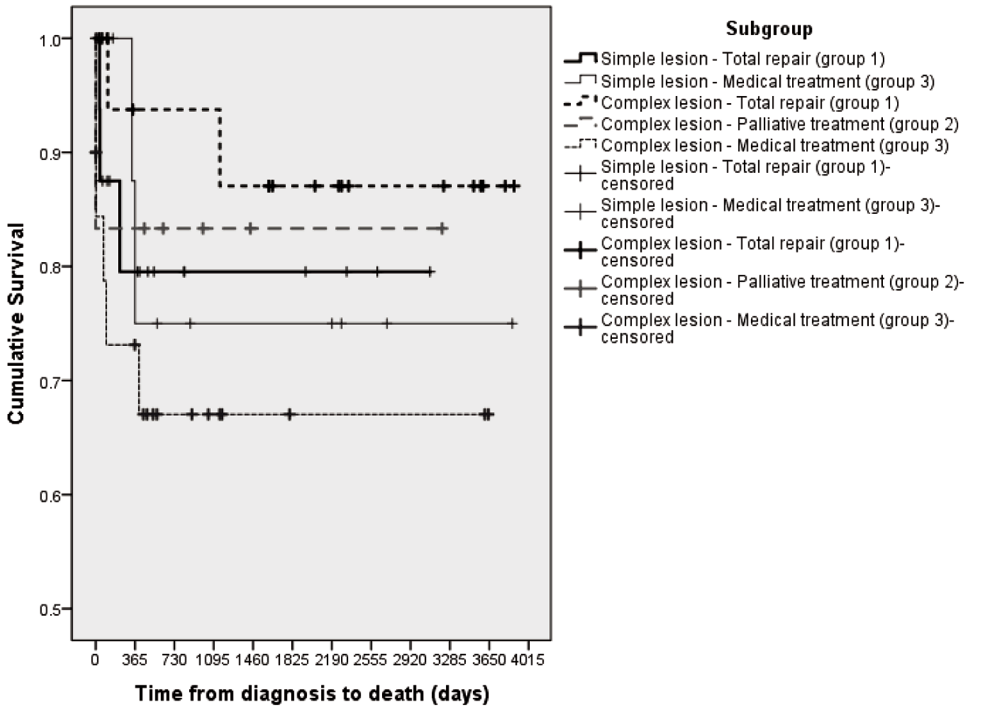

Figure 1. Cumulative survival of all PAH-CHD patients with difference treatment strategies (n=76).

proceeded to corrective surgery (group 1) including three patients that underwent transcatheter total correction (group 1), and 13 patients had medical treatment (group 3).

Survival of high-risk PAH-CHD patients

Median time from diagnosis to death or last follow-up was 554 days (IQR 103 to 2,133 days, range 0 to 3,881 days). The survival of patients with PAH-CHD is showed using the Kaplan-Meier survival curve in Figure 1. The patients were categorized into three groups according to their final treatment and divided into two subgroups according to the complexity of cardiac lesions. Primary outcome was all cause mortality, which was calculated from time of diagnosis to death. The other patients were included until the time of the last follow-up visit.

Of all 72 patients, 14 patients (19.4%) died. Five patients had simple lesion in which three patients were in group 1 (total correction), and two patients were in group 3 (medical treatment). Nine patients had complex lesions in which two patients were in group 1, one patient was in group 2 (palliative treatment), and six patients were in group 3.

One-year survival in patients with simple lesion in group 1 and 3 were 79.5% and 87.5% and patients with complex lesions in group 1, 2, and 3 were 93.8%, 83.3%, and 73.1%, respectively.

There was no statistically significant difference of survival outcome among each group (log rank test, p=0.522). With regards to the timing of death, the survival curve dramatically dropped in first year after diagnosis in all group. Those who survived three years after diagnosis tended to be alive at 10 years after diagnosis.

Pre- and post-operative factors associated with mortality of high-risk PAH-CHD

Among 28 patients who underwent corrective surgery. Four patients developed post-operative pulmonary hypertensive crisis evidenced from direct measurement from pulmonary arterial line. Three patients were dead, and one of the three patients died early after heart surgery from pulmonary hypertensive crisis. Another two patients died from other causes unrelated to pulmonary hypertension. The pre-operative cardiac catheterization data including age at surgery, baseline hemoglobin, mPAP, Qp:Qs, Rpi, Rp:Rs, and aortic saturation, intraoperative factors including cardiopulmonary bypass time and aortic cross clamp time, and postoperative factors including early re-operation, duration of ICU stay, and duration of hospital stays were not associated with mortality (Table 2).

Table 2. Clinical characteristics and pre and post-operative factors of patients who underwent surgical intervention according to their follow-up status (n=28)

Total (n=28)	Status; n (%)		p-value*
	Alive (n=25)	Dead (n=3)	
Age at surgery (months); median (IQR)	38 (20, 87)	8 (7, 12)	0.004
Severity at Cath	4 (16)	1 (33)	0.459
Acidosis[1] (n=26**)	7 (30)	1 (33)	0.919
Post-operative pulmonary arterial hypertension[2] (n=26**)	13 (57)	2 (66)	0.696
Post-operative pulmonary hypertensive crisis[3] (n=26**)	2 (9)	2 (66)	0.009*
Re-operation (n=26**)	2 (9)	1 (33)	0.209
Hb (g/dl); median (IQR)	13.7 (12.0, 14.4)	11.8 (11.0, 12.5)	0.125
mPAP (mmHg); median (IQR)	57 (45, 64)	58 (55, 67)	0.673
Qp:Qs; median (IQR)	0.9 (0.7, 1.3)	1.3 (1.1, 2.1)	0.075
Rpi (Wood unit·m^2); median (IQR)	9.1 (8.1, 10.5)	8.4 (6.0, 8.7)	0.106
Cardiopulmonary bypass time (minutes) (n=26**); median (IQR)	145 (69, 207)	148 (50, 216)	0.880
Aortic cross clamp time (minutes) (n=26**); median (IQR)	116 (45, 127)	90 (29, 112)	0.352
Duration of ICU stay (days) (n=26**); median (IQR)	5 (3, 7)	2 (2,7)	0.442
Hospital stay (days) (n=26**); median (IQR)	17 (14, 20)	28 (2, 34)	0.490

Hb=hemoglobin; mPAP= mean pulmonary artery pressure; Qp:Qs=pulmonary to systemic blood flow ration; Rpi=indexed pulmonary vascular resistance; IQR=interquartile range

Data were analyzed with chi-square test, n (%) or Mann-Whitney test, median (IQR)

* Statistical significance level of 0.05, ** 28 patients underwent surgical repair but 2 of them had no operative data due to the surgeries were performed from another hospital (n=26; alive=23, dead=3)

[1] Acidosis mean intraoperative arterial blood gas with pH under 7.25, [2] Post-operative PA pressure monitoring with evidence PAP ≥25 mmHg, [3] Post-operative pulmonary hypertensive crisis with evidence from PA pressure monitoring

Pulmonary hypertensive crisis after percutaneous intervention and surgery

None of 16 patients who underwent percutaneous intervention in both total repair and palliative treatment groups had post-catheterization clinical suspicion of pulmonary hypertensive crisis.

Discussion

Around 50% of PAH in children have underlying CHD (PAH-CHD)[7]. Patients with long standing systemic to pulmonary shunting may lead to gradual increase PVR and pulmonary arterial pressure (PAP). Finally, they may develop irreversible PVD or Eisenmenger syndrome. The current treatment strategy aims to perform corrective surgery before the development of irreversible PVD. Nevertheless, in developing countries in which medical access are limited, many patients are late presenters who may come to medical attention only when their symptoms are severe. The decision for surgery in these late presenters especially those with severely increased PVR is still problematic. In the past, lung biopsy was used to determine the histological changes of pulmonary vasculature as an indicator to assess operability of the patient with PAH. However, the reliability is low because the lung biopsy only represents random area of the lungs at one point of time, which may not represent total lungs pathology. Patient's age also needs to be considered as young patients under two years old are often operable even with advanced pulmonary vasculature changes[13]. The current goal standard to assess operability is right heart catheterization to determine patients' hemodynamic based on PVR, PVR-to-SVR ratio, and vasoreactivity test. Still, no absolute consensus exists for the cut-off threshold of PVR, or PVR-to-SVR ratio that are safe for surgical repair. Moreover, the studies about treat-and-repair strategy in PAH-CHD are still inconsistent and long-term outcomes have not been studied[8,14]. Even in the patients with favorable hemodynamic data, they may still develop post-operative pulmonary hypertensive crisis[8]. There is uncertainty about which pre-operative hemodynamic data are best correlated with post-operative outcomes and long-term outcomes[15]. The best method to determine the threshold of operability is still unknown. In the present study, the authors retrospectively investigated the outcome of CHD patients deemed to be at high

operative risk based on the expert consensus on the level of PVR using PVRi greater than 6 Wood unit·m² and PVR/SVR ratio higher than 0.3.

The present study analyzed survival of PAH-CHD with different treatment strategies. The results found that the survival rates were similar whether the patients underwent total surgical repair, palliative treatment, or conservative with medical management. The mortality of the present study PAH-CHD patients was high in the early years after diagnosis of PAH, which was comparable with many previous reports. A study from Netherland[16] showed that children with PAH-CHD survival varied upon the different subgroup, some had better and others had worse survival comparing with idiopathic pulmonary arterial hypertension (iPAH) diagnosed in children, and iPAH diagnosed in adulthood. Among PAH-CHD, the patients who underwent defect closure had the most unfavorable outcomes. The death rate after repair was worse than the patients without repair and iPAH was identical with the report from the studies from the United Kingdom[7] and Italy[5]. Interestingly, Eisenmenger syndrome patients even with the worst exercise capacity, functional capacity, and hemodynamics had better survival than post repair PAH-CHD patients[5,7,17]. A possible explanation for superior prognostic outcome in Eisenmenger syndrome comparing with post cardiac defect correction was the elimination of right to left shunt in patients with high PVR may increase rate of RV failure[5]. The 3-year survival of the present study patients range from 67% to 87%, and the survival rate remained stable afterward. The results were different from the earlier reports where the survival gradually declined over the years. The survival bias in the present study patients might be from the fact that many of the patients were young and might represent only the tip of the iceberg in which the most severe patients might expire before they could present to the hospital (immortal time bias). Moreover, most of the present study patients had low aortic saturation with a mean 83.8±7.2%, and a low Qp:Qs with a mean of 1.0±0.5, which indicated that the patients already had right to left shunt across the defects.

The authors also studied the factors that could affect the early perioperative death among the high-risk patients. Pulmonary hypertensive crisis accounted for 33% of post-operative death. There was no difference in mortality rate in different age, baseline hemoglobin, mPAP, Qp:Qs ratio, cardiopulmonary bypass time, and aortic cross clamp time. Moreover, post-procedural pulmonary hypertensive crisis in the high-risk patients were only developed in patients who underwent surgery, not in patients underwent interventional cardiac catheterization. Nevertheless, the authors could not conclude that patients with PVRi greater than 6 Wood unit·m² and a PVR/SVR ratio of greater than 0.3 would benefit from closing the defect either surgically or percutaneous transcatheter treatment. The robust risk factors to determine mortality of the high-risk patients were still uncertain[15]. This might be because the development of pulmonary vascular changes among different cardiac lesions were not similar and could affect treatment outcomes. Still, no good parameters nor absolute cut-off points could accurately assess the operative risk and mortality in high-risk patients with PVD.

Limitations of the present study were small number of patients. The retrospective aspect of the study and the quality of life among those patients were not explored due to retrospective nature of the study. Further research to determine general well-being of patients in each group should be done to answer this question.

Conclusion

According to the present study, the mortality of high-risk PAH-CHD patients that either underwent corrective surgery, palliative, or conservative medication treatment were high in the first year after PAH initial diagnosis and subsequently remain steady. The overall survival was not different between treatment options, and there was no evidence or consensus that could strongly recommend which treatment was the proper treatment for PAH-CHD. Management decision for an individual high-risk PAH-CHD patient requires comprehensive clinical assessment to balance the treatment risks and benefits before individual clinical judgment.

What is already known on this topic?

According to the recent ACHD guideline, there are cut-off points for operable CHD-PAH patients. However, no consensus guideline is made for those who fall into grey zone.

What this study adds?

The authors reported the treatment outcomes among different type of final treatment in the grey zone high risk patients. The result showed that despite pushing the patients into aggressive treatment such as total correction, the mortality rate was not different from other treatments options.

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Conflicts of interest

The authors declare that they have no conflict of interest with the contents of this article.

References

1. Galie N, Manes A, Palazzini M, Negro L, Marinelli A, Gambetti S, et al. Management of pulmonary arterial hypertension associated with congenital systemic-to-pulmonary shunts and Eisenmenger's syndrome. Drugs 2008;68:1049-66.
2. Lopes AA, Barst RJ, Haworth SG, Rabinovitch M, Al Dabbagh M, Del Cerro MJ, et al. Repair of congenital heart disease with associated pulmonary hypertension in children: what are the minimal investigative procedures? Consensus statement from the Congenital Heart Disease and Pediatric Task Forces, Pulmonary Vascular Research Institute (PVRI). Pulm Circ 2014;4:330-41.
3. Diller GP, Gatzoulis MA. Pulmonary vascular disease in adults with congenital heart disease. Circulation 2007;115:1039-50.
4. Duffels MG, Engelfriet PM, Berger RM, van Loon RL, Hoendermis E, Vriend JW, et al. Pulmonary arterial hypertension in congenital heart disease: an epidemiologic perspective from a Dutch registry. Int J Cardiol 2007;120:198-204.
5. Manes A, Palazzini M, Leci E, Bacchi Reggiani ML, Branzi A, Galiè N. Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: a comparison between clinical subgroups. Eur Heart J 2014;35:716-24.
6. Balint OH, Samman A, Haberer K, Tobe L, McLaughlin P, Siu SC, et al. Outcomes in patients with pulmonary hypertension undergoing percutaneous atrial septal defect closure. Heart 2008;94:1189-93.
7. Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: the UK Pulmonary Hypertension Service for Children 2001-2006. Heart 2009;95:312-7.
8. Beghetti M, Galiè N, Bonnet D. Can "inoperable" congenital heart defects become operable in patients with pulmonary arterial hypertension? Dream or reality? Congenit Heart Dis 2012;7:3-11.
9. Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, et al. Pediatric pulmonary hypertension: Guidelines from the American Heart Association and American Thoracic Society. Circulation 2015;132:2037-99.
10. Rosenzweig EB, Abman SH, Adatia I, Beghetti M, Bonnet D, Haworth S, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Respir J 2019;53:1801916.
11. Apitz C, Hansmann G, Schranz D. Hemodynamic assessment and acute pulmonary vasoreactivity testing in the evaluation of children with pulmonary vascular disease. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart 2016;102 Suppl 2:ii23-9.
12. Cunningham ME, Berger JT. Pediatric pulmonary hypertensive crisis medications: A stepping stone for the future. Pediatr Crit Care Med 2016;17:465-6.
13. Viswanathan S, Kumar RK. Assessment of operability of congenital cardiac shunts with increased pulmonary vascular resistance. Catheter Cardiovasc Interv 2008;71:665-70.
14. Akagi S, Kasahara S, Sarashina T, Nakamura K, Ito H. Treat-and-repair strategy is a feasible therapeutic choice in adult patients with severe pulmonary arterial hypertension associated with a ventricular septal defect: case series. Eur Heart J Case Rep 2018;2:yty033.
15. Giglia TM, Humpl T. Preoperative pulmonary hemodynamics and assessment of operability: is there a pulmonary vascular resistance that precludes cardiac operation? Pediatr Crit Care Med 2010;11(2 Suppl):S57-69.
16. van Loon RL, Roofthooft MT, Hillege HL, ten Harkel AD, van Osch-Gevers M, Delhaas T, et al. Pediatric pulmonary hypertension in the Netherlands: epidemiology and characterization during the period 1991 to 2005. Circulation 2011;124:1755-64.
17. Barst RJ, Ivy DD, Foreman AJ, McGoon MD, Rosenzweig EB. Four- and seven-year outcomes of patients with congenital heart disease-associated pulmonary arterial hypertension (from the REVEAL Registry). Am J Cardiol 2014;113:147-55.