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Long-term follow-up of subvalvular aortic stenosis in children: a single-centre experience

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Abstract

Objective: The aim of this study is to evaluate clinical and surgical outcomes of children with subaortic stenosis, to determine the risk factors for surgery and reoperation and to compare isolated subaortic stenosis and those concomitant with CHDs. *Methods:* The study involved 80 children with subaortic stenosis. The patients were first classified as isolated and CHD group, and the isolated group was further classified as membranous/fibromuscular group. The initial, pre-operative, post-operative and the most recent echocardiographic data, demographic properties and follow-up results of the groups were analysed and compared. The correlation of echocardiographic parameters with surgery and reoperation was evaluated. *Results:* There was a significant male predominance in all groups. The frequency of the membranous type was higher than the fibromuscular type in the whole and the CHD group. The median time to the first operation was 4.6 years. Thirty-five (43.7%) patients underwent surgery, 5 of 35 (14%) patients required reoperation. The rate of surgery was similar between groups, but reoperation was significantly higher in the isolated group. The gradient was the most important factor for surgery and reoperation in both groups. In the isolated group besides gradient, mitral-aortic separation was the only echocardiographic parameter correlated with surgery and reoperation. *Conclusion:* Reoperation is higher in isolated subaortic stenosis but similar in membranous and fibromuscular types. Early surgery may be beneficial in preventing aortic insufficiency but does not affect the rate of reoperation. Higher initial gradients are associated with adverse outcomes, recurrence and reoperation.

Subvalvular aortic stenosis is the second most common cause of left ventricular outflow obstruction in children after valvular aortic stenosis and it accounts for 15% of left ventricular outflow obstruction in children.[1] It constitutes 1–2% of all CHDs, and there is a male predominance with a male to female ratio of 1.5–2.5.[1,2] It may be isolated or accompany other cardiac anomalies such as ventricular septal defect, coarctation of the aorta and interrupted aortic arch.[3] It may also occur after the surgical repair of congenital heart defects.[4]

Three different morphological subtypes of subaortic stenosis have been described. The most common type is the membranous type and accounts for 70–80% of the cases. It is a thin crescent-shaped membrane that is located just below the aortic valve and is usually attached to the anterior leaflet of the mitral valve. The second most common type includes a thicker fibromuscular ridge which is located slightly more inferior to the aortic valve. The most severe form is a long diffuse fibromuscular tunnel.[1–3]

Subaortic stenosis is commonly considered an acquired disease because it is rarely seen during infancy and becomes evident in the first decade. Many different aetiologies have been proposed as the cause of subaortic stenosis. One of the most strongly proposed aetiologies is the abnormalities of left ventricular outflow architecture that leads to turbulence which results in progressive thickening, fibrosis and scarring.[1,5,6] A steep angle between the muscular and conal septae is one of the most strongly proposed abnormalities of left ventricular outflow architecture. Tutar et al[4] reported that subaortic stenosis is associated with a steeper aortoseptal angle and a wider mitral-aortic valve separation. Peri-membranous ventricular septal defect and septal malalignment are other factors proposed to be associated with subaortic stenosis.[1,4–7]

Left ventricular hypertrophy occurs over time due to the increased pressure gradient. Another important complication is aortic insufficiency that develops in 70% of patients secondary to long-term exposure to high-velocity jet and incomplete coaptation due to scarring of the valve.[1,4,5] Although most patients with mild or moderate stenosis are usually asymptomatic; dyspnoea on exertion, syncope and chest pain may appear with progressive worsening of obstruction and it may eventually lead to heart failure, arrhythmia and death if left untreated.[1,2]

The choice of treatment is resection of subaortic stenosis with/without myectomy. Although the risk of early mortality is very low, reoperation is required in 15–20% of the cases.[1,3,8]

Risk factors for recurrence are increased peak gradient and early age at the time of diagnosis, distance <5 mm between the membrane and aortic valve and peak Doppler gradient of >60 mmHg.[1,9,10]

In this single-centre study, we aimed to evaluate clinical and surgical outcomes of children with subaortic stenosis, to determine the risk factors for surgery and reoperation and to evaluate the differences between the isolated subaortic stenosis and those associated with CHDs.

Material and methods

Medical records of all the patients that were followed up with the diagnosis of subaortic stenosis at Ankara University Medical Faculty Pediatric Cardiology Department between 1993 and 2020 were reviewed retrospectively. Patients with missing or insufficient demographic, echocardiographic and/or angiographic data were excluded from the study. The ethics committee of Ankara University approved the study.

Study population

Patients with a ventricular septal defect, coarctation of the aorta, tetralogy of Fallot, atrioventricular septal defect and tricuspid atresia were classified as the CHD group. Patients with isolated subaortic stenosis had no associated congenital defect or had haemodynamically insignificant defects (small atrial septal defect and patent ductus arteriosus, persistent superior vena cava, etc.). Patients in the isolated group were also classified as the membranous or fibromuscular group according to the morphological nature of the obstructing tissue. At first, the isolated and CHD groups, and then membranous and fibromuscular groups were compared in means of demographic, echocardiographic and angiographic data. Demographic data including age, gender, age at the time of diagnosis, history of catheter angiography and surgery, indications for catheter angiography and surgery, duration of follow-up, number of surgeries and history of reoperation were reviewed. Indications for surgery were:[2,7] A catheter peak-to-peak or echocardiographic mean gradient >50 mmHg at the left ventricular outflow; a catheter peak-to-peak or echocardiographic mean gradient between 30 and 50 mmHg and associated symptoms such as angina, syncope, dyspnoea or ECG changes; and progressive worsening of aortic insufficiency (more than mild). Patients with a catheter peak-to-peak or echocardiographic mean gradient <30 were followed up if they had no left ventricular hypertrophy. All the patients who underwent surgery for CHD had also resection of subaortic stenosis if it existed before the surgery.

Echocardiographic data

Echocardiographic data included the initial, pre-operative, post-operative and the most recent gradient and the degree of aortic insufficiency, the maximum gradient during follow-up, morphological type of subaortic stenosis, the distance between the aortic valve and subaortic membrane, the degree of aortoseptal angle and the measurement of mitral-aortic valve separation. Although most of the recent patients had maximum and mean gradients of the left ventricular outflow tract, the maximum gradient was used in the study because the mean gradient was missing in most patients back to the date 1990–2005.

Subaortic ridge morphology was defined using 2D echocardiography and was confirmed with surgical morphology in patients who underwent surgery. The maximum instantaneous gradient was measured using colour flow, continuous and pulsed wave Doppler. Apical 5 chamber, subcostal and suprasternal long-axis views, and the cleanest spectral Doppler envelope were used for determining maximum gradient.[11,12] Aortic insufficiency was assessed from multiple views by using colour flow Doppler and was graded qualitatively as none, trivial, mild, moderate and severe.[13] Aortoseptal angle was determined by measuring the angle between the long axis of the aortic root and proximal ascending aorta and the midline of the interventricular septum[14] (Fig 1). Mitral-aortic valve separation was measured from the hinge point of the non-coronary aortic valve leaflet to the hinge point of the anterior mitral leaflet[4] (Fig 1). Aortoseptal angle and mitral-aortic separation were measured by Dicom viewer software (MicroDicom viewer®) virtual goniometer and caliper using DICOM views.

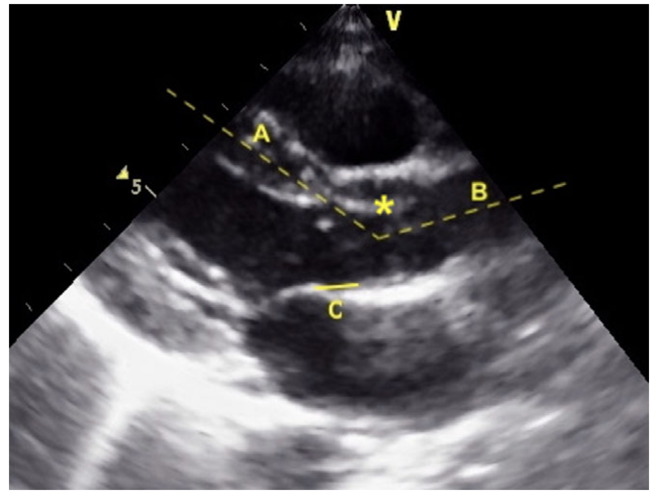

Figure 1. The measurement of the aortoseptal angle (indicated by asterix) obtained from the parasternal long-axis view in systole: the angle formed by the plane of the interventricular septum (dotted line A) and the long axis of the ascending aorta (dotted line B). Measurement of mitral-aortic valve separation: the distance from the hinge point of the non-coronary aortic valve leaflet to the hinge point of the anterior mitral leaflet (line C).

Catheter angiography

Catheter angiography included peak-to-peak gradient and the degree of aortic insufficiency. Aortic insufficiency was classified as none, trivial, mild, moderate and severe.

Statistical Analyses

Statistical analyses were performed using the statistical package program SPSS for Windows 22.0. The mean, standard deviation, and frequency were used for descriptive statistics. Student t-test and the Chi-square test were used for comparison of groups where appropriate. Pearson's chi-square was used for correlation analysis. The confidence interval was given as 95 % and statistical significance was set at $p < 0.05$.

Results

One-hundred and two patients were diagnosed with subaortic stenosis at Ankara University Medical Faculty Pediatric Cardiology Department between the dates of 1993–2020. Patients with missing echocardiographic and/or angiographic data

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Table 1. Demographic properties of the patients

	Whole group, N = 80	Isolated group, N = 45	CHD group, N = 35	Isolated versus CHD, p	Isolated group		
					Fibromuscular, N = 22	Membranous, N = 23	Membranous versus fibromuscular, p
Age*	194.9 ± 79.1	206.4 ± 77.4	180.1 ± 79.9	0.141	215.9 ± 65.7	197.4 ± 87.8	0.430
Age at the time of diagnosis*	88 ± 93.8	104.6 ± 109	66.6 ± 64.9	0.072	126.9 ± 141.8	83.3 ± 60.1	0.182
Age at the time of surgery*	107.8 ± 65.7	131.9 ± 60.6	69.1 ± 56.4	0.014	133.6 ± 51.4	129.2 ± 79	0.893
Duration to the surgery*	29.9 ± 39.7	23.7 ± 36.1	40.3 ± 45.1	0.303	23.6 ± 40.2	24 ± 30.7	0.981
Duration of follow-up*	82.4 ± 63.7	78.4 ± 64	87.5 ± 63.9	0.533	79.2 ± 58.2	77.7 ± 70.4	0.937
Duration of follow up after surgery*	84.8 ± 53.3	78.6 ± 48.4	93.8 ± 60.9	0.476	67.3 ± 41.7	103.2 ± 57.7	0.178
Sex							
Male, n (%)	55 (68.75)	30 (66.6)	25 (71.4)	0.649+	5 (22.7)	10 (43.5)	0.140+
Female, n (%)	25 (31.25)	15 (33.3)	10 (28.6)		17 (77.3)	13 (56.5)	
Type							
Fibromuscular, n (%)	29 (36.3)	22 (48.9)	7 (21.9)	0.008+	–	–	–
Membranous, n (%)	51 (63.7)	23 (51.1)	28 (80)				
Surgery for subaortic stenosis, n (%)	35 (43.7)	19 (42.2)	16 (45.7)	0.822+	11 (50)	8 (34.8)	0.373+
Reoperation for stenosis, n (%)	5 (6.3)	5 (11.1)	0	0.042+	3 (13.6)	2 (8.7)	0.598+
Number of surgeries for stenosis, n (%)							
1	30	14	16	0.049+	8	6	0.814+
2	5	5	0		3	2	

C angiography: Catheter angiography; p: Student t test; p+: Chi-square.
*Are expressed as mean±standard deviation in means of months.

were excluded. As a result, the study included a total of 80 patients: 45 patients with isolated subaortic stenosis and 35 patients with CHD and subaortic stenosis.

The demographic properties of the whole study group, CHD group and the isolated group are shown in Table 1. The distribution of CHDs was as follows: Ventricular septal defect (n = 23), coarctation of the aorta (n = 7), atrioventricular septal defect (n = 3), tetralogy of Fallot (n = 1), tricuspid atresia (n = 1). Although gender distribution was similar between groups, there was a significant male predominance in all groups ($p < 0.05$). The male/female ratio was 2.2, 2 and 2.5 in the whole, isolated and CHD group, respectively. The frequency of membranous type was significantly higher than the fibromuscular type in the whole and the CHD group ($p = 0.014$, $p = 0.001$ respectively), but it was similar in the isolated group.

A total of 35 patients had subaortic stenosis resection. Thirty patients underwent surgery only once, whereas five patients were reoperated. Twenty-six of 35 patients in the CHD group underwent surgery for CHD. Twelve had subaortic stenosis before the surgery for CHD and they had subaortic stenosis resection during the surgery. Subaortic stenosis developed after CHD surgery in 14 patients. In these patients, the mean duration for the development of subaortic stenosis was 34.91 ± 46.17 months. Only two of 14 patients, that underwent surgery for ventricular and atrioventricular septal defect had another surgery for stenosis. Two patients (both with a ventricular septal defect that did not require surgery) underwent surgery with the indication of subaortic stenosis. As a result, 16 patients in the CHD group had surgical relief of stenosis. Nineteen of 45 patients in the isolated group underwent surgery. All the patients in the isolated group underwent surgery with the indications described above but none of them underwent surgery with the indication of progressive aortic insufficiency. Five patients in the isolated group were reoperated and three of them were male. Reoperation was significantly higher in the isolated group than in the CHD group. Although the ratio of patients who underwent surgery was higher in the fibromuscular group than the membranous group, there was no significant difference in means of operation and reoperation between these two groups.

The echocardiographic and catheter angiographic data are shown in Table 2. The degree of aortic insufficiency was similar between the groups, but when aortic insufficiency was compared as none and present, the number of patients with aortic insufficiency was significantly higher in the isolated group at the last follow-up ($p = 0.026$). The distribution of aortic insufficiency at the time of diagnosis and the last follow-up in the isolated group were as follows, respectively: None: 11 versus 7, Trivial: 5 versus 6, Mild: 10 versus 13. At the last follow-up, none of the patients had severe aortic insufficiency.

Correlation analysis of the whole group revealed a positive correlation between age and gradient at the time of diagnosis ($p < 0.05$). A positive correlation between the gradient at the time

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Table 2. Echocardiographic and angiographic data of the patients

	Whole group, N = 80	Isolated group, N = 45	CHD group, N = 35	Isolated vs CHD, p	Isolated Group		
					Fibromuscular, N = 22	Membranous, N = 23	Membranous versus fibromuscular, p
Distance to the aorta (mm)*	8.72 ± 3.37	8.67 ± 3.32	8.78 ± 3.50	0.900	9.32 ± 4.29	8.18 ± 2.39	0.339
Aortoseptal angle (degree)*	129.4 ± 10.2	129.4 ± 10.2	129.5 ± 10.5	0.978	128.5 ± 12.3	130.2 ± 8.4	0.659
Mitral-aortic valve separation (mm)*	9.88 ± 3.58	9.04 ± 2.71	10.97 ± 4.30	0.052	9.29 ± 2.6	8.83 ± 2.87	0.651
Gradient at the time of diagnosis (mmHg)*	31.5 ± 22.6	38 ± 22.4	23.1 ± 20.2	0.003	37.6 ± 21.5	38.4 ± 23.8	0.901
Maximum gradient (mmHg)*	43.7 ± 25.6	49.1 ± 23.9	36.7 ± 26.3	0.030	47.4 ± 20.4	50.7 ± 27.2	0.646
Gradient at catheter angiography (mmHg)*	36.9 ± 21.3	39.6 ± 17.3	32.7 ± 26.3	0.301	38.8 ± 19	40.5 ± 16.1	0.800
Gradient prior to surgery (mmHg)*	61.8 ± 21.5	64.1 ± 19.5	57.7 ± 25.5	0.465	58.6 ± 18.4	72.6 ± 19.3	0.143
Gradient after surgery (mmHg)*	25.7 ± 17.3	27.8 ± 19.5	21.6 ± 12.11	0.366	23.4 ± 18.7	34 ± 20.1	0.251
Gradient before the last surgery (mmHg)*	75.8 ± 16.2	75.8 ± 16.2	–	–	71.3 ± 12.1	82.5 ± 24.8	0.532
Gradient at last follow-up (mmHg)*	28.2 ± 17.9	30.7 ± 15.6	24.8 ± 20.5	0.151	26.2 ± 12.1	35 ± 17.6	0.056
AI at the time of diagnosis, n (%)							
None	38 (47.5)	17 (37.7)	21 (60)	0.083+	10 (45.5)	7 (30.4)	0.606+
Trivial	17 (21.25)	9 (20)	8 (22.8)		4 (18.2)	5 (21.7)	
Mild	23 (28.75)	18 (40)	5 (14.3)		8 (36.3)	10 (43.5)	
Moderate	2 (2.5)	1 (2.2)	1 (2.9)		0	1 (4.4)	
Severe	0	0	0		0	0	
AI before surgery, n (%)							
None	12 (41.4)	10 (52.6)	2 (20)	0.332+	3 (27.3)	2 (25)	0.597+
Trivial	6 (20.7)	3 (15.8)	3 (30)		3 (27.3)	1 (12.5)	
Mild	10 (34.5)	6 (31.6)	4 (40)		5 (45.4)	4 (50)	
Moderate	1 (3.5)	0	1 (10)		0	1 (12.5)	
Severe	0	0	0		0	0	
AI after surgery, n (%)							
None	5 (17.25)	2 (10.5)	3 (30)	0.538+	2 (18.2)	0	0.409+
Trivial	7 (24.1)	5 (26.3)	2 (20)		3 (27.3)	2 (25)	
Mild	15 (51.75)	11(57.9)	4 (40)		6 (54.5)	5 (62.5)	
Moderate	2 (6.9)	1 (5.2)	1 (10)		0	1 (12.5)	
Severe	0	0	0		0	0	
AI at last follow-up, n (%)							
None	25 (31.25)	9 (20)	16 (45.7)	0.086+	7 (31.8)	2 (8.7)	0.190+
Trivial	16 (20)	10 (22.25)	6 (17.1)		5 (22.7)	5 (21.7)	
Mild	38 (47.5)	25 (55.5)	13 (37.2)		10 (45.5)	15 (65.2)	
Moderate	1 (1.25)	1 (2.25)	0		0	1 (4.4)	
Severe	0	0	0		0	0	

AI: Aortic insufficiency; p: Student t test; p+: Chi-square.
*Are expressed as mean±standard deviation.

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Table 3. Correlation analysis of both groups in means of surgery and reoperation for subaortic stenosis.

	Whole group (n = 80)				Isolated group (n = 45)			
	Surgery for subaortic stenosis		Reoperation for subaortic stenosis		Surgery for subaortic stenosis		Reoperation for subaortic stenosis	
	r	p	r	p	r	p	r	p
Age	0.187	0.096	0.231	0.039	0.249	0.099	0.271	0.071
Gender	0.160	0.153	−0.049	0.663	0.032	0.831	−0.050	0.737
Gradient at diagnosis	0.519	0.000	0.226	0.044	0.603	0.000	0.210	0.166
Maximum gradient during follow-up	0.645	0.000	0.318	0.004	0.716	0.000	0.387	0.009
Gradient at catheter angiography	0.461	0.002	0.340	0.026	0.605	0.001	0.487	0.012
Aortic insufficiency at diagnosis	0.214	0.194	0.151	0.424	0.229	0.395	0.127	0.763
Aortic insufficiency at c. angiography	0.206	0.652	0.081	0.922	0.339	0.200	0.105	0.918
Aortic insufficiency at last follow-up	0.378	0.009	0.063	0.538	0.348	0.078	0.085	0.577
Type of subaortic stenosis	−0.174	0.161	−0.128	0.254	−0.154	0.373	0.079	0.598
Distance to the aorta	−0.064	0.629	−0.118	0.371	−0.140	0.438	−0.161	0.370
Aortoseptal angle	0.111	0.430	−0.172	0.219	−0.005	0.977	−0.235	0.212
Mitral-aortic valve separation	0.264	0.056	0.176	0.208	0.448	0.013	0.423	0.020
Isolated or CHD	0.035	0.755	−0.228	0.064	–	–	–	–
Surgery for CHD	0.141	0.236	−0.179	0.168	–	–	–	–
Stenosis before CHD surgery	0.800	0.000	−0.175	0.381	–	–	–	–

C angiography: Catheter angiography; Pearson Correlation Analysis.

of diagnosis and aortic insufficiency at all times was observed. (At the last follow-up, $p = 0.000$, $r = 0.425$). Maximum gradient during follow-up was positively correlated with the gradient at the time of diagnosis, angiographic gradient, gradient before and after surgery, the gradient at the last follow-up and aortic insufficiency at all times. The mitral-aortic separation positively correlated with the age at the time of surgery and duration of time to surgery ($p = 0.014$, $r = +0.585$ and $p = 0.010$, $r = +0.578$ respectively) whereas aortoseptal angle positively correlated with gradient after surgery ($p = 0.001$, $r = +0.702$).

Correlation analysis of the isolated group revealed a positive correlation between age at the time of diagnosis and aortic regurgitation at catheter angiography ($p = 0.006$, $r = +0.525$) and after surgery ($p = 0.015$, $r = +0.547$). The gradient at the time of diagnosis was positively correlated with age ($p = 0.030$, $r = 0.323$), mitral-aortic separation ($p = 0.028$, $r = +0.401$) and aortic insufficiency at all times in the isolated group. The gradient at the last follow-up was positively correlated with aortic insufficiency at the last follow-up ($p = 0.006$, $r = +0.405$).

Factors correlated with surgery and reoperation for subaortic stenosis for the whole and isolated group are shown in Table 3.

Correlation of mitral-aortic separation, distance to the aorta, and aortoseptal angle with demographic, echocardiographic and angiographic parameters in the isolated group are shown in Table 4. Among these three parameters, mitral-aortic separation was the only parameter that correlated with surgery and reoperation.

Discussion

Subaortic stenosis is the second most common cause of left ventricular outflow obstruction in children, and it may be isolated or accompany other cardiac anomalies.[1] It is more common in males with a male to female ratio of 1.5:1–2.5:1.[1] In our study, there was a significant male predominance as previously reported and the male to female ratio was 2.2, 2 and 2.5 in the whole, isolated and CHD group, respectively. Subaortic stenosis is associated with other CHD's in more than half of the patients.[15,16] The most common additional malformations are ventricular septal defect and coarctation of the aorta with a ratio of 10–48% and 6–20%, respectively.[1] Thirty-five patients in our study had CHD and the ratio of CHD was 43.75%. Similar to previous reports, the most common additional malformations in our study were ventricular septal defect (28.75%) and coarctation of the aorta (8.75%). The most common type is the membranous type which accounts for 70–80% of cases.[1,17,18] Although 63.7 and 80% of cases in the whole and CHD group had membranous type; the frequency of membranous and fibromuscular type was similar in the isolated group (51.1% versus 48.9%) in our study. The mean age at the time of surgical resection was significantly lower in the CHD group. This is because the patients who underwent surgery for CHD also had subaortic stenosis resection irrespective of the severity of the stenosis.

Aortic insufficiency is an important complication that may develop in 50–70% of these patients over time.[1,17] Unsurprisingly, in our study, the frequency of aortic insufficiency increased from 52.5%, 62.3%, and 40% to 68.75%, 80%, and 54.3% at the last follow-up in the whole, isolated and CHD group, respectively. The association between a higher gradient and aortic insufficiency has been confirmed by the previous studies[18–20]. In our study gradient at the time of diagnosis and maximum gradient during follow-up was positively correlated with aortic insufficiency at all times, as previously reported. Besides gradient, mitral-aortic separation and surgery were also positively correlated with aortic insufficiency at the last follow-up. The correlation of gradient and surgery with aortic insufficiency is not surprising,

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Table 4. Correlation of echocardiographic parameters

	Distance to the aorta		Aortoseptal angle		Mitroaortic separation	
	r	p	r	p	r	p
Age	0.235	0.189	−0.148	0.434	0.501	0.005
Age at the time of diagnosis	0.549	0.001	−0.028	0.881	0.307	0.098
Duration of follow-up	−0.242	0.174	0.026	0.892	0.475	0.008
Distance to aorta	–	–	−0.465	0.025	−0.110	0.619
Gradient at the time of diagnosis	−0.154	0.392	0.327	0.078	0.401	0.028
Maximum gradient	−0.215	0.231	0.266	0.155	0.395	0.031
Gradient at catheter angiography	0.065	0.784	0.106	0.675	0.524	0.026
Gradient after surgery	0.081	0.775	0.723	0.008	0.289	0.363
Gradient at the last follow-up	−0.002	0.991	0.097	0.611	−0.038	0.841
Aortoseptal angle	−0.465	0.025	–	–	−0.064	0.738
Mitroaortic separation	−0.110	0.619	−0.064	0.738	–	–
Operation for subaortic stenosis	−0.140	0.438	−0.005	0.977	0.448	0.013
Reoperation for subaortic stenosis	−0.161	0.370	−0.235	0.212	0.423	0.020
Type of subaortic stenosis	−0.172	0.339	0.084	0.659	−0.086	0.651
Aortic insufficiency at diagnosis	−0.174	0.333	0.304	0.102	0.270	0.149
Aortic insufficiency after the surgery	−0.267	0.335	0.520	0.083	−0.131	0.686
Aortic insufficiency at last follow-up	−0.141	0.433	−0.062	0.746	0.402	0.028

C angiography: Catheter angiography; Pearson Correlation Analysis.

as one of the proposed mechanisms of aortic insufficiency is long-term exposure to high-velocity jet. The degree of aortic insufficiency was similar between the groups, but when aortic insufficiency was compared as none and present, the number of patients with aortic insufficiency was significantly higher in the isolated group at the last follow-up ($p = 0.026$). We think that this may be due to two reasons: The primary disease of the patients in CHD may also cause aortic insufficiency; the patients in the CHD group had surgical resection earlier than the isolated group and the mean maximum gradient of the CHD group was significantly lower. Brauner et al[21] and Somerville et al[22] also reported that early surgical intervention can be beneficial in preventing progressive damage to the aortic valve.

Subaortic stenosis constitutes 20% of obstructions that require intervention in children.[14] The treatment of choice is surgical resection. The risk of early mortality of surgery is very low, but subaortic stenosis reoccurs in 20–30% of the patients after successful surgical resection.[1,3,8] Uysal et al[2] reported that 64.6% of 66 children with subaortic stenosis underwent surgery and only 1 of the15 patients with recurrence required a second surgery. Tal et al[3] reported that 26 of 34 patients with isolated subaortic stenosis underwent surgery and only 3 (12%) patients required reoperation. Two of these patients in this study were reoperated because of progressive aortic insufficiency. Binsamalah et al[23] reported that 12 (14%) of 84 patients who underwent resection of isolated subaortic stenosis required reoperation and one patient required reoperation twice at a median follow-up of 9.3 years. The median time to the first operation was 4.6 years. In our study, a total of 35 (43.7%) patients underwent surgery for subaortic stenosis. 16 (45.7%) and 19 (42.2%) patients in the CHD and isolated group underwent surgical resection. Although the rate of surgery was similar between the groups, 12 of 16 patients with CHD had surgical resection as they underwent surgery for CHD. All the patients in the isolated group underwent surgery with the indications described above but none of them underwent surgery or reoperation with the indication of progressive aortic insufficiency. Twenty-six of the patients in the isolated group did not undergo surgery. The distribution of aortic insufficiency in this subgroup at the time of diagnosis and the last follow-up respectively were as follows: None: 11 versus 7, Trivial: 5 versus 6, Mild: 10 versus 13. None of these patients had moderate or severe aortic regurgitation. We think that progression of aortic insufficiency in patients with lower gradients is slow. Therefore clinicians should feel safer in this group of patients and should prefer close follow-up instead of early surgery. The rate of reoperation was 14% at a mean follow-up of 84.8 ± 53.3 months and all the reoperated patients were in the isolated group. We believe that this difference is because most of the patients in the CHD group had surgical resection irrespective of the severity of the stenosis as they underwent surgery for CHD. Although the ratio of patients who underwent surgery was higher in the fibromuscular group than the membranous group, there was no significant difference in means of operation and reoperation between the fibromuscular and membranous groups.

Subaortic stenosis may cause progressive obstruction in children but the rate of progression varies among patients. Several factors have been opposed in the development of subaortic stenosis but factors leading to rapid progression are still unclear.[1,4–7] Surgical resection is the ultimate treatment for the relief of obstruction. The most and well-known predictor of surgery is the gradient across left ventricular outflow tract.[1,7,21,24] Aortic and mitral annulus z score, longer left ventricular ejection time, the distance of the membrane to the aorta during systole, and other left-sided lesions have been proposed to correlate with surgery.[20,24] In our study, the gradient at the time of diagnosis and the maximum

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gradient during follow-up were the only predictors of surgery in both groups. The role of abnormalities in left ventricular outflow architecture in the development of subaortic stenosis has been previously shown. A steeper aortoseptal angle and wider mitral-aortic separation are the most strongly proposed anomalies.[4,25] In our study, mitral-aortic valve separation was positively correlated with surgery and reoperation just in the isolated group but in contrast to previous reports, we did not find any correlation between the aortoseptal angle and surgery. Although similar to previous studies we found a positive correlation between mitral-aortic valve separation and surgery/reoperation, this result must be interpreted carefully as in our study mitral-aortic valve separation was not indexed to body surface area. Tutar et al[4] and Kalfa et al[25] both used an aortoseptal angle of <130° as a cut-off value and Tutar et al[4] also reported that an aortoseptal angle of <130° is a highly sensitive marker for possible development of subaortic stenosis. We failed to show any correlation of aortoseptal angle with surgery and reoperation even when we used 130° as a cut-off value in patients who underwent surgery for subaortic stenosis.

Although inadequate resection may be a factor for reoperation, reoperation is required in 15–20% of the cases with subaortic stenosis despite successful resection.[17] Increased peak gradient and early age at the time of diagnosis, tunnel-type stenosis, distance <5 mm between the membrane and aortic valve, peak Doppler gradient of >60 mmHg, concomitant cardiovascular defects (esp. coarctation of the aorta), younger age at initial surgery are risk factors for recurrence and reoperation.[1,9,10,18] Abushaban et al[18] reported that age <6 years at initial repair to be an independent predictor of reoperation. In our study, all patients who were reoperated had a peak gradient of <25 mmHg after surgery except one patient who had a peak gradient of 50 mmHg. The earliest reoperation was 73 months after the first surgery in a patient with a post-operative gradient of 15 mmHg. Only one of these patients had the first operation at <6 years of age. None of the seven patients with coarctation of the aorta had reoperation. In our study, the maximum gradient during follow-up, the gradient at the time of diagnosis and catheter angiography were the most important factors for reoperation, as expected.

Aortoseptal angle, mitral-aortic separation and distance of membrane to the aorta are known to correlate with the development of subaortic stenosis, surgery and reoperation. In our study, among these parameters, only mitral-aortic separation correlated with surgery and reoperation in the isolated group. Contradictory to the previous reports, we failed to show any correlation of aortoseptal angle and distance of membrane to the aorta with reoperation. Aortoseptal angle just positively correlated with the gradient at the time of the diagnosis and after surgery.

Study limitations

This study is subject to the usual limitations of a retrospective study. The sample size is limited due to the rarity of the disease. Most of the data analysed are derived from echocardiography which is an operator-dependent examination. As the study covers 27 years, the examinations were performed by different paediatric cardiologists which may have some effect on the accuracy of the measurements. Another limitation is that none of the patients had tunnel-type stenosis. Also, the role of the aortic annulus in recurrence was not evaluated because some patients lack the data to calculate z scores of the aortic annulus.

Conclusion

Left ventricular outflow gradient is the most important predictor of the disease course. Higher initial gradients are associated with adverse outcomes, recurrence and reoperation. Progressive aortic insufficiency by itself is rarely an indication for surgery in patients with lower gradients. Early surgery may be beneficial in preventing aortic insufficiency but does not affect reoperation. The clinicians must evaluate these patients with regular close follow-ups and perform echocardiographic measurements precisely for surgical decision-making. Because the rate of reoperation and recurrence is high, and early surgery has no benefit on reoperation, the clinicians should avoid surgery unless it is really indicated.

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Ethical standards. The authors assert that all procedures contributing to this work follow the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the ethics committee of Ankara University.

References

1. Friedland-Little J, Zampi J, Gajarski R. Aortic stenosis. In: Allen HD, Shaddy RE, Penny DJ, Cetta F, Feltes TF (eds). Moss and Adams' heart disease in infants, children, and adolescents including the fetus and young adult. Wolters Kluwer, Philadelphia, 2016: 1989–2036.
2. Uysal F, Bostan OM, Signak IS, Semizel E, Cil E. Evaluation of subvalvular aortic stenosis in children: a 16-year single-center experience. Pediatr Cardiol 2013; 34: 1409–1414.
3. Tal N, Golender J, Rechtman Y, Tidhar D, Erez E. Long-term aortic valve function in patients with or without surgical treatment for discrete subaortic stenosis. Pediatr Cardiol 2021; 42: 324–330.
4. Tutar HE, Atalay S, Turkay S, Gumus H, Imamoglu A. Echocardiographic, morphologic, and geometric variations of the left ventricular outflow tract: possible role in the pathogenesis of discrete subaortic stenosis. Angiology 2000; 51: 213–221.
5. Shar JA, Keswani SG, Grande-Allen KJ, Sucosky P. Computational assessment of valvular dysfunction in discrete subaortic stenosis: a parametric study. Cardiovasc Eng Technol 2021. Online ahead of print. Doi: 10.1007/s13239-020-00513-8.
6. Barkhordarian R, Wen-Hong D, Li W, Josen M, Henein M, Ho SY. Geometry of the left ventricular outflow tract in fixed subaortic stenosis and intact ventricular septum: an echocardiographic study in children and adults. J Thorac Cardiovasc Surg 2007; 133: 196–203.
7. Mulla S, Siddiqui WJ. Subaortic stenosis. StatPearls, Treasure Island, FL, 2021.
8. Vogt J, Dische R, Rupprath G, de Vivie ER, Kotthoff S, Kececioglu D. Fixed subaortic stenosis: an acquired secondary obstruction? A twenty-seven year experience with 168 patients. Thorac Cardiovasc Surg 1989; 37: 199–206.
9. Geva A, McMahon CJ, Gauvreau K, Mohammed L, del Nido PJ, Geva T. Risk factors for reoperation after repair of discrete subaortic stenosis in children. J Am Coll Cardiol 2007; 50: 1498–1504.
10. Pickard SS, Geva A, Gauvreau K, del Nido PJ, Geva T. Long-term outcomes and risk factors for aortic regurgitation after discrete subvalvular aortic stenosis resection in children. Heart 2015; 101: 1547–1553.
11. Lopez L, Colan SD, Frommelt PC, et al. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the

American Society of Echocardiography Pediatric and Congenital Heart Disease Council. J Am Soc Echocardiogr 2010; 23: 465–495, quiz 576-467.
12. Baumgartner HC, Hung JC-C, Bermejo J, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J Cardiovasc Imaging 2017; 18: 254–275.
13. Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2013; 14: 611–644.
14. Masse DD, Shar JA, Brown KN, Keswani SG, Grande-Allen KJ, Sucosky P. Discrete subaortic stenosis: perspective roadmap to a complex disease. Front Cardiovasc Med 2018; 5: 122.
15. Newfeld EA, Muster AJ, Paul MH, Idriss FS, Riker WL. Discrete subvalvular aortic stenosis in childhood. Study of 51 patients. Am J Cardiol 1976; 38: 53–61.
16. Choi JY, Sullivan ID. Fixed subaortic stenosis: anatomical spectrum and nature of progression. Br Heart J 1991; 65: 280–286.
17. Devabhaktuni SR, Chakfeh E, Malik AO, Pengson JA, Rana J, Ahsan CH. Subvalvular aortic stenosis: a review of current literature. Clin Cardiol 2018; 41: 131–136.
18. Abushaban L, Uthaman B, Selvan JP, Al Qbandi M, Sharma PN, Mariappa TV. Long-term follow-up and outcomes of discrete subaortic stenosis resection in children. Ann Pediatr Cardiol 2019; 12: 212–219.
19. McMahon CJ, Gauvreau K, Edwards JC, Geva T. Risk factors for aortic valve dysfunction in children with discrete subvalvar aortic stenosis. Am J Cardiol 2004; 94: 459–464.
20. Karamlou T, Gurofsky R, Bojcevski A, et al. Prevalence and associated risk factors for intervention in 313 children with subaortic stenosis. Ann Thorac Surg 2007; 84: 900–906, discussion 906.
21. Brauner R, Laks H, Drinkwater DC Jr., Shvarts O, Eghbali K, Galindo A. Benefits of early surgical repair in fixed subaortic stenosis. J Am Coll Cardiol 1997; 30: 1835–1842.
22. Somerville J, Stone S, Ross D. Fate of patients with fixed subaortic stenosis after surgical removal. Br Heart J 1980; 43: 629–647.
23. Binsalamah ZM, Spigel ZA, Zhu H, et al. Reoperation after isolated subaortic membrane resection. Cardiol Young 2019; 29: 1391–1396.
24. Carlson L, Pickard S, Gauvreau K, et al. Preoperative factors that predict recurrence after repair of discrete subaortic stenosis. Ann Thorac Surg 2021; 111: 1613–1619.
25. Kalfa D, Ghez O, Kreitmann B, Metras D. Secondary subaortic stenosis in heart defects without any initial subaortic obstruction: a multifactorial postoperative event. Eur J Cardiothorac Surg 2007; 32: 582–587.

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