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# NATURAL HISTORY OF CONGENITAL ISOLATED MILD AORTIC VALVE AND MILD PULMONARY VALVE STENOSIS: A SINGLE-CENTER FOLLOW-UP STUDY

## KONJENİTAL İZOLE HAFİF AORT KAPAK VE HAFİF PULMONER KAPAK DARLIĞININ DOĞAL SEYRİ: TEK MERKEZLİ BİR TAKİP ÇALIŞMASI

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### ABSTRACT

**Objective:** Most of the available information on the natural history of aortic stenosis (AS) and pulmonary stenosis (PS) in children is based on studies carried out over the past 35-40 years using cardiac catheterization. This study aimed to reveal the natural history of congenital isolated mild valvular AS and PS in children using serial Doppler echocardiographic examinations.

**Materials and Methods:** A total of 125 children, 50 with mild AS and 75 with mild PS, who underwent Doppler echocardiography were included in this study. The prognoses of mild AS and PS were compared according to age, gender, and valvular gradient at the time of initial diagnosis.

**Results:** The mean age of patients was 26.1±37.6 months at diagnosis. The mean follow-up duration was 27.65±21.60 (1-120) months. There was a significant decrease in the final gradient of the PS group compared to the baseline (23.58±6.97 vs. 19.88±11.21 mmHg, p=0.001). In the AS group, there was an increase in the final gradient, which was more pronounced in patients ≤1-year-old (22.42±6.12 vs. 27.74±14.12 mmHg, p=0.002). Four percent of patients in the PS group and 12% of patients in the AS group progressed to moderate to severe stenosis. All patients who progressed in the PS group were ≤1-year-old and male.

**Conclusion:** The results showed that mild PS had a better prognosis than mild AS and that the risk of progression in AS was higher. Careful follow-up should be performed in mild PS cases ≤1-year-old, especially in boys, since progression may be detected, even if infrequently. Mild AS should also be followed closely, as the disease may show progressive characteristics in all age groups.

**Keywords:** Congenital, aortic stenosis, pulmonary stenosis, natural history, pediatrics, echocardiography

### ÖZET

**Amaç:** Hafif aort darlığı (AD) ve hafif pulmoner darlığın (PD) doğal seyri hakkındaki bilgilerin birçoğu geçmiş 35-40 yıllık kardiak kateterizasyon kullanılarak yapılmış olan çalışmalara dayandırılmaktadır. Bu çalışmanın amacı, çocuk hastalarda izole hafif valvüler AD ve izole hafif valvüler PD'nin doğal seyrini, seri Doppler ekokardiyografik ölçümler ile ortaya koymaktı.

**Gereç ve Yöntem:** Bu çalışmaya hafif AD tespit edilen 50 ve hafif PD tespit edilen 75, toplam 125 çocuk dahil edildi. Hafif AD ve PD'nin klinik seyirleri cinsiyet, ilk tanı anındaki yaş ve valvüler gradiyente göre karşılaştırıldı.

**Bulgular:** Tanı yaşı ortalaması 26,1±37,6 ay (1 gün-13 yaş) idi. Çocukların ortalama izlem süresi 27,65±21,60 (1-120) aydı. PD grubunun final gradiyentlerinde başlangıca göre belirgin azalma saptandı (19,88±11,21'e karşı 23,58±6,97 mmHg, p=0,001). AD grubunda bir yaş altı hastalarda daha belirgin olmak üzere tüm hastaların final gradiyentlerinde artış saptandı (27,74±14,12'ye karşı 22,42±6,12 mmHg, p=0,002). AD grubunda final gradiyentin ortalaması, PD grubuna göre daha yüksekti (27,74±14,12'ye karşı 19,88±11,21 mmHg, p=0,001). PD grubunda toplamda hepsi erkek ve ≤1 yaş olan %4 hastada orta-ileri darlığa progresyon görüldü. AD grubunun %12'sinde orta-ileri darlığa progresyon görüldü. Hafif AD olanlardan iki hastaya, hafif PD olanlardan ise bir hastaya girişim yapıldı.

**Sonuç:** Çalışmamızda hafif PD'nin hafif AD'ye göre seyrinin daha iyi olduğu ve AD'nin progresyon gösterme riskinin daha yüksek olduğu gösterildi. Bir yaş ve altındaki, özellikle erkek hafif PD olgularında sık olmasa da progresyon saptanabileceğinden dikkatli takip yapılmalıdır. Hafif AD ise, hastalık her yaş grubunda progresif özellik gösterebileceğinden yakın takip edilmelidir.

**Anahtar Kelimeler:** Konjenital, aort darlığı pulmoner darlığı, doğal seyir, pediatri, ekokardiyografi

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## INTRODUCTION

Valvular aortic stenosis (AS) is defined as left ventricular outflow tract obstruction at the aortic valve level and is the fifth most common congenital heart lesion. Its prevalence is between 4-7%. Valvular pulmonary stenosis (PS) is defined as obstruction at the pulmonary valve level in the right ventricular outflow tract and is the fourth most common congenital heart lesion. Its prevalence varies between 8-10% (1, 2). Most of the existing information on the natural history of mild AS and mild PS is based on serial studies using cardiac catheterization carried out over the past 15-20 years (1, 3, 4). Doppler echocardiography has been used frequently in cases of mild to moderate AS and PS, as it is a non-invasive diagnostic method, facilitates diagnosis and treatment, and can be used with patients of all ages (5). Cardiac catheterization is a highly invasive diagnostic method for these patients. Furthermore, Doppler echocardiography provides more information regarding valve thickness and stenosis than catheterization procedures (5, 6). This study aimed to demonstrate the natural history of congenital isolated mild valvular AS and congenital isolated mild valvular PS in children by comparing them according to age and gender using serial Doppler echocardiographic measurements.

## MATERIAL AND METHODS

The patients (n=125) were those with congenital isolated valvular AS (n=50) and congenital isolated valvular PS (n=75), who underwent Doppler echocardiography in the Department of Pediatric Cardiology.

The patients were divided into two subgroups according to their age at the time of diagnosis as ≤1-year-old and >1-year-old. All patients had mild stenosis at initial diagnosis (pressure gradient less than 41 mmHg measured via Doppler echocardiography). Echocardiographic measurements were obtained retrospectively from medical records.

The exclusion criteria were as follows: i) patients who had only a single echocardiographic examination); ii) patients with additional cardiac anomalies except for small patent ductus arteriosus and patent foramen ovale; iii) patients with abnormal ventricular function; and iv) patients with systemic diseases or genetic disorders.

The study was approved by the Istanbul Kanuni Sultan Süleyman Training and Research Hospital Ethics Committee (Date: 25.06.2009, No: 279). The study conforms to the principles outlined in the Declaration of Helsinki.

### Transthoracic Doppler echocardiography

The study was performed using the Acuson 128/XP 10 echocardiography system and an age-appropriate transducer. Pulmonary and aortic valve morphologies and the status of the ventricles were evaluated by two-dimensional echocardiography. A quantitative assessment of the severity of valve stenosis was estimated using the aortic and pulmonic valve pressure gradient. The transvalvular pressure gradient (P) calculated from the peak instantaneous continuous-wave Doppler echocardiographic velocity measurements obtained using the Bernoulli equation was used to assess the severity of stenosis, as follows: $P=4x(\text{maximum velocity})^2$ (7).

### Statistical analysis

Statistical analysis was performed with SPSS 19.0 for Windows (IBM Corp. since v. 19.0, Chicago, IL, USA). Continuous data was expressed as the mean±SD, categorical data was expressed as number and percentages. Kruskal–Wallis test was used for comparison among non-parametric variables between groups. Mann Whitney U test was used for comparisons of parameters between two groups. A Chi-square test was used to assess the differences in categorical variables between the groups. Intraclass correlation analysis was used to examine the relationships between parameters. A p-value <0.05 was considered statistically significant.

## RESULTS

The children in the study population (n=125) were girls (n=51, 41%) and boys (n=74, 59%). The ages of the children at initial diagnosis ranged from 1 day-13 years, with an average of 26.1±37.6 months. The duration of follow-up ranged from 1 month-10 years, with an average of 27.7±21.6 months from initial diagnosis. The children were divided into the following two groups: mild PS group (n=75) and, mild AS group (n=50). While the age of 63% (n=79) of the children at initial diagnosis was ≤1-year-old, 37% (n=46) of the children were >1-year-old. There were no statistically significant differences between the duration of follow-up for the children in the AS and PS groups (p>0.05). In the mild PS group, the number of children ≤1-year-old was higher at initial diagnosis than in the mild AS group. (n=60, 80% vs. n=19, 38%, p=0.001). The ratio of boys to girls in the AS group was statistically significantly higher than that of the PS group (n=37, 74% vs. n=37, 49%, p=0.006) (Table 1).

There was no statistically significant difference between the initial gradients of the AS and PS groups (22.42±6.12 vs. 23.58±6.97 mmHg, p=0.380). However, the final gradient was statistically significantly higher in the AS group than in the PS group (27.74±14.12 vs. 19.88±11.21 mmHg, p=0.001). In children with PS, the decrease in the final gradient compared to the initial gradient was statistically significant (23.58±6.97 vs. 19.88±11.21 mmHg, p=0.001). In children with AS, the increase in the final gradient compared to the initial gradient was statistically significant (22.42±6.12 vs. 27.74±14.12 mmHg, p=0.002) (Figure 1).

**Table 1:** Comparison of age, gender, and follow-up duration of the groups

| | PS group (n=75) | AS group (n=50) | p-value |
|---|---|---|---|
| **Age at initial diagnosis** | | | |
| ≤1 year, n (%) | 60 (80%) | 19 (38%) | 0.001 |
| >1 year, n (%) | 15 (20%) | 31 (62%) | |
| **Gender** | | | |
| Girl, n (%) | 38 (51%) | 13 (26%) | 0.006 |
| Boy, n (%) | 37 (49%) | 37 (74%) | |
| **Follow-up duration (months)** | 26.6±21.1 (20) | 29.3±22.6 (23) | 0.386 |

There was a significant difference between the levels of change in the final gradients between the AS and PS groups compared to the initial gradients (p=0.001). Children with AS had a higher rate of increase in terms of the final gradient relative to the initial gradient as compared to children with PS (60% vs. 24%). In contrast, children with PS had a higher rate of decrease in terms of the final gradient relative to the initial gradient compared to children with AS (65% vs. 26%).

In the children with PS, all 31 girls aged ≤1 year at diagnosis had a mild final gradient. Of the 29 boys aged ≤1 year at diagnosis, the final gradient for 26 of them was mild, for two was moderate, and for one was significant. The final gradient of all children with PS aged >1 at diagnosis was mild. In the children with AS, five girls aged ≤1 year at diagnosis had a mild final gradient, and one had a moderate final gradient. Ten boys aged ≤1 year at diagnosis had a mild final gradient while one had a moderate final gradient, and two had a severe final gradient. Of the seven girls aged >1 year at diagnosis, six had a mild final gradient while one had a moderate final gradient. Of the 24 boys aged >1 year at diagnosis, 23 had a mild final gradient while one of them had a moderate final gradient (Table 2).

In the PS group, the initial gradients of the children aged ≤1-year-old were statistically significantly higher than the initial gradients of those aged >1-year-old (24.63±6.79 vs. 19.40±6.25 mmHg, p=0.013). There was no statistically significant difference between the final gradients of the children according to age at diagnosis (20.83±11.75 vs. 16.07±7.94 mmHg, p=0.160). In children ≤1-year-old, the decrease in the final gradient compared to the initial gradient was statistically significant (24.63±6.79 vs. 20.83±11.75 mmHg, p=0.002). In children >1-year-old, there was no statistically significant change in the final gradient compared to the initial gradient (19.40±6.25 vs. 16.07±7.94 mmHg, p=0.136) (Figure 2A).

In the AS group, in children aged ≤1-year-old, the increase in the final gradient compared to the initial gradient was

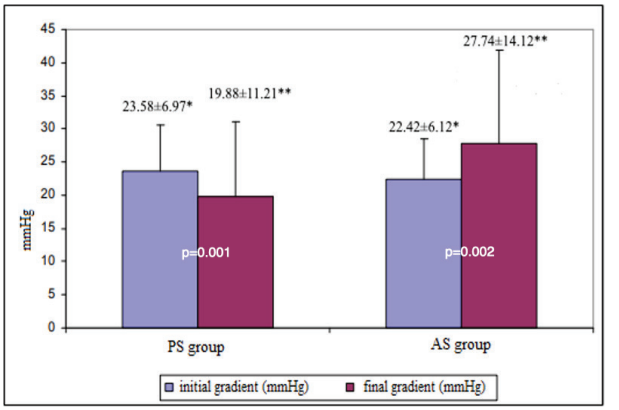


**Figure 1:** Comparison of the initial and final gradients of the children with PS and AS

*: p=0.380, **: p=0.001

statistically significant (21.84±7.08 vs. 31.95±19.28 mmHg, p=0.002). In children aged >1-year-old, there was no statistically significant change in the final gradient compared to the initial gradient (22.77±5.55 vs. 25.16±9.18 mmHg, p=0.121). There were no statistically significant differences between the initial and final gradients of the children according to age at diagnosis (Figure 2B).

When comparing children with PS in terms of gender, the decrease in the final gradient compared to the initial gradient for the girls was statistically significant (22.76±5.90 vs. 17.71±7.53 mmHg, p=0.001). However, for boys, there was no statistically significant change in the final gradient compared to the initial gradient (24.43±7.92 vs. 22.11±13.78 mmHg, p=0.133) (Figure 3A).

In girls with AS, the increase in the final gradient compared to the initial gradient was statistically significant (20.23±5.38 vs. 26.54±13.02 mmHg, p=0.010). Again, for the boys, the increase in the final gradient compared to the initial gradient was statistically significant (23.19±6.24 vs. 28.16±14.63 mmHg, p=0.030) (Figure 3B).

Bicuspid aortic valves were detected in 18 of the 50 children with mild AS, and no statistical difference was found between those with and without bicuspid valves in terms of age at initial diagnosis (p=0.777), final gradients (p=0.730), and follow-up durations (p=0.412).

There was a statistically significant difference in the changes in the final gradients compared to the initial gradients between children with PS and AS at ≤1 year of age. A decrease was seen in the final gradients from the baseline in children with mild PS, while an increase was seen in children with mild AS (-3.80±10.37 vs. 10.10±17.03 mmHg, p=0.001).

There was a statistically significant difference in the changes in final gradients compared to initial gradients between children with PS and AS at >1 year of age. A decrease was

**Table 2:** Distribution of final gradients and follow-up durations by age and gender in children with mild aortic and pulmonary stenosis

| | Age at initial diagnosis | Gender | Final gradient | Follow-up duration (months) |
|---|---|---|---|---|
| Aortic stenosis | ≤1 year | Girls (n=6) | Mild: 5 | 17.8±7.4 |
| | | | Moderate: 1 | 19 |
| | | | Severe: 0 | - |
| | | Boys (n=13) | Mild: 10 | 17.0±10.9 |
| | | | Moderate: 1 | 14 |
| | | | Severe: 2 | 16.7±10.4 |
| | >1 year | Girls (n=7) | Mild: 6 | 38.8±40.6 |
| | | | Moderate: 1 | 18 |
| | | | Severe: 0 | - |
| | | Boys (n=24) | Mild: 23 | 36.8±21.0 |
| | | | Moderate: 1 | 17 |
| | | | Severe: 0 | - |
| Pulmonary stenosis | ≤1 year | Girls (n=31) | Mild: 31 | 26.3±25.3 |
| | | | Moderate: 0 | - |
| | | | Severe: 0 | - |
| | | Boys (n=29) | Mild: 26 | 24.8±18.4 |
| | | | Moderate: 2 | 44.0±7.1 |
| | | | Severe: 1 | 2 |
| | >1 year | Girls (n=7) | Mild: 7 | 19.9±13.0 |
| | | | Moderate: 0 | - |
| | | | Severe: 0 | - |
| | | Boys (n=8) | Mild: 8 | 38.1±14.2 |
| | | | Moderate: 0 | - |
| | | | Severe: 0 | - |

**Table 3:** Comparison of changes in final gradients from initial gradients in PS and AS groups according to age at diagnosis

| Age | | Change in final gradient from baseline (mmHg) | p-value |
|---|---|---|---|
| ≤1 year | PS group | -3.80±10.37 | 0.001 |
| | AS group | 10.10±17.03 | |
| >1 year | PS group | -3.33±10.42 | 0.024 |
| | AS group | 2.39±7.22 | |

seen in the final gradients from the baseline in children with mild PS, while an increase was seen in children with mild AS (-3.33±10.42 vs. 2.39±7.22 mmHg, p=0.024) (Table 3).

## DISCUSSION

Children with congenital mild valvular PS and mild valvular AS with congenital intact septum without any additional cardiac pathology were included in our study. We aimed to reveal the natural history of children with PS and AS whose initial diagnosis ages were ≤1 and >1 and to provide accurate data on their prognoses for their families. Our study was conducted with a total of 125 children, 51 (41%) girls and 74 (59%) boys. Age at diagnosis ranged from one day to 13 years, and the children were examined

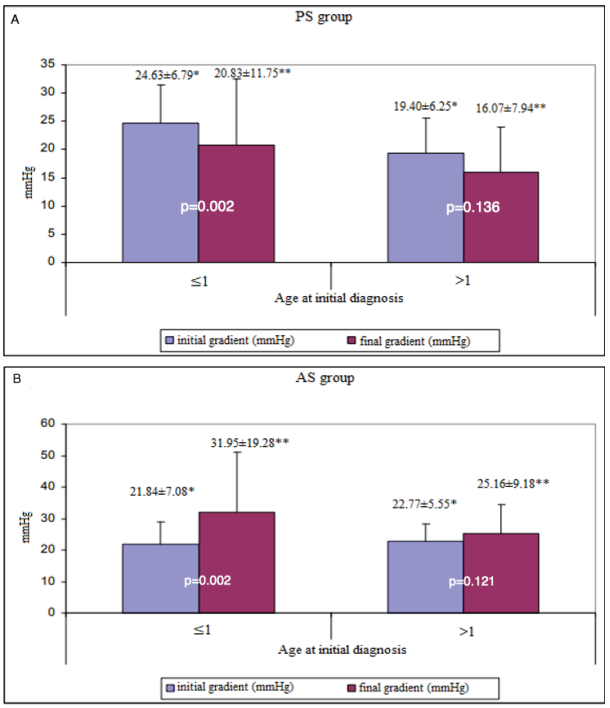


**Figure 2: A)** Comparison of the initial and final gradients of the children with PS according to the age at initial diagnosis
*: p=0.013, **: p=0.160

**B)** Comparison of the initial and final gradients of the children with AS according to the age at initial diagnosis
*: p=0.365, **: p=0.508

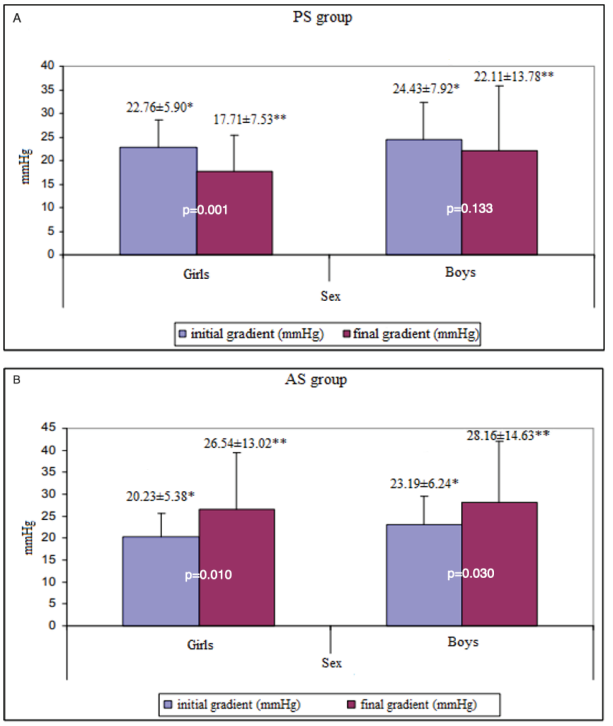


**Figure 3: A)** Comparison of the initial and final gradients of the children with PS according to the gender
*: p=0.362, **: p=0.298

**B)** Comparison of the initial and final gradients of the children with AS according to the gender
*: p=0.141, **: p=0.731

in two groups: PS (n=75) and AS (n=50). The most important results of our study were as follows: i) when the two homogeneous groups with no statistical differences in baseline gradients and mean follow-up times were compared, we found that the natural histories of patients with mild PS were better than those with mild AS; ii) while all of the children with progressive PS were boys, two-thirds of the children with progressive AS were also boys; iii) in children with PS at ≤1-year-old, progression was significantly more pronounced than in children >1-year-old; iv) in children with AS, the progression at ≤1-year-old was found to be significant compared to those >1-year-old; and iv) it was determined that the rate of progression in children with mild PS, whether ≤1 or >1-year-old, was more often benign than in children with mild AS who had similar follow-up periods.

The age at diagnosis of 63% of the children was ≤1 year. The reason for such early diagnosis was that the study was conducted in a maternity hospital where every newborn is examined early. The age at diagnosis of children with PS was earlier than those with AS. The age at first diagnosis was ≤1 year in 80% of the children with PS while it was >1 year in 62% of the children with AS.

Studies have shown that PS is equally common in boys and girls and that AS is four times more common in boys (8-10). In our study, while the boy/girl ratio of children with PS was equal, it was 3:1 in children with AS, which is consistent with the literature.

Considering the distribution of the final gradients in children with mild AS, it was observed that 8% had moderate AS and 4% had severe AS. That is, the progression of mild AS was observed in 12% of our children. Progression was higher in children with mild AS at ≤1 year old than in children aged >1 year. Of the 19 children with mild AS at ≤1 year of age, progression was detected in 21% of cases, while it was only detected in 6% of the 31 children aged >1 year. In the AS group 66% of children who progressed were boys.

In a study that included 142 children with mild AS, there was clinical progression within ten years of initial diagnoses in only 12% of the children (10). However, in our study, progression was detected in 12% of the children over a much shorter time, just 29.3±22.6 months.

Kitchiner et al. studied 187 children who presented with mild congenital AS; 63% were boys. Additional cardiac

lesions were present in 51 children. The median age at presentation was two years (range, 0-15), and the median duration of follow-up was ten years (range, 1-28). Thirty two patients (17%) progressed to require intervention (28 surgical, five balloon valvuloplasty) at a median age of 10.5 years. As a result of their study, they recommended follow-up into adulthood (11). In contrast, children with additional cardiac lesions were excluded from our study. Intervention was required in two of our children (4%) with mild AS who presented with progression at follow-up. The shorter median follow-up period and the exclusion of patients with additional cardiac anomalies in our study can be explained as the reason for the lower rate of intervention.

According to the literature, the course of valvular PS is benign in children with a systolic gradient below 40 mmHg in the first year of life. In the study "Natural History Study of Congenital Heart Defects", 261 children were evaluated; the researchers concluded that the risk of progression was higher in children under four years of age who had high initial gradients. Only 22 children under the age of two were included in that study (12). In the second "Natural History Study of Congenital Heart Defects" study, patients with a gradient of 25 mmHg and below were followed, and no increase was detected (13). Both studies concluded that mild PS is a static lesion and rarely progresses. Mody et al. enrolled 68 patients with isolated valvular PS diagnosed by cardiac catheterization. They concluded that mild stenosis in infants <1-year-old could become severe later in life, while mild stenosis at >1-year-old was unlikely to become severe. The study showed that moderate to severe stenosis was progressive in all age groups (14).

However, studies in the neonatal period suggested that PS is a progressive lesion. A study concluded that mild PS was a non-static pathology that should be followed carefully, especially in infants. This study observed that 25% of infants with mild PS during the neonatal period developed significant stenosis in the later period, and half of these underwent surgery (15). Anand et al. followed 51 infants with asymptomatic PS in 1997 and observed rapid progression that required surgery in 6 (15%) of them (8). Finally, Rowland et al. examined 56 infants with mild PS with a diagnosis age of <1 month, and progression was detected in 16 patients (1).

In the present study, a significant decrease was found in the final gradients of children aged ≤1 year and >1 year with mild PS. All children with progressive mild PS were ≤1-year-old and boys. Of 60 the children ≤1-year-old with mild PS, two (3%) progressed to moderate stenosis and one (1.5%) to severe stenosis. Balloon valvuloplasty was required in one patient who progressed to severe stenosis.

Our study is one of few aiming to examine the natural history of children with isolated aortic and isolated pulmonary stenosis. The literature contains studies from the previous 40-50 years; aside from the present study, no similar current studies yet exist.

Our study has limitations as well as strengths. First of all the sample size was relatively small because the data was derived from a single center. The follow-up period was short and the adult age echocardiographic measurements of the patients were not available.

## CONCLUSION

Based on the results of this single-center follow-up study, congenital mild valvular PS was shown to have a benign course in cases detected after one year of age. However, children diagnosed before the age of one year, especially boys, should be followed up more carefully because progression may be detected, including significant progression, although it is not common. Cases of congenital mild valvular AS should be followed closely, as the disease shows progressive characteristics in all age groups, especially those under one year old.

**Informed Consent:** Written consent was obtained from the participants.

**Ethics Committee Approval:** This study was approved by the Ethical Committee of the Kanuni Sultan Suleiman Training and Research Hospital (Date: 25.06.2009, No:279).

**Peer Review:** Externally peer-reviewed.

**Author Contributions:** Conception/Design of Study- K.Ö.; Data Acquisition- S.B., K.Ö.; Data Analysis/Interpretation- K.Ö., P.K.Ö.; Drafting Manuscript- P.K.Ö.; Critical Revision of Manuscript- K.Ö.,S.B., P.K.Ö.; Approval and Accountability- S.B., P.K.Ö., K.Ö.

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