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RESEARCH

Surgical outcomes and long-term follow-up of patients with large ventricular septal defects with severe pulmonary arterial hypertension: single-center experience

Ciddi pulmoner arteryal hipertansiyonlu geniş ventriküler septal defektli olgularının cerrahi sonuçları ve uzun dönem takibi: tek merkez deneyimi

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Abstract

Purpose: In this retrospective study, pediatric patients who underwent surgery for large ventricular septal defect (VSD) with severe pulmonary arterial hypertension (PAH) were evaluated in detail in terms of clinical characteristics, and long-term results, and reinterpreted with the current surgical criteria.

Materials and Methods: Twenty-four patients who underwent surgery for large VSD due to PAH between 1994 and 2005 were included in the study. The patients were divided into two groups according to their pulmonary vascular resistance index (PVRI) and compared (group 1 with PVRI <6 WU.m² and group 2 with PVRI ≥ 6 WU.m²). The patients with PVRI 6-8 WU.m² were accepted as being in the gray zone and were evaluated in detail.

Results: Age at diagnosis ranged from 5 months to 17 years (median: 5 years). PVRI ranged between 3 and 18.4 WU.m² (median PVRI was 5 WU.m².) According to the PVRI, 13 patients were accepted as group 1, and 11 patients were accepted as group 2. mPAP, PVR/SVR, and last PAP values were found statistically significantly lower in group 1 than in group 2. The median postoperative follow-up time was 6 years (range, 1 month-18 years). PAH was seen in 15/24 (62.5%) patients. Severe PAH was observed in seven of these 15 patients and all were in group 2 (four had PVRI ≥8WU.m² and three had PVRI 6-8 WU.m²).

Conclusion: Patients with large VSD with severe PAH should be carefully evaluated before surgery to more accurately identify suitable candidates.

Keywords:. Congenital heart disease, pulmonary arterial hypertension, ventricular septal defect

Öz

Amaç: Bu retrospektif çalışmada, şiddetli pulmoner arteryal hipertansiyonlu (PAH) geniş ventriküler septal defekt (VSD) nedeniyle ameliyat edilen pediatrik hastalar, klinik özellikleri ve uzun dönem sonuçları açısından ayrıntılı olarak değerlendirilmiş ve güncel ameliyat kriterleri ile yeniden yorumlanmıştır.

Gereç ve Yöntem: 1994-2005 yılları arasında PAH'lı geniş VSD nedeni ile ameliyat edilen ve takibi yapılan 24 çocuk hasta çalışmaya dahil edildi. Hastalar pulmoner vasküler resiztans indexine(PVRI) göre iki gruba ayrıldı ve karşılaştırıldı (grup 1:PVRI <6 WU.m² olan olgular, grup 2: PVRI ≥ 6 WU.m² olan olgular). PVRI 6-8 WU.m² olan olgular gri bölgede kabul edildi ve detaylı olarak değerlendirildi.

Bulgular: Tanı yaşı 5 ay ile 17 yıl (medyan: 5 yıl) arasındaydı. Ortanca PVRI 5 WU.m² olup 3 -18,4 WU.m² arasında değişmekteydi. PVRI' ye göre 13 hasta grup 1, 11 hasta ise grup 2 olarak kabul edildi. Grup 1'de grup 2'ye göre istatistiksel olarak anlamlı olarak mPAP, PVR/SVR ve son PAP değerleri düşük bulundu. Ameliyat sonrası ortanca takip süresi 6 yıl (1 ay-18 yıl) olup takipte 15 hastada (%62,5) PAH görüldü. Bu 15 hastanın 7'sinde şiddetli PAH gözlenmiş olup bu 7 hastanın tamamı grup 2'deydi (dördünde PVRI ≥8WU.m² ve üçünde PVRI 6-8 WU.m²).

Sonuç: Şiddetli PAH gelişmiş geniş VSD'si olan hastalarda, ameliyat için uygun adayları daha doğru bir şekilde belirlemek için ameliyattan önce klinik ve özellikle hemodinamik durumları dikkatlice değerlendirilmelidir.

Anahtar kelimeler: Doğuştan kalp hastalığı, pulmoner arteriyal hipertansiyon, ventriküler septal defekt

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INTRODUCTION

Pulmonary hypertension (PH) is a common complication of congenital heart disease (CHD) with uncorrected left-to-right shunt, primarily ventricular septal defect (VSD)[1]. Small VSDs are usually not hemodynamically significant; however, left-to-right shunting in large VSD left untreated in the early period may lead to changes in the pulmonary vascular endothelium, resulting in the development of pulmonary arterial hypertension (PAH)[2]. Severe PAH is an important cause of morbidity and mortality for VSD[3].

If VSD with PAH is treated surgically at an early age, the pulmonary artery pressure may decrease to normal levels without the development of permanent pulmonary vascular disease. VSD repair carries a high risk of mortality and poor prognosis, especially in patients with large VSD with severe PAH[2,4]. Therefore, to make a surgical decision for a child with VSD who has developed PAH, the patient should be evaluated in detail. Cardiac catheterization allows us to clarify the diagnosis, determine the hemodynamic status, and identify operable patients by performing the acute vasoreactivity test (AVT). Although it was stated that surgery could be performed in patients with a pulmonary vascular resistance index (PVRI) of <8 WU.m² in previous criteria, surgical/transcatheter defect closure is recommended if the PVRI is <6 WU.m² according to current criteria, and surgery is not recommended in patients with a PVRI of >8 WU.m²[2,4,5]. However, in patients with a PVRI of 6-8 WU.m², which is considered the gray zone, and sometimes even in patients with a PVRI of >8 WU.m² with a positive evaluation in an AVT, the decision for surgery can be made.

Among surgical patients, there may be patients with residual PAH in the postoperative period or patients who re-develop PAH during follow-up, both due to the nature of the disease and because the patients were not selected correctly in preoperative evaluations. Evaluation of the early and long-term clinical results of patients with VSD who have undergone surgery with significant PAH is critical in determining the risk of residual PAH, especially in patients in the gray zone [6]. We hypothesized that patients with VSD in the gray zone should be evaluated in more detail to choose treatment options according to current criteria. This study aimed to provide information about patients with PAH (especially those in the gray zone) by retrospectively evaluating 24 pediatric surgical patients with large VSD and PAH, some of whom were in the gray zone, in terms of long-term follow-up results according to current and old surgical criteria.

MATERIALS AND METHODS

Sample

Pediatric patients aged 0-18 years who were diagnosed as having large VSD and severe PAH and followed up at the Pediatric Cardiology Clinic of Ankara Hospital of Başkent University Faculty of Medicine between 1994 and 2005 were included in the study. The files of patients with large VSD and PAH who underwent surgery were evaluated. Patients with genetic, metabolic, and lung disease, additional congenital heart disease, and patients with missing information in the file were excluded from the study. Our clinic is well known as a reference tertiary center in the diagnosis and surgical treatment of congenital heart diseases, we have patients from many parts of Turkey and have a very extensive and detailed archive. Patients with comorbid disease diagnoses were excluded from the study. At our clinic, the surgical procedures of the patients were performed by pediatric cardiovascular surgeons who also have long-term clinical experience in their field, and pre-and postoperative cardiac examinations of the patients were performed by pediatric cardiologists with long-term clinical experience in their field.

This study was approved by the Baskent University Institutional Review Board (Project No: KA22/312). The study protocol was conducted in accordance with the ethical guidelines of the 1975 Helsinki Declaration, as revised in 2008.

Data collection

The clinical and echocardiography findings, cardiac catheterization, hemodynamic data, surgical procedures, and follow-up of the patients were evaluated retrospectively. The patients were evaluated based on eligibility criteria before the decision for surgery. Large VSD was defined as VSD with the diameter of the defect equal to or larger than the size of the aortic orifice. PAH is defined as a mean pulmonary arterial pressure (mPAP) of ≥25 mm Hg, a pulmonary capillary wedge pressure (PCWP) of <15 mm Hg, and a PVRI of ≥3 WU.m² [5]. The PVRI relates the absolute value of PVR to the patient's

body surface area to account for the effect of body size on blood flow.

Patients were grouped in terms of surgery decisions related to PAH severity based on the current criteria for PAH. Patients were divided into two groups according to their PVRI. Group 1 consisted of patients with VSD with a PVRI of <6 WU.m² and patients with a PVRI of ≥6 WU.m² were allocated to group 2. The groups were compared according to their clinical characteristics, surgery time, follow-up time, and residual or re-development of PAH during follow-up. The clinical characteristics and follow-up of patients with a PVRI between 6-8 WU.m² who were accepted as being in the gray zone were evaluated in detail.

AVTs were performed to evaluate suitability for surgery in patients with a PVRI of >8 WU.m² because these patients had been accepted as being inoperable according to the criteria for PAH at the time when the patients underwent surgery. AVT was performed at that time with 100% oxygen inhalation and hemodynamics were reassessed 10-15 minutes later. A reduction in mPAP of ≥20 mm Hg and left-right shunt ratio (Qp/Qs) >1.5, a PVRI and PVR/SVR decrease of more than 20%, and consequently a PVRI of <8 WU.m² were considered as positive AVT. Patients with a PVRI of <8 WU.m² according to AVT results underwent surgery, and a PVRI of >8 WU.m² was considered inoperable [5].

Pulmonary arterial pressure (PAP) was evaluated using echocardiography (ECHO) based on tricuspid regurgitation jet velocity during follow-up. A mean PAP of 25-50 mm Hg on ECHO was mild PAH and a mean PAP of >50 mm Hg on ECHO was considered severe PAH.

Statistical analysis

Statistical analysis was performed using the SPSS version 23.0 software package (SPSS, Inc., Chicago, IL, USA). Categorical variables are shown as the number of cases (n) with percentages (%), and quantitative variables are shown as mean±standard deviation (SD). The normality of distribution was assessed using the Shapiro–Wilk test for continuous data. The comparisons between groups were evaluated using the Mann–Whitney U test for quantitative values, and the Chi-square (χ^2) test was used for categorical variables. A p-value of <0.05 was considered statistically significant.

RESULTS

Thirty-three pediatric patients who underwent surgery for large VSD due to PAH at our hospital between 1994 and 2005 were evaluated. Nine patients (five patients with additional congenital heart disease, one with Down syndrome, one with lung disease, and two patients with inadequate medical records) were excluded from the study. A total of 24 patients were included in the study. The sample was predominantly female (14 females, 10 males). Age at diagnosis ranged from 5 months to 17 years (median: 5 years). PVRI ranged between 3 and 18.4 WU.m² and the median PVRI was 5 WU.m² (Table 1).

Nine patients (37.5%) had a PVRI of less than 4 WU.m², nine patients (37.5%) had a PVRI between 4-8 WU.m², and six patients had a PVRI greater than 8 WU.m². When patients were evaluated according to current surgical eligibility criteria, it was observed that the PVRI was 3-6 WU.m² in 13 patients, and ≥6 WU.m² in 11 patients. The PVRI was between 6 and 8 WU.m² in five patients.

According to current criteria for PAH, 13 patients with a PVRI of <6 WU.m² were accepted as group 1, and 11 patients with a PVRI of ≥6 WU.m² were accepted as group 2. mPAP, PVR/SVR, and last PAP values were found statistically significantly lower in group 1 than in group 2 ($p<0.001$, $p=0.001$, and $p=0.014$, respectively). Qp/Qs ratio was higher in group 1 than in group 2 ($p=0.002$). A comparison of the groups is given in Table 1.

AVT was performed in six patients who had a PVRI of >8 WU.m², and surgery was decided for six patients whose PVRI decreased below 8 WU.m² as a result of AVT. Preoperative lung biopsy was performed on nine patients in total, four of whom had a PVRI of ≥8 WU.m².

The age of surgery of the patients ranged from 1 year to 18 years (median: 6 years) and the surgical age of four patients was less than 2 years. The median age of surgery was 3.5 years in group 1, and 6 years in group 2. All VSDs were closed with a patch; VSD closure was performed with a fenestrated patch on one patient who had a PVR >8 WU.m². This patient underwent surgery aged 10 years, and re-developed PAH was seen 1 year after the procedure. Although bosentan was started as an anti-PAH treatment during follow-up, the patient died in the 9th year postoperatively. The median postoperative follow-up time was 6 years (range, 1 month-18 years) and most

patients (17/24, 70.8%) had longer than 5 years of follow-up. PAH was seen in 15/24 (62.5%) patients. Eight (33.3%) patients had residual PAH in the first month postoperatively, and seven patients (29%) re-developed PAH between 1 month and 12 years (median: 6 years) after surgery. PAH developed in four patients after the 5th year of follow-up. It was seen that all patients who re-developed PAH were aged over 2 years at the time of surgery. Severe PAH was seen in seven patients. All of these seven patients with severe PAH had a PVRI of ≥6 WU.m², but severe PAH was also seen in four of six patients with a PVRI of ≥8 WU.m². Therefore, three of the seven patients with severe PAH were in the gray zone.

Table 1. Characteristics of total patients and comparison of patients with PVRI <6 WU.m² and ≥6 WU.m²

Variable	Total (n:24)	PVRI <6WU.m² (n:13)	PVRI ≥ 6 WU.m² (n:11)	p-value
	Median (Min-max)	Median (Min-max)	Median (Min-max)	
Age at Surgery (years)	6 (1-18)	3.5 (1-16)	6 (1-18)	0.51
Sex (male/female)	10/14	6/7	4 /7	0.064
mPAP (mm Hg)	66 (30-108)	56 (30-82)	82 (65-108)	**<0.001**
PVRI (WU.m²)	5 (3-18.4)	3.25(3-5.4)	9(6.3-18.4)	**<0.001**
SVRI (WU.m²)	16.6 (11.3-28.7)	16.6 (12.6-28.7)	18.1 (11.3-27)	0.92
PVR/SVR	0.25 (0.08-0.84)	0.17 (0.08-0.33)	0.48 (0.23-0.84)	**0.001**
Qp/Qs	2.45 (1.13-7.25)	3.14 (2-7)	1.53 (1.13-2.6)	**0.002**
Acute vasoreactivity test	6	-	6	
Postoperative PAH (n)	15	6	9	0.62
Severe PAH	7	-	7	
Mild PAH	8	6	2	
Last mPAP (mm Hg)	41 (25-84)	35 (25-43)	54 (28-84)	**0.014**
PAH development time	6 y (1 m-12 y)	3.5m (0-12 y)	2.5 y (0- 11 y)	0.092
Anti-PAH treatment	3	-	3	
Follow-up time	6 y (1 m-18 y)	3.5 y (1 m-18 y)	7 y (1 m-10 y)	0.74
Exitus	2	-	2	

PAH: Pulmonary arterial hypertension, PAP: Pulmonary arterial pressure, PVR: Pulmonary vascular resistance, PVRI: Pulmonary Vascular Resistance index, SVR: Systemic vascular resistance, m: month, y: year

The postoperative follow-up period of two patients with PVRI ≥8 WU.m² was 1 month. The follow-up time of the remaining four patients with PVRI ≥8 WU.m² ranged between 5 and 16 years. These four patients had severe PAH, and the time to re-development of PAH ranged from 1 to 5 years after surgery. Two of four patients died in the 5th and 8th postoperative years of severe PAH (Table 2).

Five patients with a PVRI of 6-8 WU.m² were accepted as being in the gray zone. They had a long follow-up ranging between 7 and 16 years. All five showed re-development of PAH in the follow-up (two patients developed mild PAH and three developed severe PAH). One patient was on bosentan treatment. The re-development time of PAH in these patients ranged from 5 years to 11 years after surgery and there were no patients died among those in the gray zone (Table 2). Anti-PAH treatment was not given to any patients before the surgery; however, bosentan was given to three patients who developed severe PAH during follow-up as anti-PAH treatment.

Table 2. Comparison of patients with PVRI 6-8 WU.m2 and ≥8 WU.m2

Variable	PVRI 6-8 WU.m² (n=5)	PVRI ≥ 8 WU.m² (n=6)
	Median (Min-max)	Median (Min-max)
Age at Surgery (years)	6 (1-18)	7.5 (2-16)
Sex (male/female)	1/4	3/3
mPAP (mm Hg)	70 (54-108)	84.5 (71-100)
PVRI (WU.m2)	7.1 (6.3-7.9)	10.1 (9-18.4)
SVRI (WU.m2)	18 (14.2-21.3)	20 (11.3-27)
PVR/SVR	0.4 (0.32-0.49)	0.67 (0.35-0.84)
Qp/Qs	1.94 (1.22-2.67)	1.15 (0.23-1.9)
Last mPAP (mm Hg)	52 (28-64)	59 (41-84)
PAH development time	9.5y (5-11 y)	2 y (1-5 y)
Postoperative severe PAH (n)	3	4
Follow up time	9 y (7-16 y)	6 y (1 m-16 y)
Anti-PAH treatment	1	2
Exitus	-	2
Acute vasoreactivity test (n)	-	6
mPAP (mm Hg)		74 (42-88)
PVRI (WU.m2)		5.9 (3.9-7.3)
SVRI (WU.m2)		22.3 (11-23)
PVR/SVR		0.28 (0.19-0.53)
Qp/Qs		2.5 (1.8-4)

PAH: Pulmonary arterial hypertension, PAP: Pulmonary arterial pressure, PVR: Pulmonary vascular resistance, PVRI: Pulmonary Vascular Resistance index, SVR: Systemic vascular resistance, m: month, y: year.

DISCUSSION

PAH is a common complication of CHD with uncorrected left-to-right shunt. In the literature, repair of systemic-pulmonary shunt-PAH constitutes 5-15% of pediatric patients with PAH, primarily VSD[7,8]. Making a decision about the correct time for surgery for a child with VSD who has developed PAH is important to avoid postoperative complications and decrease morbidity and mortality[9]. The present study gives some important information on pediatric patients with large VSD and severe PAH related to surgical criteria and outcomes with long-term follow-up.

In the literature, surgery is recommended in patients with VSD who develop PAH before the age of 2 years because the resulting abnormal pulmonary vascular remodeling often becomes irreversible over time [2]. Aydemir et al. suggested that in infants with severe PAH, early surgical repair (before 3 months) of isolated VSDs was related to more favorable results independent of the type of VSD or the surgical techniques performed [10]. Haneda et al. conducted a study to show the late results after the correction of VSD with severe PAH in 58 patients. In their study, the age of the patients at the time of surgery ranged from 2 months to 32 years (average 4.1 years)[11]. The authors emphasized that a patient with VSD associated with severe but reversible PAH should be surgically corrected before the age of 2 years. The admission age of the patients in our study ranged from 5 months to 17 years, and four patients underwent surgery between the ages of 1 and 2 years. None of these patients who underwent surgery at an early age developed severe PAH in the follow-up, even though the preoperative PVRI of one of these patients was >6 WU.m². In line with the literature, we also think that patients who can undergo surgery in the early period may have a better prognosis.

At the Fifth World Pulmonary Hypertension Symposium (WPHS) (Nice, 2013) and the Sixth WPHS (Nice, 2018), it was recommended that

patients with a PVRI of <4 WU.m² could be corrected, patients with PVRI >8 WU.m² could not be corrected, and patients with a PVRI between 4 and 8 WU.m² should be evaluated carefully by a qualified specialist in terms of eligibility for surgery[12,13]. In 2019, an updated consensus statement on the diagnosis and treatment of pediatric PAH recommended that patients with congenital cardiovascular shunts with a baseline PVRI of <6 WU.m² or PVR/SVR of <0.30 were eligible for correction. In addition, AVT was recommended for patients with a baseline PVRI of >6 WU.m² and/or PVR/SVR >0.3[4].

The present study consists of patients treated before the PAH treatment update of 2019. Therefore, the patients underwent surgery according to previous recommendations about PAH. Approximately one-third of our patients had a PVRI between 4 and 8 WU.m², also, about one-quarter of our patients had a PVRI of >8 WU.m² and the decision for surgery for these patients was made by applying AVT as was suggested. When these patients were reevaluated according to current criteria, 20.8% of the patients (PVRI between 6 and 8 WU.m²) who were accepted as being in the gray zone, could be reconsidered for surgical eligibility. However, the patients with a PVRI of >8 WU.m², which accounted for 25% of all of the patients with PAH, would be considered inoperable according to the current criteria of PAH.

AVT is an important step to show the risk status of patients and the decision for surgery. Especially in patients with a PVRI of 6-8 WU.m² (the gray zone), sometimes, even in patients with a PVRI of >8 WU.m², AVT evaluation is performed and defect closure is recommended if the PVRI is <6 WU.m². If the PVRI is >8 WU.m², surgery is not recommended[5]. Using data from the Inhaled Nitric Oxide as a Preoperative Test (INOP Test I) study, Ronald W. Day compared the criteria of the 5th WPHS guidelines and updated consensus statement from 2019 to investigate how accurately current guidelines would identify patients with correctable and uncorrectable congenital cardiovascular shunts. Dr. Day concluded that the guidelines based upon baseline hemodynamic measurements did not provide accurate guidance for identifying patients with correctable or uncorrectable congenital cardiovascular shunts and increased pulmonary vascular resistance and the accuracy of a preoperative evaluation could be increased with AVT[14]. In our study, AVT was performed on six patients with a PVRI of ≥8 WU.m², and the decision for surgery was made as a result of AVT regression to <8 WU.m² in all six patients. Four of the six patients with a PVRI of ≥8 WU.m² had follow-ups, all four patients developed PAH after surgery and two patients died of severe PAH. Although the number of cases was low, the mortality rate of patients with a PVRI a ≥8 WU.m² was approximately 50% after surgery in the present study.

The PVRI was between 6 and 8 WU.m² in five patients in our study. AVT was not performed for these patients because it was not required at the time. We were able to perform a long-term observation for patients in the gray zone. Although all patients in the gray zone showed PAH re-development during the follow-up period, two had mild PAH, and only one patient was put on bosentan therapy. Additionally, the mean time to re-development of PAH in these patients occurred later than in patients with a PVRI of ≥8 WU.m². There were no deaths in patients in the gray zone. The current criteria for surgical eligibility may prevent the risk of adverse outcomes after surgery.

Patients with VSD remain at risk of developing PAH even after the correction of their cardiac defect. In the literature, the incidence of developing PAH is reported in a wide range[15]. The THALES registry reported that 4.5% of all patients with VSD-PAH had post-correction residual PAH[16]. In the VSD-PAH study conducted by Haneda et al., the authors observed postoperative PAH in 12/26 (46.1%) patients. Two of these patients were reported to be aged under 2 years, and 10 patients were older than 2 years[11]. In the present study, 15 (62.5%) of the surgical patients with VSD-PAH developed PAH postoperatively, seven of whom had severe PAH. In terms of PAH development time in these 15 patients, eight patients had postoperative residual PAH and seven patients showed re-developed PAH during follow-up (the median time of PAH development was 6 years). In this context, we think that the preoperative hemodynamic changes of the patients, as well as the AVT response, should be carefully evaluated in the decision for surgery. Post-operative follow-up is also critical in checking for residual PAH.

Our study has some important limitations. First, the present study is retrospective and a single-center study with a small study population. We used only oxygen for AVT in our patients because inhaled nitric oxide or inhaled iloprost were not used in our clinic

during the studied period. Finally, the treat-and-repair option may apply to patients whose PVR is at the border or to those whose PVR has not reached the desired level despite a significant decrease. The treat-and-repair strategy may increase the chance of treatment in carefully selected patients[3,17,18]. In the period when our patients underwent surgery, the treat-and-repair strategy was not used in our clinic because it was not known as a widely used method.

In conclusion, large VSD can cause PAH to develop in later life unless surgical correction is performed at an early age. Preoperative evaluation is very important in patients with large VSD and severe PAH to accurately identify suitable candidates for surgery. Patients with VSD in the gray zone should be evaluated in more detail to choose treatment options according to current criteria. Considering the standard guidelines, the preoperative hemodynamic changes of patients, as well as their AVT response, should be carefully evaluated in the decision for surgery and these patients should be followed carefully during the postoperative period.

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