

Original Article

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Subvalvular membranous aortic stenosis in Swedish children, a retrospective cohort study between 1994 and 2019

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Abstract

Background and aim: Membranous subaortic stenosis is a CHD with high recurrence-rate despite surgical treatment. This study investigated the outcome of operated patients and possible predictors for recurrence. **Methods:** Retrospective review of all patients ($n = 38$) ≤ 18 years of age operated for membranous subaortic stenosis between 1994–2019 at Sahlgrenska University Hospital. The primary outcomes were recurrence, reintervention, and mortality. Predictors of recurrence and reintervention were secondary outcomes. **Results:** Median age (range) at diagnosis, initial intervention, and last follow-up were 2.3 (0.003–17.2), 5.3 (0.03–17.5) and 17.5 (3.6–20.4) years, respectively. Median follow-up time was 9.9 (0.01–19.5) years. 61% were males, and 53% had other associated CHD. 19 patients (56%) developed recurrence and 7 (21%) underwent reintervention. One patient died peri-operatively. Age ≤ 5 years at first intervention increased the likelihood of reintervention. Postoperative peak/mean gradients were higher in patients with disease recurrence.

The median echocardiographic peak-/mean gradients at initial diagnosis, pre-, postoperative, and at last follow-up were 61/36, 83/50, 16/8, and 19/17 mmHg respectively ($p < 0.0001$ pre/post). Pre-/postoperative peak gradients were linearly correlated, decreasing by 80% pre-/postoperatively ($p < 0.01$). Presence of symptoms and the preoperative peak gradient were positively associated ($p < 0.001$) with a peak gradient threshold value of > 90 mmHg. The distance between the subaortic stenosis membrane and the aortic valve was inversely correlated to the preoperative peak-gradient ($p < 0.01$). **Conclusions:** Reintervention following surgical intervention of membranous subaortic stenosis is common. A positive correlation exists between high pre- and postoperative peak-gradient. A low postoperative peak gradient may be important in avoiding recurrence.

Introduction

Subvalvular aortic stenosis is a progressive CHD and the second most common type of left ventricular outflow obstruction. It accounts for 15–20% of all fixed obstructions in the left ventricular outflow tract and 1% of all CHD.^{1,2} The three primary subtypes of subvalvular aortic stenosis are characterised by a 1) thin, crescent-shaped membrane (membranous subaortic stenosis), representing 75–85% of all cases, (2) fibromuscular ridge, and 3) diffuse fibromuscular tunnel-like narrowing.³ Various pathophysiological mechanisms are thought to contribute to the development of membranous subaortic stenosis, including anatomical factors that increase turbulence and shear stress. A genetic predisposition may also exist.⁴

Diagnosis of subvalvular aortic stenosis typically utilises echocardiography for visualisation of morphology and includes Doppler for estimation of pressure gradients.^{5,6} Time of diagnosis varies across clinical centres, with the most common age-range being between 1 and 5 years.^{7,8} With a growing availability of echocardiography, which enables earlier diagnosis, most current cases are asymptomatic at the time of diagnosis aside from the possible presence of a systolic murmur. The range of symptoms associated with late diagnosis includes dyspnoea, angina, fatigue, syncope, palpitations, arrhythmias, heart failure, and may, in rare cases, result in death.^{3,5}

There are no current guidelines for the paediatric population concerning indications and ideal timing for surgical intervention. Surgery is the only definite treatment of subvalvular aortic stenosis and may include simple resection of the membrane, complementary myectomy, or the

more complex Ross-Konno procedure.^{3,9} While surgery often is effective in reducing pressure gradients, early postoperative complications can occur. These include atrioventricular block, ventricular septal defect, damage to the aortic or mitral valve, and infective endocarditis.

Long-term complications following surgical correction of subvalvular aortic stenosis include a high rate of recurrence and progression of aortic regurgitation. The risk of disease recurrence is estimated to range from 6 to 35%, but has varied between studies, partly due to differing definitions of what constitutes a recurrence.^{2,10} Depending on the severity of the relapsing subvalvular aortic stenosis, patients may require surgical reinterventions. Previously identified predictors of disease recurrence and the need for surgical reintervention include younger age at primary surgery, presence of aortic regurgitation, higher pre- and postoperative peak-gradient, short distance between the aortic valve and the subaortic membrane, anatomical variations of the outflow tract as well as presence of other CHDs.^{2,7,8,10–17} Given the severity of the condition, identifying and validating predictors for disease recurrence would hold significant clinical importance.

Materials and method

Study population and data collection

A systematic retrospective chart review was conducted to identify patients that had undergone either primary or reintervention corrective surgery for membranous subaortic stenosis at the Queen Silvia's Children's Hospital in Gothenburg between 1st of January 1994 and 31 of December 2019 ($n = 44$). Since 1994, paediatric cardiac surgery has been centralised to two centres in Sweden (Gothenburg and Lund), each covering 50% of the population. Patients were excluded if the primary diagnosis was not membranous subaortic stenosis or if the performed surgery was not primarily aimed at correcting membranous subaortic stenosis, thereby also excluding other subtypes of subvalvular aortic stenosis. Furthermore, patients with a primary diagnosis of supra- and valvular AS and valvular AS were excluded. Presence of cardiomyopathy or complex combined defects that required a heart-transplantation were also excluded. After exclusions, the final study sample consisted of 38 patients. The review included medical records at initial diagnosis, pre- and postoperation, as well as the latest (if the patient had not reached adulthood) or last follow-up before reaching 18 years of age.

Outcomes, variables and definitions

The clinical decision of surgical intervention was reached following holistic consideration by the team of clinicians involved in the care of each patient. Indications for both primary and recurring surgery in this cohort of patients included a peak-/mean gradient $> 64/40$ mmHg measured by Doppler as well as presence and severity of aortic regurgitation and/or left ventricular hypertrophy. Disease recurrence was defined as an increase in the peak gradient by $> 50\%$ at the last follow-up compared to the postoperative peak gradient. Additionally, a peak gradient > 16 mmHg at follow-up was required.

The primary outcomes of this study were recurrence of membranous subaortic stenosis, need for reintervention, and mortality. Secondary outcomes included the identification of potential predictors of recurrence and reintervention.

Information on demographics, associated cardiac conditions, comorbidities, clinical signs, symptoms, echocardiography, ECG

findings and surgical reports were extracted from the charts. Class of functionality was rated from 1 to 4 according to a modified version of the New York Heart Association classification, in which symptoms varied between 1 (asymptomatic) and 4 (suffering from symptoms even at rest). Symptoms included dyspnoea, chest pain, palpitations/arrhythmia, syncope, and fatigue. Aortic, mitral, and tricuspid valve regurgitation were graded from 0.5 (minimal) to 4 (severe) with increments of 0.5 points (i.e. 0, 0.5, 1, etc.). Accentuation of aortic, mitral, and tricuspid regurgitation was, respectively, defined as an increase of at least 0.5 points postoperative compared to preoperative.

M-mode echocardiography data on dimensions and wall thickness were collected. Z-scores for left ventricular systolic and diastolic dimensions as well as intraventricular septal and left ventricular posterior wall thickness were calculated using algorithms derived from the data published by Lester *et al.*¹⁸ A Z-score > 2 for septal and/or left ventricular posterior wall thickness was used to define hypertrophy.

Statistical analysis

Statistical tests were calculated using SPSS v. 27 (IBM, New York, NY, USA). Graphs were constructed using Graph Pad Prism v. 9 (San Diego, CA, USA). Basic statistical measurements including the median, range etc. were calculated using Microsoft Excel v.16 (Microsoft, Redmond, WA, USA).

Continuous variables (except for Z-scores) were log-transformed prior to data analysis, to achieve a close-to-normal data distribution, as well as homogeneity of variance between groups. The study groups were compared using either independent samples or paired T-tests. Non-parametric Mann-Whitney tests were calculated where assumptions of parametric tests were violated based on histograms, Q-Q plots, as well as Levene's test for homogeneity of variances. For categorical variables, the difference between groups was analysed using continuity corrected Chi-squared tests. Fisher's exact test was used when the expected number of cases was below 5 for any cell of the contingency table. Statistical significance was defined as a p -value < 0.05 . Linear correlation analyses were conducted for pairwise analyses of continuous variables.

Kaplan–Meier survival-analysis was conducted based on the overall survival-rate from reintervention, followed by comparative analysis through Mantel–Cox testing of patients ≤ 5 and > 5 years of age at primary intervention.

Results

Basic characteristics and surgical outcomes (Table 1)

A total of 38 patients met the inclusion criteria (61% male). An associated CHD was found in 20 patients (53%), while 19 (50%) had an extra-cardiac condition. 11 (29%) patients had developmental delay and/or a genetic syndrome. Eight patients (21%) had undergone cardiothoracic surgery prior to the primary membranous subaortic stenosis surgery. The median age at diagnosis was 2.3 years (0.003–17.2 years), at primary surgery 5.3 years (0.03–17.5), and at reintervention 6.9 years (4.2–12.6). The median time from primary surgery to last or latest follow-up was 9.9 years (range 0.01–19.5 years). During follow-up, 19 (56%) developed disease recurrence and 7 (21%) underwent reintervention (Figure 1). One patient had additional reinterventions and underwent 3 surgeries in total. Kaplan–Meier-derived estimated freedom of reoperation was 82% at a mean follow-up of 9.4 years (Figure 2a).

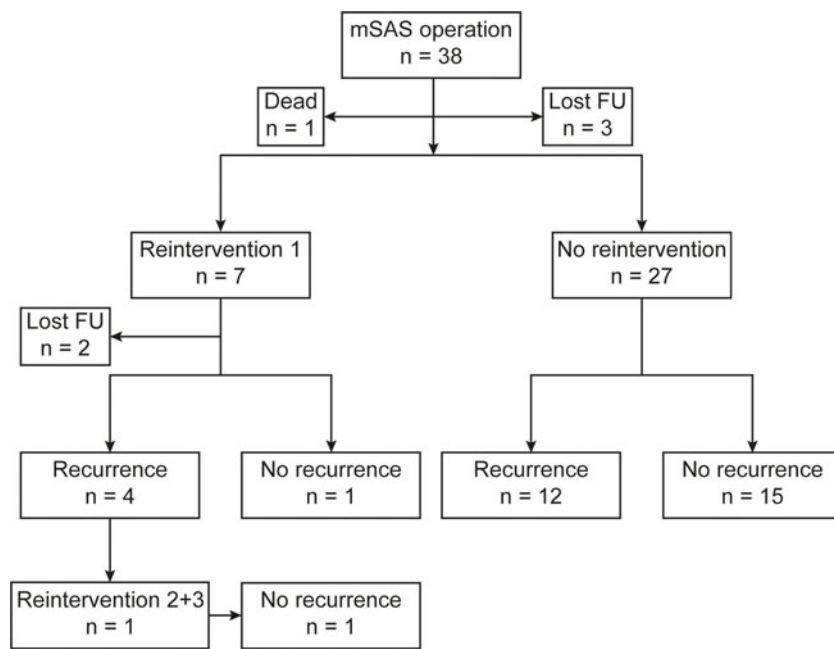


Figure 1. Flowchart of surgical interventions and follow-up. Abbreviations: mSAS = membranous subaortic stenosis; n = number of patients; FU = follow-up.

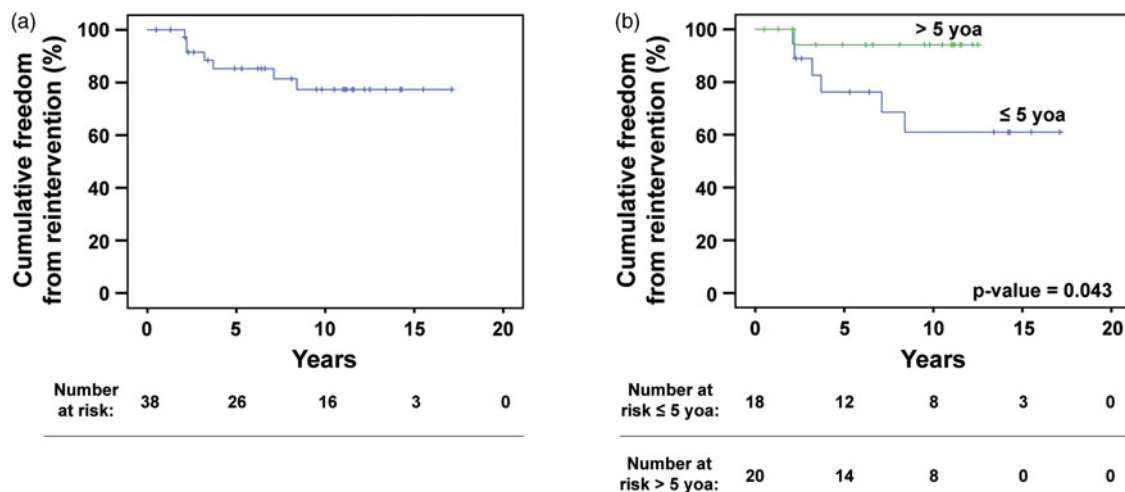


Figure 2. Cumulative freedom from reintervention. (a) Kaplan-Meier curve demonstrating the overall freedom from reintervention. One patient > 5 years of age died postoperatively following primary surgery. Seven patients required reintervention before reaching 18 years of age. (b) Kaplan-Meier curves comparing freedom from reintervention between patients who underwent primary surgery before (blue) and after (green) 5 years of age. Patients younger than 5 years at their initial operation were significantly more likely to require reintervention before reaching adulthood (6 and 1 cases of reintervention, respectively, $p \approx 0.043$).

All patients underwent membrane resection during their primary surgery, and 4 (11%) had a combined resection with myectomy. Furthermore, 6 patients (16%) had concomitant cardiac surgery. Peri-and/or postoperative complications occurred for 24 patients (63%). One case (3%) of peri-operative death occurred, due to suspected air embolism causing myocardial infarction and subsequent fatal ischaemic brain damage during ECMO-treatment. Most complications were of mild severity with newly onset or accentuated aortic, mitral, or tricuspid regurgitation, and 5 patients (15%) had newly onset left bundle branch block. An additional 3 patients displayed left bundle branch block after reintervention, one of which had confirmed persisting left bundle branch block.

Clinical characteristics (Table 2)

Most patients were asymptomatic at diagnosis (75%) and preoperatively (73%). All patients displayed preoperative systolic murmurs, while only 4 (11%) patients had a diastolic murmur. At last follow-up, 15 patients (68%) had a persistent systolic murmur, while diastolic murmur was observed for 2 patients (8%).

All patients had sinus rhythm during all ECG recordings. Preoperative ECG showed signs of left ventricular hypertrophy in 7 (22%) and 1 (3%) of patients based on sV1 and rV6, respectively. Only 3 (14%) patients with left ventricular hypertrophy showed concordant signs of hypertrophy in both ECG sV1 measurements and echocardiographic diastolic septal examinations.

Table 1. Demographics, comorbidity, thoracic intervention and outcome for Gothenburg's surgically treated mSAS-patients

	n	Quantity	%	Median (range)
Study participants		38		
Sex (male/female)	38	23/15	61/39	
Prematurity (<w.37 at birth)	22	6	27	
mSAS (patients)	38	38	100	
Other congenital heart disease (patients)	38	20	53	
Chordae-malformation (cases)		3	8	
Coarctation of the aorta (cases)		2	5	
Bicuspid aortic valve (cases)		5	13	
Patent ductus arteriosus (cases)		7	18	
Ventricular septal defect (cases)		7	18	
Valvular aortic stenosis (cases)		6	16	
Other CHD (cases)		5	N/A	
Extra-cardiac diseases (patients)	38	19	50	
Gastrointestinal and/or liver disease (cases)		3	8	
Developmental delay (cases)		7	18	
Genetic syndrome/chromosomal defect (cases)		7	18	
Other (cases)		18	N/A	
Previous cardiothoracic surgery (patients)	38	8	21	
Aortic commissurotomy (cases)		3	8	
Coarctation of the aorta (cases)		1	3	
Patent ductus arteriosus (cases)		4	11	
Ventricular septal defect (cases)		1	3	
Age and follow-up (years)				
Age at diagnosis	31			2.3 (0.003-17.2)
Time from diagnosis to primary surgery	31			1.6 (0.02-7.1)
Age at primary surgery	38			5.3 (0.03-17.5)
Time from primary surgery to first reintervention	7			3.2 (2.1-8.4)
Age at first reintervention	7			6.9 (4.2-12.6)
Time from primary surgery to latest/last follow-up	30			9.9 (0.01-19.5)
Age at latest/last follow-up	30			17.5 (3.6-20.4)
Primary surgical intervention for mSAS				
Resection of the membrane (patients)	38	38	100	
Resection + myectomy (patients)	38	4	11	
Other combined cardiac surgery (patients)	38	6	16	
Repair of mitral chordae (cases)	38	2	5	
Patent ductus arteriosus (cases)	38	2	5	
Aortic commissurotomy (cases)	38	1	3	
VSD (cases)	38	1	3	
Patent foramen ovale (cases)	38	1	3	
Body surface area at surgery (m ²)	34			0.82 (0.22-1.73)
ECC-time during primary surgery (min)	36			55 (34-156)
Complications after primary surgery (patients)	38	24	63	
Deceased due to heartfailure peri-/postop. (cases)	38	1	3	

(Continued)

Table 1. (Continued)

	n	Quantity	%	Median (range)
New onset or accentuated AR (cases)	38	5	13	
New onset or accentuated MR (cases)	38	6	16	
New onset or accentuated TR (cases)	38	6	16	
New onset LBBB (cases)	33	5	15	
Pericardial effusion requiring treatment (cases)	38	5	13	
Reccurrence and reintervention				
Number of reinterventions (I/II/III)	34	6/0/1	18/0/3	
Significantly increased peak gradient at follow-up among patients without reintervention (patients)	27	12	44	
Significantly increased peak gradient at follow-up after first reintervention (patients)	5	4	80	

Abbreviations: mSAS = membranous subvalvular aortic stenosis; n = participants without missing data; VSD = ventricular septal defect; ECC = extracorporeal circulation; peri- = perioperative; postop., postoperative; AR = aortic regurgitation; MR = mitral regurgitation; TR = tricuspid regurgitation; LBBB = left bundle branch block.

Echocardiographic characteristics (Table 3 and 4)

The median peak gradient progressed from 61 mmHg at diagnosis to 83 mmHg preoperatively, 16 mmHg post-operatively, and 19 mmHg at follow-up (Table 3, Figure 3). Preoperative function-class and preoperative peak-gradients were positively associated (Table 4, $p < 0.001$). All patients (10/34) with functional class > 1 had preoperative peak gradients ≥ 90 mmHg. The mean value peak gradient for patients with functional class > 1 was significantly higher compared to patients with functional class 1 (113 and 73 mmHg, respectively, $p < 0.001$). The pre-and post-operative peak gradients were positively linearly correlated (Table 4, Figure 4, $r \approx 0.47$, $k \approx 0.16$, $p < 0.01$). A negative correlation was observed between the preoperative peak gradient and the distance between the subaortic stenosis membrane and the aortic valve. A shorter distance was overall associated with a higher preoperative peak gradient (Table 4, $r \approx -0.44$, $p < 0.01$).

Septal diastolic wall thickness Z-score > 2 , indicative of left ventricular hypertrophy, was observed for 22 (92%) patients preoperatively (Table 3), while left ventricular posterior wall diastolic thickness Z-score > 2 was present for only 11 (46%) patients. Diastolic septal and left ventricular posterior wall thickness were positively correlated (Table 4, $r \approx 0.57$, $p < 0.01$). No significant correlation was, however, observed between the septal Z-score and the preoperative peak-gradient.

Aortic regurgitation > 1 was observed in three (19%) patients at diagnosis (Table 3), 8 patients (24%) preoperatively, 3 patients (8%) postoperatively, and 8 patients (27%) at last follow-up. A significant increase in aortic regurgitation was observed when comparing the absence (aortic regurgitation = 0) to the presence (aortic regurgitation > 0) of aortic regurgitation preoperatively and at last follow-up (Table 4, Figure 5, $p < 0.05$).

Predictors of recurrence and reintervention (Table 5)

Predictors of recurrence were analysed by comparing patients in the recurrent group ($n = 19$) to those in the non-recurrent group ($n = 15$). Due to missing follow-up data, 3 patients that had not undergone reintervention were excluded from the analysis. Both the postoperative peak gradient and the postoperative mean gradient were significantly higher ($p < 0.05$) in patients who developed recurrence. Additionally, valvular AS tended to be more common in patients which developed disease recurrence ($p \approx 0.053$). Most other variables did not differ significantly between

patients with and without recurrence, including sex, newly debuted left bundle branch block, distance between the subaortic stenosis membrane/aortic valve, preoperative peak gradient, preoperative mean-gradient, septal diastolic wall thickness, and presence of aortic regurgitation.

In terms of reintervention, patients who underwent primary surgery before 5 years of age had a significantly higher risk of reintervention compared to patients that had undergone surgery after 5 years of age (Figure 2b, $p \approx 0.043$), as determined by Kaplan-Meier survival-analysis and Mantle-Cox testing.

Discussion

The major findings of this retrospective review of surgically treated paediatric membranous subaortic stenosis patients were that a majority of patients developed recurrence, resulting in a need of reintervention for 21%. Mortality was rare and occurred in only one case. Postoperative peak and mean pressure gradients were elevated in patients who ultimately developed recurrence. Furthermore, patients who underwent primary surgery before 5 years of age had a significantly higher risk of reintervention.

Membranous subaortic stenosis surgery is relatively safe but is associated with high recurrence rate

Based on our study's definition of recurrence (peak gradient increase $> 50\%$ compared to the postoperative peak-gradient and a minimum peak gradient of > 16 mmHg), we observed a recurrence rate of 56% in this retrospective cohort. This is relatively high compared to what has been reported in other studies,^{2,3,10} which might be due to varying definitions of recurrence. Frequent recurrence, despite successful surgical intervention, highlights the progressive nature of membranous subaortic stenosis.¹⁹ In contrast, only 21% of patients in this study required reintervention, which is consistent with findings from previous studies.^{12,16,20,21} Residual cell populations derived from the subaortic membrane, damaging blood jets causing shear stress, as well as the existence of different genetical disease subtypes might explain the temporary improvement following surgery.

A positive correlation between preoperative and postoperative peak-gradient was observed. Furthermore, high residual post-operative peak- and mean pressure gradients were identified as potential predictors of recurrence, as postoperative pressure gradients were significantly higher in the group of patients that

Table 2. Symptoms, clinical signs and ECG of Gothenburg's surgically treated mSAS-patients

	n	Quantity	%
Symptoms/signs at diagnosis (cases)			
Functionality classification (grade I/II/III/IV)	20	15/5/0/0	75/25/0/0
Dyspnoea	18	3	17
Chest pain	17	2	12
Syncope	22	3	14
Systolic murmur	24	24	100
Diastolic murmur	24	4	17
Symptoms/signs preop. (cases)			
Functionality classification (grade I/II/III/IV)	33	24/8/1/0	73/24/3/0
Dyspnoea	31	4	13
Chest pain	32	3	9
Syncope	32	3	9
Systolic murmur	33	33	100
Diastolic murmur	35	4	11
Symptoms/signs at latest/last follow-up (cases)			
Functionality classification (grade I/II/III/IV)	29	27/2/0/0	93/7/0/0
Dyspnoea	29	0	0
Chest pain	30	2	7
Syncope	29	0	0
Systolic murmur	22	15	68
Diastolic murmur	26	2	8
ECG at diagnosis (cases)			
Sinus rhythm	15	15	100
AV-block I	9	2	22
Prolonged QRS-time	10	0	0
RBBB	12	1	8
LBBB	12	0	0
Prolonged QTc-time	8	1	13
ECG preop. (cases)			
Sinus rhythm	36	36	100
AV-block I	34	1	3
Hypertrophy sV1	32	7	22
Hypertrophy rV6	33	1	3
Prolonged QRS-time (ms)	34	6	18
RBBB	34	3	9
LBBB	34	0	0
Prolonged QTc-time (ms)	34	2	6
ECG postop. (cases)			
Sinus rhythm	31	31	100
AV-block I	31	6	19
Prolonged QRS-time (ms)	31	9	29
RBBB	33	4	12
LBBB	34	5	15
Prolonged QTc-time (ms)	30	5	17

(Continued)

Table 2. (Continued)

	n	Quantity	%
ECG at latest/last follow-up (cases)			
Sinus rhythm	23	23	100
AV-block I	15	3	20
Prolonged QRS-time (ms)	15	2	13
RBBB	15	0	0
LBBB	16	1	6

Abbreviations: ECG, electrocardiogram; mSAS, membranous subvalvular aortic stenosis; n, participants without missing data; preop, preoperatively; AV-block, atrioventricular block; RBBB, right bundle branch block; LBBB, left bundle branch block; sV1, s-wave in V1; rV6, r-wave in V6; postop, postoperatively.

eventually suffered disease recurrence. This was in agreement with previous studies.^{8,10,11,13} Our findings suggest that delaying surgery for “too long”—e.g. until the preoperative peak gradient exceeds 40 mmHg—could prevent reaching a normal postoperative peak-gradient < 10 mmHg.²² The importance of achieving a low postoperative peak-gradient has been discussed since Attie et al²³ suggested that moderately elevated post-op peak gradient did not predict disease recurrence. However, several subsequent studies, e.g. Brauner et al,¹¹ have reported and verified that an increased postoperative pressure gradient constitutes a predictor of future reintervention.¹³ Furthermore, earlier studies have suggested that higher gradients might also potentially increase the risk for sudden death.²⁴ Our results support that postoperative peak- and mean gradients may be predictive of disease recurrence. Therefore, it is possible that an aggressive surgical approach aimed at minimising the postoperative pressure gradient¹² combined with early intervention before the preoperative peak-gradient has become too elevated (i.e. > 40 mmHg) could be favourable in avoiding future recurrence. It should, however, be noted that even aggressive surgery may not be successful in preventing disease recurrence. Anatomical variations of the left ventricular outflow tract and an architecture which results in turbulent blood flow may constitute factors that are not completely correctable through surgery. Due to the complex pathophysiological nature of membranous subaortic stenosis and the risks associated with surgery, the optimal surgical method and timing for correcting membranous subaortic stenosis need to be further investigated.

Importantly, younger age at the time of primary surgery has been suggested to be predictive of recurrence, which could imply that early intervention results in an increased risk of recurrence.^{8,16,20,21} In the current study, age < 5 years at initial intervention was a significant predictor for reintervention, corroborating the results of previous studies. Could early surgery itself trigger the recurrence, or do the patients who require surgical intervention at a younger age constitute a distinct, more aggressive disease phenotype⁸? If the latter is true, earlier intervention at lower gradients could potentially be beneficial for these patients, in order to minimise the risk of a residual pressure gradient. A more aggressive surgical technique, however, also increases the risk of perioperative complications and is no guarantee for avoiding disease recurrence.^{3,20} Notably, we did not find preoperative peak- and mean gradients to be significantly elevated in the patients that developed disease recurrence. Limited sample size and study power may explain this discrepancy in comparison to previous studies, which have demonstrated that preoperative pressure gradients are predictive of reintervention.^{2,8,10,11,15,20,21}

Other studies have suggested that a shorter distance between the subaortic membrane and the aortic valve is predictive of reintervention.^{13,15,16,20,21} No significant difference for the subaortic membrane/aortic valve distance was observed between the recurrence and non-recurrence groups in our study. This may, possibly, be explained by the relatively small sample size of the study. Notably, we observed a negative correlation between the subaortic membrane/aortic valve distance and the preoperative peak-gradient. This suggests that a shorter subaortic membrane/aortic valve distance may lead to a greater obstruction, resulting in a higher preoperative peak-gradient.

The low mortality and rate of complications were in line with other publications.^{14,20,21} Aortic regurgitation has been observed to progress over time in several previous publications,^{11,12,19} irrespective of surgical intervention. Damaging jets caused by the subaortic membrane or residual membrane tissue has been suggested as a possible mechanism for aortic regurgitation progression.⁵ The increased portion of patients that had developed aortic regurgitation at last follow-up compared to the preoperative timepoint was therefore to be expected.

Most patients with membranous subaortic stenosis remained asymptomatic until surgical intervention

Most patients in this study of surgically treated patients with membranous subaortic stenosis were asymptomatic and diagnosed due to the initial finding of a systolic murmur. Notably, we observed an association between functional class and the preoperative peak-gradient at a threshold value of 90 mmHg. These findings challenge the conclusions of Brauner et al,¹¹ who reported no clear correlation between symptoms and the preoperative peak-gradient. On the other hand, Aboulhosn et al.⁵ reported that development of symptoms related to membranous subaortic stenosis was a negative prognostic factor that should prompt surgery. The findings by Aboulhosn et al. suggest that surgery should be performed well before clinical deterioration to the point when symptoms arise, which, according to our study, would be before their peak-gradient exceeds 90 mmHg. It should be noted that all patients who exceed a preoperative peak gradient of 90 mmHg do not report any symptoms. As demonstrated previously, including by Darcin et al.^{3,10,12}, most patients with membranous subaortic stenosis remain asymptomatic throughout childhood and adolescence. Nevertheless, the prognostic impact of a symptomatic clinical presentation could be of great practical and clinical value - especially in regions where the availability of echocardiography is limited. By examining presence of function class > 1 and

Table 3. Echocardiographic data of Gothenburg's surgically treated mSAS-patients

	n	Quantity	%	Median (range)
Echo at diagnosis				
Peak gradient (mmHg)	28			61 (16 - 145)
Mean gradient (mmHg)	10			36 (15 - 90)
Aortic regurgitation (AR, 0-4)	16			0.5 (0.0 - 1.5)
AR>1	16	3	19	
Mitral regurgitation (MR, 0-4)	11			0.0 (0.0 - 1.0)
Tricuspid regurgitation (TR, 0-4)	9			0.0 (0.0 - 1.5)
Echo preop.				
Peak gradient (mmHg)	37			83 (19 - 158)
Mean gradient (mmHg)	25			50 (19 - 86)
FS (%)	28			46 (35 - 57)
AR (0-4)	34			0.75 (0.0 - 2.0)
AR>1	34	8	24	
MR (0-4)	34			0.0 (0.0 - 1.0)
TR (0-4)	32			0.0 (0.0 - 1.0)
Left ventricle end systolic dimension (Z-score)	24			-2.58 (-4.87 - 2.83)
Left ventricle end diastolic dimension (Z-score)	26			0.04 (-3.50 - 6.41)
Septal diastolic wall thickness (Z-score)	24			3.78 (0.95 - 7.33)
Septal diastolic hypertrophy (Z-score>2)	24	22	92	
Posterior left ventricular wall diastolic thickness (Z-score)	24			1.92 (-0.40 - 5.58)
Posterior left ventricular wall diastolic thickness hypertrophy (Z-score>2)	24	11	46	
Distance SAS membrane and aortic valve (mm)	28			4.3 (1 - 10)
Echo postop.				
Peak gradient (mmHg)	36			16 (4 - 55)
Mean gradient (mmHg)	18			8 (3 - 21)
FS (%)	23			39 (24 - 55)
AR (0-4)	36			0.75 (0.0 - 2.0)
AR>1	36	3	8	
MR (0-4)	9			1.0 (0.5 - 2.5)
TR (0-4)	9			0.5 (0.5 - 2.0)
Echo at latest/last follow-up				
Peak gradient (mmHg)	32			19 (6 - 73)
Mean gradient (mmHg)	16			17 (3 - 34)
FS (%)	19			38 (30 - 50)
AR (0-4)	30			1.0 (0.0 - 2.5)
AR>1	30	8	27	
MR (0-4)	17			0.0 (0.0 - 2.0)
TR (0-4)	16			0.0 (0.0 - 1.0)

Abbreviations: mSAS, membranous subvalvular aortic stenosis; n, participants without missing data; Echo, echocardiography; AR, aortic regurgitation; MR, mitral regurgitation; TR, tricuspid regurgitation; preop, preoperatively; FS, fractional shortening; SAS, subvalvular aortic stenosis; postop, postoperatively.

Table 4. Primary intervention. Continuous variables analysed by Pearson's correlation, categorical variables by Chi-square-tests

	Pearson's r-value	Chi-square-test statistic	p-value
Function class (1/>1) vs. peak gradient (≤ 90 / >90 mm Hg) preop.		17.8	$p < 0.001$
Peak gradient preop. vs. peak gradient postop.	0.47		$p < 0.01$
Distance between subaortic membrane and AoV vs. peak gradient preop.	-0.44		$p < 0.01$
Septal diastolic wall thickness (Z-score) vs. posterior diastolic wall thickness (Z-score) preop.	0.57		$p < 0.01$
Septal diastolic wall thickness (Z-score) vs. peak gradient preop.	0.24		NS
Aortic regurgitation (grade 0/>0) preop. versus last follow-up		4.42	$p < 0.05$
Aortic regurgitation grade preop. vs. Peak gradient preop.	0.30		$p < 0.10$

Abbreviations: preop = preoperative; postop = postoperative; AoV = aortic valve.

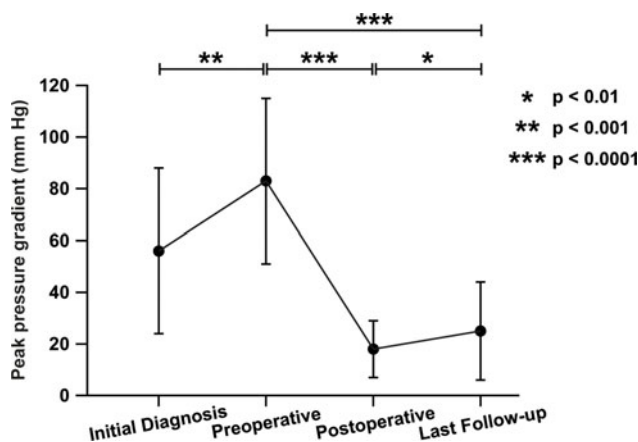


Figure 3. Progression of peak pressure gradients from diagnosis until follow-up. Mean value of the peak pressure gradient $\pm$ standard deviation at each time point. Number of patients with available data were 28 at diagnosis, 37 preoperatively, 36 postoperatively and 32 at last follow-up. Paired student's T tests: * p -value < 0.01 , ** p -value < 0.001 , *** p -value < 0.0001 .

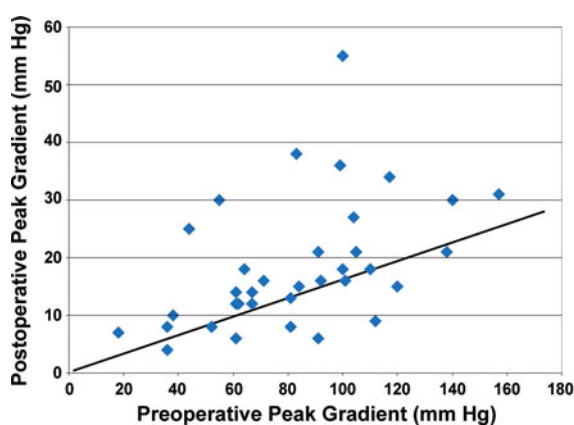


Figure 4. Correlation between pre- and postoperative peak gradients. A positive linear correlation between pre- and postoperative peak pressure gradients was observed, $r \approx 0.47$, $p < 0.01$ and $k \approx 0.16$.

symptoms, patients with a high peak gradient (> 90 mmHg) could plausibly be identified and referred for closer examination with echocardiography and subsequent surgery.

Demographic characteristics, comorbidities, and ECG findings in patients with membranous subaortic stenosis

The current study sample had a male/female ratio consistent with previous studies,^{7,8,13,16,19–21} as patients with membranous subaortic stenosis were predominantly boys. Unlike previous studies, we did not observe any overrepresentation of females in the patient group with disease recurrence.^{3,10} The age at diagnosis (median 2.3 years) as well as age at primary surgery (median 5.3 years) corresponded well with data from other studies.^{8,12,20}

The prevalence of other CHD including valvular AS (53%) was consistent with previous studies,^{7,20} although the reported prevalence of specific diagnoses has varied between studies. Valvular AS tended to be more common in patients who developed recurrence ($p \approx 0.053$). Although several patients had both membranous subaortic stenosis and valvular AS, surgical correction of valvular AS through commissurotomy occurred in only 1/6 cases. As membranous subaortic stenosis and valvular AS may preferentially be corrected simultaneously, it would be valuable to explore whether valvular AS is routinely corrected during surgery for membranous subaortic stenosis in other cohorts.

Interestingly, we observed a relatively high prevalence of genetic conditions and/or developmental delay in the patient cohort, which has not been observed in previous retrospective studies of membranous subaortic stenosis.⁸

Lastly, it seems that there is no strong correlation between left ventricular hypertrophy and ECG-changes in sV1 and rV6. While 92% demonstrated left ventricular hypertrophy based on echocardiographic measurement of the diastolic septal wall thickness, only 22 and 3% exhibited signs of left ventricular hypertrophy based on ECG leads sV1 and rV6, respectively. ECG and echocardiographic measurements were concordant for only 3 patients (14%) with left ventricular hypertrophy. ECG may, therefore, not be considered a sensitive indicator for cardiac hypertrophy in patients with membranous subaortic stenosis.

Limitations

Although all eligible patients, i.e. half of all patients with membranous subaortic stenosis in Sweden surgically treated between 1994 and 2019, were included in the current study, the sample size and study power were limited. Modest, clinically significant differences between groups may therefore have been overlooked. This may, for example, have been the case when patients with and without disease recurrent were compared for a

Table 5. Differences between patients with and without recurrent mSAS

	All (sd)	Recurrence (sd)	Non-recurrence (sd)	p-value
Quantity	34	19	15	NS
Sex (male)	57%	53%	67%	NS
Congenital aortic stenosis	5	5	0	0.053
Age at diagnosis (years)	3.2 (3.8)	2.2 (2.2)	4.4 (4.7)	NS
Age at primary surgery (years)	5.6 (3.7)	5.1 (3.1)	6.3 (4.4)	NS
Time between primary intervention and last Fu (years)	9.1 (5.5)	9.9 (5.4)	7.9 (5.5)	NS
Age at last Fu (years)	14.6 (4.7)	14.8 (4.4)	14.3 (5.1)	NS
Newly debuted LBBB post-op	5	5	0	NS
Distance between SAS-membrane and aortic valve (mm)	5.1 (3.5)	5.6 (3.3)	4.5 (3.5)	NS
Pre-op. Peak gradient (mmHg)	84.9 (25.5)	91.3 (30.8)	76.8 (32.7)	NS
Pre-op. Mean gradient (mmHg)	48.6 (18.1)	52.1 (19.4)	44.5 (15.5)	NS
Post-op. Peak gradient (mmHg)	17.7 (10.8)	21.3 (11.2)	14.1 (8.7)	0.018
Post-op. Mean gradient (mmHg)	8.1 (4.4)	10.1 (3.6)	6.4 (4.7)	0.047
Pre-op septal diastolic diameter (Z-score)	3.7 (1.4)	3.9 (1.7)	3.5 (1.0)	NS
Aortic regurgitation pre-op. (presence)	73%	73%	73%	NS
Aortic regurgitation post-op. (presence)	84%	88%	80%	NS
Body surface area (m^2)	0.82 (0.32)	0.82 (0.28)	0.84 (0.39)	NS
ECC-time (min)	58.6 (16.3)	60.9 (14.3)	56.9 (19.2)	NS

Abbreviations: mSAS, membranous subvalvular aortic stenosis; sd, standard deviation; LBBB, left bundle branch block; postop, postoperatively; SAS, subvalvular aortic stenosis; preop, preoperatively; ECC, extracorporeal circulation.

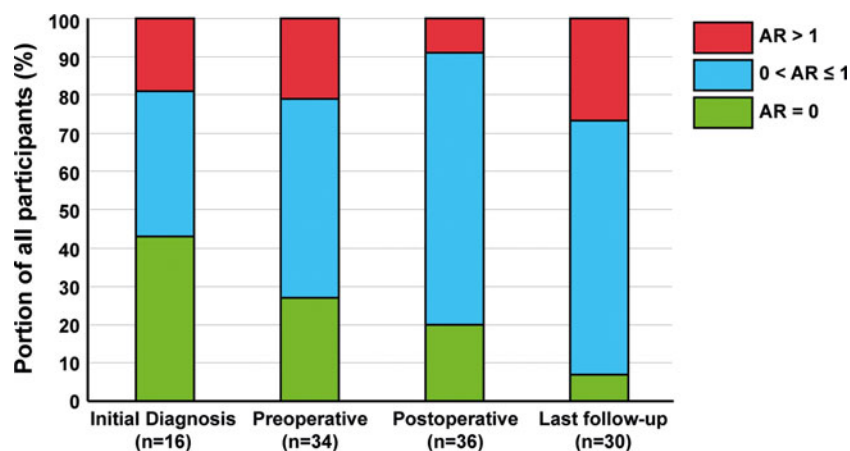


Figure 5. Progression of aortic regurgitation from initial diagnosis until last follow-up. AR = 0 (green) constitutes no aortic regurgitation (AR), $0 < AR \leq 1$ (blue) constitutes aortic regurgitation of mild severity and $AR > 1$ (red) constitutes aortic regurgitation of at least moderate severity.

number of putative predictor variables of recurrence. The results of the conducted statistical tests should be considered exploratory.

As patients treated over the span of three decades were included in the study, clinical protocols for echocardiographic examinations and assessment of valvular regurgitation may have changed over the course of the study. Furthermore, the follow-up time was restricted to 18 years of age, resulting in a relatively short follow-up time in some cases.

Lastly, there are different perspectives on how to define recurrence of membranous subaortic stenosis; should it be limited to severe cases requiring reinterventions or should it include milder relapses as well? If so, what threshold-gradients should be used? In this study, we defined recurrence to include both patients who underwent reintervention and those with moderate disease

progression after the primary intervention. This broader definition addresses the gap in literature that often focuses only on reinterventions. While predictors for reintervention are important, identifying predictors for less severe recurrences is also vital due to the less favourable prognosis for these patients.

Conclusions

Surgery for membranous subaortic stenosis is an effective therapy but has a high rate of recurrence and reintervention. A clear correlation exists between high pre- and postoperative peak gradients. Development of symptoms is associated with a high preoperative peak gradient. Low postoperative peak gradients may be important for avoiding recurrence.

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Competing interests. None.

Ethical standard. This study was conducted following approval of the local ethics committee at the University of Gothenburg (DNR 518-16 including supplementary application). The study was limited to retrospective follow-up after surgical treatment of CHD, and all personal data were anonymised and encrypted prior to publication. Patients were, therefore, not individually asked to participate.

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