ORIGINAL ARTICLE

Eastern Journal of Medicine

East J Med 24(2): 146-154, 2019
DOI: 10.5505/ejm.2019.24654

Evaluation of Pediatric Patients With Severe Pulmonary Arterial Hypertension

Serdar Epçaçan[1*], Mehmet Gökhan Ramoğlu[1], Emrah Şişli[2], Çayan Çakır[3], Zerrin Karakuş Epçaçan[4], Mustafa Orhan Bulut[5]

[1]University of Health Sciences, Van Education and Research Hospital, Department of Pediatric Cardiology, Van, Turkey
[2]University of Health Sciences, Van Education and Research Hospital, Department of Pediatric Cardiovascular Surgery Van, Turkey
[3]University of Health Sciences, Van Education and Research Hospital, Department of Cardiology, Van, Turkey
[4]University of Health Sciences, Van Education and Research Hospital, Department of Pediatrics, Van, Turkey
[5]University of Health Sciences, Dr. Siyami Ersek Hospital for Cardiology and Cardiovascular Surgery, Department of Pediatric Cardiology, Istanbul, Turkey

ABSTRACT

Pulmonary arterial hypertension (PAH) is an important cause of morbidity and mortality. Congenital heart disease associated PAH (APAH-CHD) and idiopathic PAH are classified in Group 1 PAH. There are limited studies about pediatric patients with PAH. The aim of our study is to evaluate the clinical, diagnostic and treatment characteristics of pediatric PAH.

53 consecutive patients with PAH in a 7 years' study period were retrospectively analyzed. Clinical, echocardiographic and cardiac catheterization findings and targeted treatment modalities were noted.

Thirty (56.6%) patients were male and mean age at diagnosis was 5.2±4.30 years. All patients were classified as group 1 consisting of APAH-CHD and idiopathic PAH. Patients with Eisenmenger syndrome were the largest group. Ventricular septal defect was the most CHD associated with PAH overall. Atrial septal defect, patent ductus arteriosus, atrioventricular septal defect, aortopulmonary window, double inlet left ventricle, double outlet right ventricle, d-transposition of great arteries and truncus arteriosus were other congenital heart malformations were detected. Targeted therapy were given to 34 patients (%64.1%), of them, 22 were under monotherapy, while 12 were under combined therapy. Bosentan was the most chosen drug in all. NYHA FC, exercise capacity with 6MWT improved well by targeted therapy.

Life quality and survey are improved with the targeted therapies in pediatric patients with PAH. Single drug or combination therapies including bosentan, tadalafil and inhaled iloprost are effective, safe and well tolerated with rare and minor side effects in pediatric patients with group 1 PAH.

Key Words: Pulmonary arterial hypertension, child, targeted therapy

Introduction

Pulmonary arterial hypertension (PAH) is an important cause of morbidity and mortality resulting with heart failure and death, if untreated (1,2). Pulmonary and systemic artery pressures are equal in intra-uterine period and there after pulmonary artery pressure decreases with born and in general, reaches to the adult levels in postnatal 2-3 months (3). It is assumed that PAH affects more than 25 million people worldwide (4). Congenital heart disease associated PAH (APAH-CHD) can develop as a result of a variety of lesions, mainly due to the left-to-right shunt lesions while there is no underlying cause detected in idiopathic PAH (iPAH). In time, pulmonary vascular remodeling develops reflecting as an increase in pulmonary vascular resistance (PVR) leading to reversible or irreversible vaso-occlusive pulmonary disease (5). In recent years, it is reported that with introduction of targeted treatment modalities in these rare cases, considerable rates of survival have been achieved. The targeted treatment modalities include endothelin-1 receptor antagonists (ERA) (6), phosphodiesterase-5 inhibitors (PDE-5i) (7) and prostaglandin analogs or receptor antagonists (8). The aim of our study is to evaluate the clinical, diagnostic and treatment characteristics of pediatric patients with PAH.

***Corresponding Author:** Serdar Epçaçan, University of Medical Sciences, Van Education and Research Hospital, Department of Pediatric Cardiology, Süphan district, İpek yolu street, 65400, Edremit, Van, Turkey.
E-mail: drserdar1980@gmail.com, Phone: +90 (505) 454 14 84, Fax: +90 (432) 212 19 54
Received: 01.10.2018, **Accepted:** 23.10.2018

Table 1. Baseline demographic, clinic and hemodynamic features of the patients

	All patients, n:53	APAH-CHD, n: 49					iPAH, n:4
		Eisenmenger S. n:25	Left-to-right shunts (correctable) n: 19	Left-to-right shunts (non-correctable) n: 3	PAH with coincidental CHD n:1	Post-operative PAH n: 1	
Age at diagnosis, year	5.33±4.30	6.56±5.34	4.0±2.81	5.0±2.64	7	7	3,37±3.14
Gender (%, n)							
Female	43.4%, 23	40%, 10	47.4%, 9	33.3%, 1			75%, 3
Male	56.6%, 30	60%, 15	52.6%, 10	66.7%, 2	100%, 1	100%, 1	21%, 1
WHO FC (%, n)							
II	43.4%, 23	20%, 5	84.2%, 16	33.3%, 1			25%, 1
III	49.1%, 26	68%, 17	15.8%, 3	66.7%, 2	100%, 1	100%, 1	50%, 2
IV	7.5%, 4	12%, 3					25%, 1
6 MWDT, meters	311.45±41.03	309.37±42.69		333.33±57.73	300	325	308.33 ±38.18
Hemodynamics							
mSAP, mmHg	76.05±15.77	80.44±16.99	71.31±12.27	65.66±20.3	67	90	74.25± 22.55
mPAP, mmHg	65.05±19.38	74.08±19.36	52.68±11.30	51.33±8.08	54	98	75.75± 15.08
PVRI, WU/m²	9.10±5.62	11.86±5.24	4.75±1.51	6.83±1.87	5	7	15.75± 7.93

Table 2. PVR index ranges of the patients under ambient air or 21% FiO2 if intubated

PVRI (WU/m2)	number of patients	percentage, %
>3 , <6	18	34
≥6 , <10	20	37.7
≥10, <20	10	18.9
≥20	5	9.4

Materials and Methods

In this retrospective study, pediatric patients who were diagnosed and under follow-up for PAH, between December 2011 and September 2018 were included. Along with demographic and clinical characteristics, treatment and follow-up records were collected comprised of New York Heart Association (NYHA) functional class (FC), 6-minute walk distance test (6MWDT), echocardiographic and catheterization measurements. In all patients, the diagnosis of PAH was confirmed by cardiac catheterization and acute pulmonary vasoreactivity test (AVT) was performed. Patients less than one-year-old who had a diagnosis of a severe or systemic APAH-CHD and additionally patients who were pulmonary hypertensive by means of clinical evaluation and echocardiography but the PVR was <3 woods were not included in the study. The response to AVT and operability criteria was done according to AHA/ATS guidelines (3).

All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

The statistical analysis was performed using Statistical Package for Social Sciences Software, version 21. Demographic and clinical variables were summarized with descriptive statistics. Categorical variables were summarized as absolute frequency and percentage, whereas continuous variables were summarized as mean and standard deviation (SD). Student's t test was used to conduct analysis as appropriate. P value of <0.05 was considered as significant.

Table 3. Characteristics of targeted treatment and response to therapy

	All patients n:34	APAH-CHD n:30				iPAH n:4
		Eisenmenger S. n:25	Left-to-right shunts (non-correctable) n: 3	PAH with coincidental CHD n:1	Post-operative PAH n: 1	
Monotherapy (%, n)	64.7%, 22	64.0%, 16				
Bosentan	59.8%, 20	60%, 15	100%, 3	100%, 1		25%, 1
Macitentan	2.9%, 1	4%, 1				
Tadalafil	2.9%, 1					25%, 1
Combination therapy (%, n)	35.3%, 12					
Bosentan, Iloprost	17.65%, 6	24%, 6				
Bosentan, Tadalafil	14.7%, 5	12%, 3			100%, 1	25%, 1
Bosentan, Tadalafil, Iloprost	2.9%, 1					25%, 1
WHO FC after treatment (%, n)						
II	85.3%, 29	88%, 22	100%, 3		100%, 1	75%,3
III	14.7%, 5	12%, 3		100%, 1		25%, 1
6 MWDT after treatment, meters	392.04±51.97	395.31±55.69	383.33±62.91		400	375.00 ±35.35

Results

In all 53 patients, the mean age at the time of the diagnosis and by the current age at the end of the study date were 5.33 ± 4.30 years (6 months – 15 years) and 9.63 ± 4.63 years (1.5 – 20 years), respectively. Thirty (56.6%) patients were male. The mean duration of follow-up was 3.91 ± 1.92 years (6 months – 7 years). Nine (16.9%) patients had Down syndrome. The most common complaint was fatigue (49%) following by dyspnea (30.1%), palpitation (24.5%), chest pain (20.7%), tachypnea (20.7%), respectively. 27 patients (50.9%) had cyanosis and 8 patients (15.1%) had clubbing. The initial demographic, clinical and hemodynamic characteristics of the patients including NYHA FC, 6MWDT and cardiac catheterization measurements are revealed in Table 1.

All of the patients were on group 1 PAH (Figure 1), including all subgroups of APAH-CHD (%92.45) and iPAH (7.55%).

Eisenmenger syndrome (ES) was the largest group (47.17%) following by patients with left-to-right shunted correctable CHD (35.85%). Figure 2 demonstrates CHD in patients with ES and figure 3 CHD in patients with correctable left-to right shunted CHD. In addition, three patients had left-to-right shunted but noncorrectable CHD (5.66%) one patient had post-operative PAH (1.9%) who were operated for VSD and another patient had PAH with suspected coincidental CHD (1.9%) who was operated for ASD.

The most frequent CHD was ventricular septal defect (VSD) (84.9%, n:45) in overall patients. VSD was found to be an isolated single defect in 32.1% of the patients (n:17) while it was together with other various cardiac abnormalities in 52.8% (n:25). Simple heart defects such as atrial septal defect (ASD), patent ductus arteriosus (PDA), atrioventricular septal defect (AVSD), aortopulmonary window (APW) and complex defects such as double inlet left ventricle (DILV), double outlet right ventricle (DORV), d-transposition of great arteries (d-TGA) and truncus arteriosus were detected in various frequencies (Figure 4).

Cardiac catheterization was done for all patients and an acute pulmonary vasoreactivity test was performed by using inhaled iloprost in 92.5% of patients or nitric oxide in 7.5% of patients. AVT was positive for 19 patients (%35.8) while the remaining had a negative response. Mean PVRI

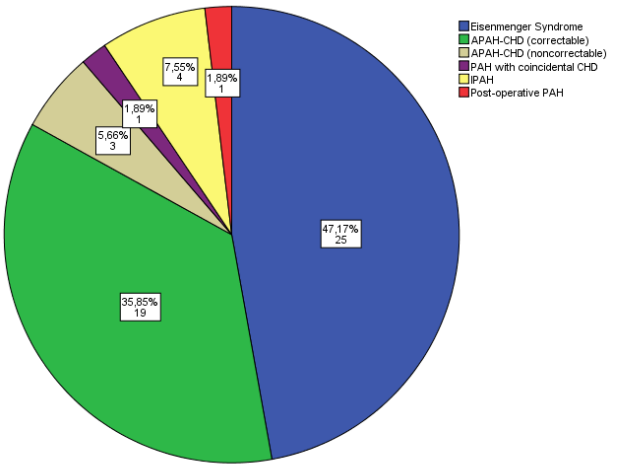

Fig. 1. The distribution of diagnosis regarding the groups and subgroups

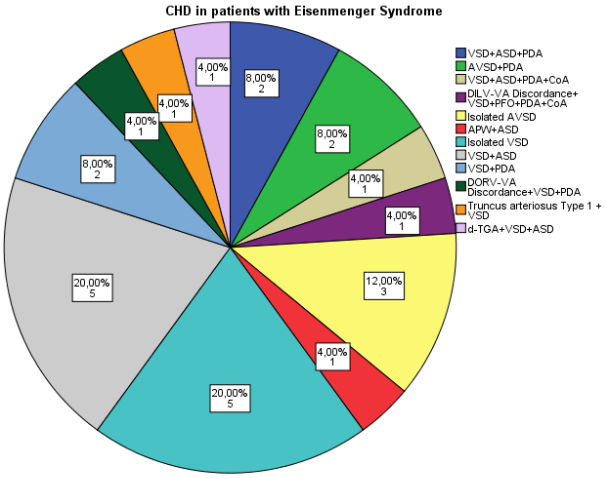

Fig. 2. CHDs in patients with Eisenmenger syndrome

was 9.04±5.66 Woods Unit overall. Table 2 shows the PVRI ranges of all patients.

Regarding 34 (64.2%) patients who were inoperable and had received target treatment for PAH; combined targeted therapy with bosentan plus iloprost or tadalafil was started initially for patients whom NYHA FC was IV while a monotherapy with bosentan or tadalafil was chosen for initial therapy for patients with NYHA FC III or less. A total of 22 patients were under monotherapy (64.7%), while 12 (35.3%) patients were under combined therapy and this ratio was coming across with 41.5% and 22.7%, respectively, of whole study group. The treatment modalities with targeted drug therapy are shown on table 3. NYHA FC and exercise capacity with 6MWT were significantly improved after targeted therapy ($p<0.05$) (Table 3).

Nineteen patients (35.8%) with mean age 4.0±2.81 years (median 3 years, range: 1.5-13 years) who were found to be operable had undergone corrective surgery. Of them only two had VSD closure with fenestrated patch while the remaining had total corrective surgery. Left ventricular enlargement with a standard deviation of at least +1.73, pulmonary flow velocity obtained by PW Doppler measurement of more than 1.66 m/sec and an oxygen saturation of at least %94 was common clinical and echocardiographic features of patients who were found to be operable. In the postoperative period, none them had severe or permanent PAH. In the postoperative sixth month, 4 over 19 (21%) patients had moderate PAH. Under non-specific treatment, the pulmonary artery pressure declined in all these patients, except one (5.2%) in whom mild PAH persistent by the end of one year. Another patient, who had undergone ventricular septal defect closure in another institute while he was 7 years old, was found to have systemic PAH in catheterization, with negative acute pulmonary vascular reactivity test and so he was accepted as postoperative PAH.

The most common drug-associated side-effect was liver aminotransferase increase in patients who received bosentan (9.3%) and oral/nasal mucosal depredation (14.2%) and headache (14.2%) in patients who received iloprost. No side effect developed in patients who received tadalafil. Compliance with medication was 100% in patients who received bosentan and tadalafil, and 83.3% in patients under treatment of iloprost. In one patient older than 18 years an increase in liver enzymes was developed due to bosentan, the medication was shifted to macitentan. The increase in liver enzymes substantiated in other two patients in whom the medication dose was substantially increased (62.5mg BID to 125mg BID) as for the body weight. Drug increasement was withdrawn and liver aminotransferases regressed to normal values. The medication was halted in another patient with Down syndrome who was receiving bosentan, because of leucopenia and anemia. He had also an accompanying lower respiratory tract infection at that time. Bosentan medication was reinstituted in these patients after 2 weeks and thereafter, no side-effect was detected.

As for all patients, two (3.7%) patients died during the follow-up period. One of them had undergone atrial septal defect closure when he was seven years old in another institute and diagnosed as PAH co-incidental with CHD after a couple of months. The other one was a patient with Down syndrome and complete atrioventricular septal

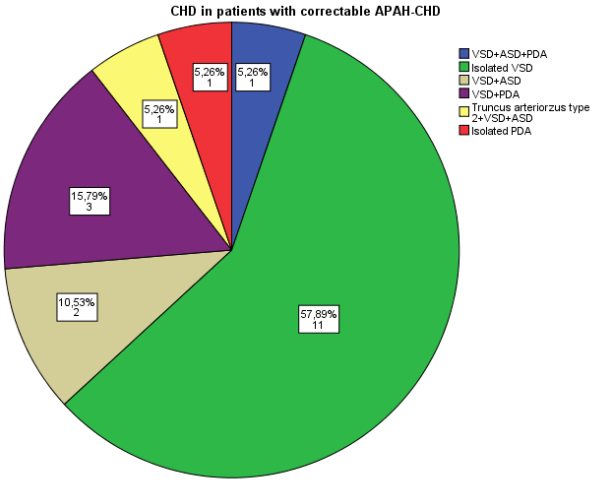

Fig. 3. CHDs in patients with correctable left-to right shunted defects

defect with PAH. It was considered as operable but his family did not give consent for a high-risk surgery. This patient had multiple hospitalizations for pneumonia and died due to severe pneumonia, sepsis and multi-organ failure.

Discussion

World Health Organization (WHO) defined pulmonary arterial hypertension; as a mean pulmonary artery pressure (mPAP) ≥25 mmHg with a pulmonary artery wedge pressure PAWP <15 mmHg and a PVR >3 WU at sea level in patients older than 3 months of age and classified into five groups. Pulmonary arterial hypertension associated with congenital heart disease and idiopathic pulmonary arterial hypertension are classified in Group 1. Congenital heart disease associated pulmonary arterial hypertension is classified into four subgroups: Eisenmenger Syndrome; PAH associated with prevalent systemic to pulmonary shunts; PAH with coincidental CHD and postoperative PAH (9) . Although recently some changes are presented at 5th World Symposium on Pulmonary Hypertension (NICE 2018); they are not published yet. In our study the patients were classified according to the 2013 WHO classification of pulmonary hypertension.

Although the exact prevalence of APAH-CHD in adult and pediatric population is unclear, epidemiologic data is being tried to be established by national databases and multi-center registries. For adult population, prevalence of PAH is estimated to be 15-50 cases per million (10) where its estimated prevalence is 10 cases per million in childhood (11). The prevalence of APAH-CHD in PAH was reported as 10% in the REVEAL study (12) where, the prevalence of ES was reported as 7.6% (13). In our study APAH-CHD was the largest group accompanying 92.5% of the patients, where iPAH was in 7.5% overall. APAH-CHD was consisting of Eisenmenger Syndrome: 47.2 % (n: 25), correctable CHD with left to right shunt (35.8 %), non-correctable CHD with left-to-right shunt (5.7%), PAH with coincidental CHD (1.9 %), and postoperative PAH (1.9 %). Although the disease is more common in adulthood, early diagnosis and accurate treatment is crucial because the pulmonary vascular changes may be observed after the age of 2 years. Large VSD's, atrioventricular septal defects, large ASD, PDA and many other cardiac defects may lead to ES (14). . In our study, the most common congenital heart defect was VSD (84.8%, n:45) overall followed by ASD (35.8%), PDA (%30.2), AVSD (9.4%), patent foramen ovale (PFO) (3.8%), truncus arteriosus (3.8%), APW (%1.9), DILV-VA discordance (1.9%), DORV-VA discordance (1.9%), d-TGA with large VSD (1.9%) and aortic interruption with large VSD and PDA (1.9%). VSD, ASD and PDA were in association with other CHDs in 52.8%, 30.1% and 28.3%, respectively. In contrast they were isolated defects in 32.1%, 5.7%, 1.9 % of all, respectively. When CHDs in patients with ES were analyzed, again VSD was the most common (88%) followed by ASD (48%), PDA (36%), AVSD (20%), DORV-VA discordance (4%), DILV-VA discordance (4%), d-TGA with VSD (4%) and APW (4%).

Although the prevalence of the disease in childhood is similar in both sexes, it is reported that there is female predominance after puberty (3). In our study, there was a male predominance (56.6%). Shortness of breath, fatigue, chest pain, palpitation, syncope and easy fatigability are common symptoms in patients with pulmonary hypertension; but rarely cyanosis, clubbing, coagulation abnormalities, cerebrovascular accidents and sudden death may be observed (5). In our study the most common complaint was easy fatigability (49%); cyanosis and clubbing was present in 50.9 % (n: 27) and 15.1% (n: 8) of the cases, respectively. Exercise intolerance is common in these group of patients and most of the cases are in NYHA Class II or over (13). The distribution of patients according to NYHA Functional Class (FC) at admission were as follows: NYHA FC IV: 7.5% (n: 4), NYHA FC III: 49.1% (n: 26), and NYHA FC II: 43.4% (n: 23). There was significant improvement in NYHA functional class after treatment with majority of

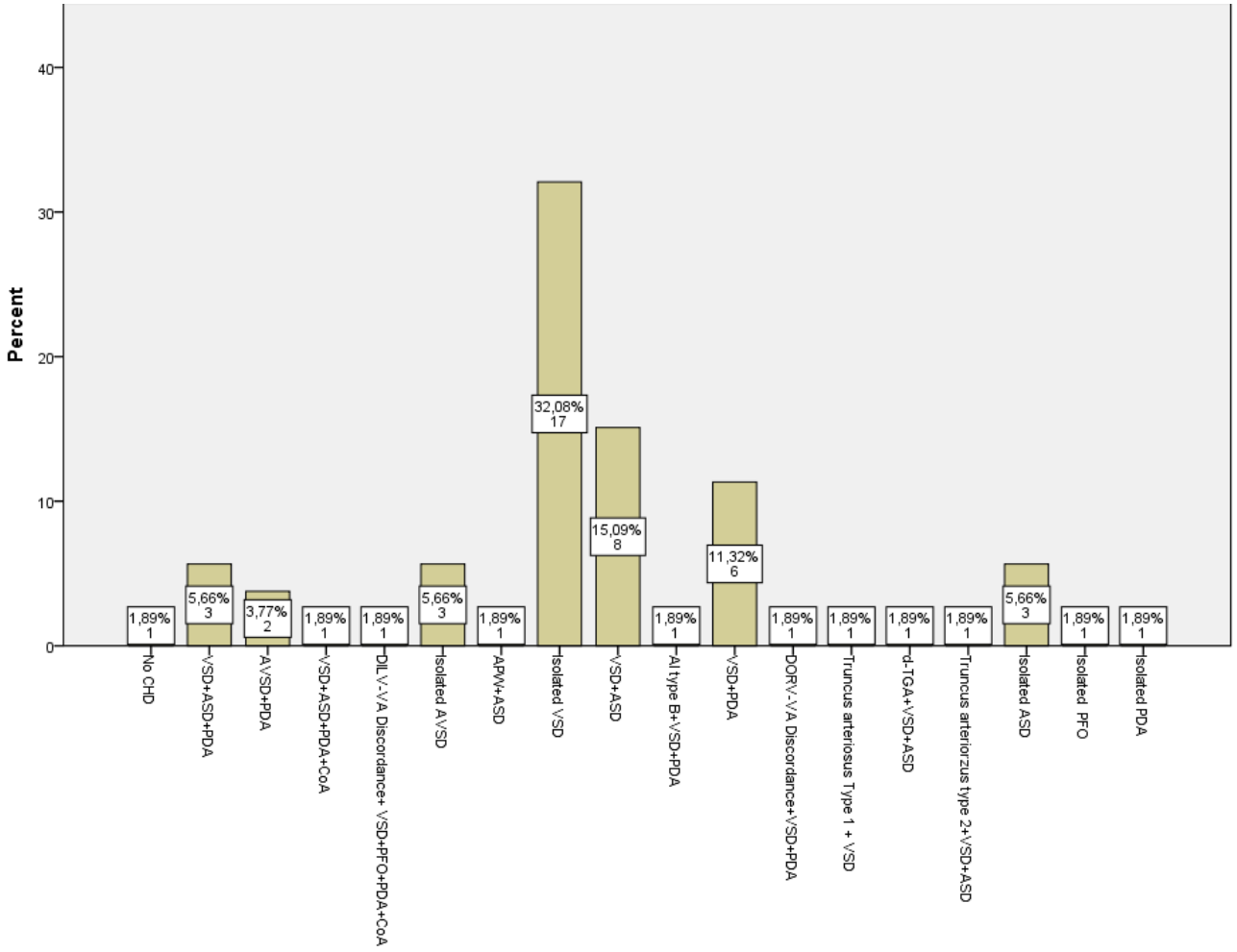

Fig. 4. CHDs detected in all patients

the patients on NYHA FC II (85.3%), no NYHA FC IV and the remaining on NYHA FC III. The 6-minute walk distance test is commonly used to determine and to follow up exercise related desaturation and exercise tolerance. Also 6MWDT is used to define prognosis of the disease and there are studies reporting standard references for pediatric and adult population (15). Patients with a 6MWDT < 300 m and patients are classified in high risk group whereas patients with a 6MWDT > 500 m in low risk group (16). The mean 6MWDT was 308.82±41.40 meters at the time of admission and in 5 of the patients the 6MWDT was below 300 meters. After treatment 6MWDT was 392.04±51.97 meters where there was not any patient with 6MWDT under 300 meters and this increase was significant ($p<0.05$).

Surgical correction is contraindicated in patients with severe pulmonary vascular disease and in ES. Surgical correction may be considered in patients with pulmonary hypertension, but those who don't have irreversible pulmonary vascular disease and who have positive pulmonary vasoreactivity test. Repair should be considered if PVRI is <6 and PVR/SVR is <0.3. Repair can be beneficial in patients with a PVRI ≥6 and PVR/SVR ≥3, if AVT reveals reversibility of PAH with reduction in PVRI below 6 and PVR/SVR to <0.3. In the case of a PVRI ≥6 and PVR/SVR ≥3 and minimal responsiveness to AVT, repair is not indicated and it is reasonable to implement PAH targeted therapy and after treatment for 4-6 months, surgical correction or fenestrated patch may be considered if PVRI is <6 (3). On the other hand, according to our experience, echocardiographic findings such as left ventricular enlargement, increased pulmonary flow and a clinical finding of oxygen saturation of at least %94 seem on room air were good noninvasive clues for operability despite PAH. In our study, surgical correction was performed in 19 (35.8%) patients and only in one of them (5.2%) mild pulmonary hypertension was observed at the first year of the surgery. All the patients had total correction except two patients who had fenestrated patch for VSD. In patients with diagnosis of iPAH, interatrial septostomy (17), reverse Pott' s shunt (18) and lung transplantation (19) may be performed in selected

patients. Interatrial septostomy and stenting or reverse Pott's shunt was recommended in one patient with diagnosis of iPAH and was internalized to intensive care unit several times because of pulmonary hypertensive crisis and right ventricular failure, but none of these procedures were performed because the parents did not approve the procedures. This patient was NYHA FC IV and a 6MWT of 300 meters initially while after triple combination therapy consisting of bosentan, tadalafil and iloprost a NYHA FC III and a 6MWT of 375 meters.

There are studies reporting the efficacy of PAH specific treatments in pulmonary hypertension and the survey of these patients especially in pediatric age group is increasing. Bosentan, which is an orally active dual endothelin receptor antagonist, was reported to be effective in improving exercise capacity, NYHA functional class, and hemodynamic parameters by the BREATHE-5 study which was a multicenter, double-blind, randomized, placebo controlled study (20). In our study distribution of targeted PAH therapy, bosentan was the first choice of targeted regimens and so it was the most common agent used. It was included in almost all of the monodrug therapies and in all combination therapies. It was successful by improving exercise capacity with 6MWDT and NYHA FC alone in 62.7% of patients where a combination therapy was required in 35.3% of the patients. Elevated transaminase levels can be a serious side effect of bosentan and this is more commonly observed in patients aged ≥12 (7.8%) compared to patients younger than <12 (2.7%) (21). In our study, bosentan associated liver aminotransferase elevation had occurred in three patients (7.4%) and all of them were above 12 years old. In one of them the treatment was shifted to macitentan and in the other two dose increasement with grow-up was withdrawn and liver aminotransferase regressed to normal values. In another patient with Down syndrome, the medication was halted because of leucopenia and anemia. He had also an accompanying lower respiratory tract infection at that time. Bosentan medication was reinstituted in these patients after 2 weeks and thereafter, no side-effect was detected. There are ongoing studies for assessing the efficacy of macitentan, a new dual endothelin-receptor antagonist. The SERAPHIN study showed that macitentan improved exercise capacity and reduced morbidity and mortality in adult patients (6). Aypar et al. reported that switch from bosentan to macitentan significantly improved exercise capacity in children aged over 12 and young adults (22). In our study, bosentan was shifted to macitentan in a patient (> 18 years of age) with diagnosis of ES because of elevated liver transaminase levels as mentioned above. At 6 moths of follow-up, there was no change in echocardiographic and hemodynamic parameters and oxygen saturation but there was an improvement in 6MWDT.

There is not sufficient prospective randomized studies evaluating the efficacy of PDE-5 inhibitors specifically in APAH-CHD patients; however they are shown to be effective in PAH patients (23). Yamazaki et al. investigated the efficacy of tadalafil in pediatric PAH patients and reported that the incidence of side effects of tadalafil was significantly lower in children in comparison to adults. They also reported that there was improvement in WHO functional class, decline in mPAP and survival rates at 1 and 2 year were 98.3 % and 93.7%, respectively (24). In our study a total of 7 patients (3 iPAH and 4 ES), were given tadalafil. One patient with diagnosis of iPAH was using tadalafil monotherapy while 5 patients were using in combination with bosentan and 1 patient was using in combination with bosentan and iloprost. Tadalafil was successful in treatment of one infant with iPAH alone (follow-up time was six months). After adding tadalafil to double or triple combination therapies there was no need of additional drug employment in any of the patients. No side effect associated with tadalafil was occurred.

Inhaled iloprost may be used in children with progressive and persistent PAH, usually in combination with ERA and PDE-5 inhibitors as an off-label drug. It was reported in a prospective study that 24 weeks of inhaled iloprost therapy improved quality of life and exercise capacity but hemodynamic parameters did not improve (25). There is not sufficient data about inhaled iloprost-sildenafil and inhaled iloprost-bosentan combination therapy in pediatric age group. In our study 7 patients were under inhaled iloprost therapy. Six of them were using inhaled iloprost in combination with bosentan and one was using in combination with bosentan and tadalafil. Bosentan and iloprost combination was seemed to be effective for majority of the patients whereas, it was ineffective so tadalafil was added to combination therapy as a third drug in one patient. Headache, jaw pain and airway hyper-reactivity may occur with initiation of treatment (26). Oral/nasal mucosal depredation (14.2%) and headache (14.2%) had occurred in two separate patients receiving inhaled iloprost so in both of

them iloprost was shifted to tadalafil. The application of 6-9 dosages/day has a negative effect on patient compliance and quality of life. Compliance with medication was 83.3% in our patients under treatment of iloprost. This lack of compliance was due to denial of the inhaled treatment, application of at least 6 doses a day, inopportuneness of the patients at school age or getting out of order of the nebulizer device.

Before the advent of PAH targeted specific therapy, survival rates for PAH at 1st, 3rd and 5th years were 66%, 52% and 35%, respectively (27) but with the time studies reported increased survival rates (28). Patients with ES have 4 fold increased mortality risk compared to healthy individuals (29). In contrast to this, some studies reported that survival rates of patients with ES are higher than other PAH patients (30). Also there was no significant difference in survival rates in REVEAL study (13). In our study population patients with postoperative PAH and iPAH without any shunt had worse outcome than patients with Eisenmenger group while the coincidental PAH with surgically closed defect had the worst outcome.

Early diagnosis and accurate treatment of CHD is crucial for preventing development of PAH and ES. Left ventricular enlargement, increased pulmonary blood flow and oxygen saturation of above 94% may be clues for operability criteria. Life quality and survey are improved with the targeted therapies in pediatric patients with PAH. Single drug or combination therapies including bosentan, tadalafil and inhaled iloprost are effective, safe and well tolerated with rare and minor side effects, improving exercise capacity, 6MWDT and NHYA functional class in patients with APAH-CHD (surgically non-correctable), ES and iPAH.

References

1. Olgunturk R. Pediatric pulmonary hypertension and pulmonary arterial hypertension secondary to congenital heart diseases. Anadolu Kardiyol Derg 2010; 10: 50-56.
2. Hansmann G, Apitz C, Abdul-Khaliq H, et al. Executive summary. 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: 86-100.
3. Abman SH, Hansmann G, Archer SL, et al. Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society. Circulation 2015; 132: 2037-2099.
4. Elliott CG, Barst RJ, Seeger W, et al. Worldwide physician education and training in pulmonary hypertension: pulmonary vascular disease: the global perspective. Chest 2010; 137: 85-94.
5. Frank DB, Hanna BD. Pulmonary arterial hypertension associated with congenital heart disease and Eisenmenger syndrome: current practice in pediatrics. Minerva Pediatr 2015; 67: 169-185.
6. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med 2013; 369: 809-818.
7. 7. Tantini B, Manes A, Fiumana E, et al. Antiproliferative effect of sildenafil on human pulmonary artery smooth muscle cells. Basic Res Cardiol 2005; 100: 131 - 138.
8. Olschewski H, Simonneau G, Galie N, et al. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med 2002; 347: 322-329.
9. Simonneau G, Torbicki A, Hoeper MM, et al. Selexipag: an oral, selective prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. Eur Respir J 2012; 40: 874-880.
10. Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 2006; 173: 1023-1030.
11. Fraisse A, Jais X, Schleich JM, et al. Characteristics and prospective 2-year follow-up of children with pulmonary arterial hypertension in France. Arch Cardiovasc Dis 2010; 103: 66-74.
12. Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. Chest 2010; 137: 376-387.
13. Barst RJ, Ivy DD, Foreman AJ, et al. Four- and seven-year outcomes of patients with congenital heart disease-associated pulmonary arterial hypertension (from the REVEAL Registry). Am J Cardiol 2014; 113: 147-155.
14. Beghetti M, Galie N. Eisenmenger syndrome a clinical perspective in a new therapeutic era of pulmonary arterial hypertension. J Am Coll Cardiol 2009; 53: 733-740.
15. Galie N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the

International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009; 30: 2493-2537.

16. Mclaughlin VV, Mcgoon MD. Pulmonary arterial hypertension. Circulation 2006; 114: 1417-1431.
17. Sandoval J, Gaspar J, Pena H, et al. Effect of atrial septostomy on the survival of patients with severe pulmonary arterial hypertension. Eur Respir J 2011; 38: 1343-1348.
18. Baruteau AE, Belli E, Boudjemline Y, et al. Palliative Potts shunt for the treatment of children with drug-refractory pulmonary arterial hypertension: updated data from the first 24 patients. Eur J Cardiothorac Surg 2015; 47 3: 105-110.
19. Deville-Bonne D, Le Bras G, Teschner W, Garel JR. Ordered disruption of subunit interfaces during the stepwise reversible dissociation of Escherichia coli phosphofructokinase with KSCN. Biochemistry 1989; 28: 1917-1922.
20. Galie N, Beghetti M, Gatzoulis MA, et al. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. Circulation 2006; 114: 48-54.
21. Beghetti M, Hoeper MM, Kiely DG, et al. Safety experience with bosentan in 146 children 2-11 years old with pulmonary arterial hypertension: results from the European Postmarketing Surveillance program. Pediatr Res 2008; 64: 200-204.
22. 22. Aypar E, Alehan D, Karagoz T, et al. Clinical efficacy and safety of switch from bosentan to macitentan in children and young adults with pulmonary arterial hypertension. Cardiol Young 2018; 28: 542 - 547.
23. Galie N, Brundage BH, Ghofrani HA, et al. Tadalafil therapy for pulmonary arterial hypertension. Circulation 2009; 119: 2894-2903.
24. Yamazaki H, Kobayashi N, Taketsuna M, et al. Safety and effectiveness of tadalafil in pediatric patients with pulmonary arterial hypertension: a sub-group analysis based on Japan post-marketing surveillance. Curr Med Res Opin 2017; 33: 2241-2249.
25. Cha KS, Cho KI, Seo JS, et al. Effects of inhaled iloprost on exercise capacity, quality of life, and cardiac function in patients with pulmonary arterial hypertension secondary to congenital heart disease (the Eisenmenger syndrome) (from the EIGER Study). Am J Cardiol 2013; 112: 1834-1839.
26. Ivy DD, Doran AK, Smith KJ, et al. Short- and long-term effects of inhaled iloprost therapy in children with pulmonary arterial hypertension. J Am Coll Cardiol 2008; 51: 161-169.
27. Barst RJ, Maislin G, Fishman AP. Vasodilator therapy for primary pulmonary hypertension in children. Circulation 1999; 99: 1197-1208.
28. Barst RJ, Mcgoon MD, Elliott CG, et al. Survival in childhood pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. Circulation 2012; 125:113-122.
29. Diller GP, Dimopoulos K, Broberg CS, et al. Presentation, survival prospects, and predictors of death in Eisenmenger syndrome: a combined retrospective and case-control study. Eur Heart J 2006; 27: 1737-1742.
30. Manes A, Palazzini M, Leci E, et al. Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: a comparison between clinical subgroups. Eur Heart J 2014; 35: 716-724.