Background—Discrete subaortic stenosis is notable for its unpredictable hemodynamic progression in childhood and high reoperation rate; however, data about adulthood are scarce.

Methods and Results—Adult patients who previously underwent surgery for discrete subaortic stenosis were included in this retrospective multicenter cohort study. Mixed-effects and joint models were used to assess the postoperative progression of discrete subaortic stenosis and aortic regurgitation, as well as reoperation. A total of 313 patients at 4 centers were included (age at baseline, 20.2 years [25th–75th percentile, 18.4–31.0 years]; 52% male). Median follow-up duration was 12.9 years (25th–75th percentile, 6.2–20.1 years), yielding 5617 patient-years. The peak instantaneous left ventricular outflow tract gradient decreased from 75.7±28.0 mm Hg preoperatively to 15.1±14.1 mm Hg postoperatively (P<0.001) and thereafter increased over time at a rate of 1.31±0.16 mm Hg/y (P=0.001). Mild aortic regurgitation was present in 68% but generally did not progress over time (P=0.76). A preoperative left ventricular outflow tract gradient ≥80 mm Hg was a predictor for progression to moderate aortic regurgitation postoperatively. Eighty patients required at least 1 reoperation (1.8% per patient-year). Predictors for reoperation included female sex (hazard ratio, 1.53; 95% confidence interval, 1.02–2.30), and left ventricular outflow tract gradient progression (hazard ratio, 1.45; 95% confidence interval, 1.31–1.62). Additional myectomy did not reduce the risk for reoperation (P=0.92) but significantly increased the risk of a complete heart block requiring pacemaker implantation (8.1% versus 1.7%; P<0.005).

Conclusions—Survival is excellent after surgery for discrete subaortic stenosis; however, reoperation for recurrent discrete subaortic stenosis is not uncommon. Over time, the left ventricular outflow tract gradient slowly increases and mild aortic regurgitation is common, although generally nonprogressive over time. Myectomy does not show additional advantages, and because it is associated with an increased risk of complete heart block, it should not be performed routinely. (Circulation. 2013;127:1184-1191.)

Key Words: constriction, pathologic ■ echocardiography ■ heart defects, congenital ■ risk factors ■ surgical procedures, operative

Discrete subaortic stenosis (DSS) is notable for its unpredictable and sometimes rapid hemodynamic progression in childhood and its association with aortic regurgitation (AR), which is found in 30% to 80% of patients.1–7 Different strategies exist for the timing of surgical treatment, ranging from early (mild to moderate obstruction) to late (severe or symptomatic) repair. Early repair has been advocated to prevent aortic valve damage and thus AR progression.5–12 Nevertheless, it remains unclear whether surgery can actually alter the course of progressive AR. Furthermore, surgery is associated with a high recurrence risk and need for reoperation (8%–34%).12–18 A major factor in DSS recurrence is believed to be inadequate relief of the obstruction.19 Therefore, some groups advocate concomitant selective myectomy to achieve complete relief of the left ventricular outflow tract (LVOT) obstruction,8,18–21 whereas others have reported that the addition of myectomy does not reduce the number of recurrences.16,17,22–27

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Although postoperative outcome and risk factors for reoperation in children are well established, postoperative data for the adult population are limited.15,27,28 Therefore, the aim of this study was to identify risk factors for postoperative DSS recurrence, AR progression, and reoperation in a large cohort of adult patients who previously underwent surgical treatment for DSS.

Methods

All adult patients who previously underwent surgery for fibromuscular DSS and were seen between January 1980 and October 2011 at the Congenital Cardiac Center for Adults of one of the participating centers (Erasmus University Medical Center, Rotterdam, and Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands; University Hospital Gasthuisberg, Leuven, Belgium; and Toronto Congenital Cardiac Center for Adults located at Peter Munk Cardiac Center, Toronto, ON, Canada) were evaluated for eligibility for this study. Fibromuscular DSS was defined as a complete or incomplete encirclement of the LVOT by a membrane or short-segment stenosis consisting of fibrous or fibromuscular tissue. The baseline of this study was defined as the time of the first adult outpatient clinic visit. Eligible patients were selected from the CONgenital CORvitia (CONCOR) database (the Dutch registry for adult patients with congenital heart disease [CHD])33 and from the Leuven and Toronto local databases for adults with CHD. Although all patients followed up to a Congenital Cardiac Center for Adults were ≥17 years old, the first surgery for DSS could have been performed in childhood. Exclusion criteria were lack of serial echocardiograms, non-DSS causes for subaortic obstruction (tunnel-like subaortic narrowing, hypertrophic cardiomyopathy, accessory mitral valve tissue, or mitral valve prolapse), concomitant moderate to severe valvular aortic stenosis, transposition of the great arteries, and univentricular connections. This retrospective study was approved by the institutional review boards and ethical committees of the participating centers. Informed consent was waived.

Demographic, clinical, and surgical data were obtained from medical charts and electronic health records. All available transthoracic echocardiograms, ECGs, and exercise tests were collected. Peak systolic instantaneous LVOT gradient was derived from the continuous-wave Doppler LVOT peak flow velocity. The degree of AR was graded by experienced echocardiographers and cardiologists as mild, moderate, or severe.17,18 Left ventricular mass was calculated with the modified Devereux formula.19 In the parasternal long-axis view at end diastole, we measured the aortoseptal angle, which is the angle formed by the plane of the ventricular septum and the ascending aorta, as previously described.19,20

Statistical Analysis

The Statistical Package for Social Sciences version 19.0 (SPSS, Inc, Chicago, IL) was used for descriptive data analysis. Continuous variables were summarized as mean±SD or median and 25th to 75th percentile. Categorical variables were summarized by use of frequency and percentage. The paired t test, paired Wilcoxon, and McNemar tests were used to compare preoperative and postoperative measurements.

All statistical tests with a value of P≤0.05 were considered significant.

For advanced statistical analyses of the longitudinal and survival data, the R statistical software (version 2.15.0: www.r-project.org) was used. To assess changes in echocardiographic measurements over time while accounting for the correlation between repeated follow-up measurements in each patient, mixed-effects model analyses were used. In particular, for the postoperative LVOT gradient progression rate, a linear mixed-effects model was used,14 whereas for postoperative AR progression, a mixed-effects continuation ratio model was used. To allow flexibility in the modeling of the patient-specific longitudinal trajectories, we used natural cubic splines of time in the specification of the mixed-effects models, in both the fixed- and random-effect parts of the models. The following variables were included in the models as covariates: age at the time of surgery, age at diagnosis, sex, preoperative peak instantaneous LVOT gradient, difference between preoperative and postoperative gradients (delta), type of surgery (isolated enucleation or additional myectomy), associated CHD, and smoking. For each of the covariates in the model, its main effect and interaction with time were added, allowing different average longitudinal evolutions per covariate. Residual plots were used to validate the model assumptions, and when appropriate, transformations of the outcome variables were used in the analysis. Furthermore, to account for missing covariate data, a multiple imputation approach was used for the preoperative and postoperative LVOT gradient covariates (missing for 42 patients). Five generations of complete data sets were realized. Wald tests were used to assess which prognostic factors were most associated with the progression of peak instantaneous LVOT gradient and AR.

Probabilities of intervention-free survival from baseline were obtained by the Kaplan-Meier method. Survival of DSS patients was compared with the expected survival of the age-matched normal Dutch population.34 Patients were censored at the end of follow-up or classified as event (surgery for DSS or death). A penalized likelihood approach was used for the Cox regression model with baseline data to account for the low number of events compared with the number of covariates. A joint longitudinal and survival model and the time-dependent Cox model were used to investigate the effect of peak instantaneous LVOT gradient and AR, respectively, on the hazard ratio for intervention-free survival.36

Results

A total of 737 patients were assessed for eligibility to participate in this study. Inclusion criteria were met by 313 patients. A total of 424 patients were excluded, mainly because of LVOT obstruction resulting from another cause (n=145), no history of DSS surgery (n=149), or lack of serial echocardiographic examinations (n=74).

Baseline characteristics of the 313 patients are summarized in Table 1. Of the 313 patients, 163 patients (52.1%) had ≥1 associated CHD. Baseline LVOT diameter was 14.5±3.8 mm in women and 15.7±4.2 mm in men (P=0.19). Follow-up ranged from 1 to 31 years (median, 12.9 years; 25th–75th percentile, 6.2–20.1 years), yielding a total of 5617 patient-years. On average, 2.3±1.4 (minimum, 2; maximum, 8) echocardiographic studies were available for each patient.

Operative Outcomes

The 313 included patients underwent a total of 412 operations for DSS. The peak instantaneous LVOT gradient decreased from 75.7±28.0 mm Hg preoperatively to 15.1±14.1 mm Hg postoperatively (P<0.001). The LVOT diameter increased from 14.5±3.8 to 19.0±3.7 mm (P<0.001). In 251 patients (61%), the first surgery was performed in childhood (mean age, 12.9±6.7 years). Table 2 shows the surgical details, including concomitant surgery and postoperative complications. In those patients who did not undergo concomitant aortic valve repair or replacement during surgery for DSS, the severity of AR was unchanged postoperatively (P=0.60). Seventeen patients (4.4%) suffered from a complete heart block postoperatively, requiring pacemaker implantation. Patients who underwent an additional myectomy more frequently developed complete heart block than patients who underwent isolated enucleation (8.1% and 1.7%, respectively; P=0.005).
One death occurred within 30 days after surgery for DSS resulting from heart failure. Ten patients (mean age, 49.1±16.5 years) died during follow-up (0.18% per patient-year; Figure 1A). Five deaths were for cardiac reasons (4 heart failure and 1 septic shock after endocarditis). In 2 patients, the cause of death was metastasized cancer. Three patients died suddenly during follow-up (unknown cause of death, no autopsy; age, 19, 30, and 48 years; all had an LVOT gradient <30 mm Hg at last follow-up visit, 2 had an associated ventricular septal

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Operated DSS Patients</th>
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</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
</tr>
<tr>
<td>Age at baseline, y</td>
</tr>
<tr>
<td>Age at DSS diagnosis, y</td>
</tr>
<tr>
<td>Body surface area, m²</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
</tr>
</tbody>
</table>

Associated CHD anomalies, previously repaired, n (%)*

| None                  | 150 (47.9) |
| Ventricular septal defect | 72 (23.0); 15 (4.8) |
| Atrial septal defect    | 18 (5.8); 4 (1.3) |
| Valvular aortic stenosis| 29 (9.3); 2 (0.6) |
| Coarctation of the aorta| 48 (15.3); 10 (3.2) |
| Persistent ductus arteriosus| 20 (6.4); 8 (2.6) |
| Shone complex           | 10 (3.2); 0 (0.0) |

Aortoseptal angle, degrees 124.7±15.9

Left atrial diameter (indexed for BSA, mm/m²), mm 42.4±11.7 (22.8±5.3)

Left ventricular mass (indexed for BSA, mm/m²), g 222.0±86.3 (120.1±42.8)

LV end-diastolic diameter (indexed for BSA, mm/m²), mm 49.1±7.5 (27.1±4.4)

LV end-systolic diameter (indexed for BSA, mm/m²), mm 29.5±7.4 (16.3±4.3)

LV fractional shortening, % 40.3±9.0

E/A ratio 1.5±0.6

E/E’ ratio 11.9±6.0

Maximum exercise capacity, % from norm 82.1±20.4

Sinus rhythm 295 (94.2)

Heart frequency, bpm 72.5±14.5

QRS duration, ms 114.9±28.9

PR time, ms 160.5±30.9

NYHA class I, n (%) 290 (92.9)

Smoking, n (%) Never 211 (67.4) Former 26 (8.3) Current 64 (20.4) Unknown 12 (3.8)

BSA indicates body surface area; CHD, congenital heart disease; DSS, discrete subaortic stenosis; LV, left ventricular; and NYHA, New York Heart Association. Values are median (25th–75th percentile) or mean±SD as appropriate.

*Diagnoses are not mutually exclusive.

### Table 2. Surgical Details for 412 Discrete Subaortic Stenosis Operations

<table>
<thead>
<tr>
<th>Operated DSS Patients</th>
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</thead>
<tbody>
<tr>
<td>Age at time of surgery, y</td>
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<tr>
<td>Pre-operative peak LVOT gradient, mm Hg</td>
</tr>
<tr>
<td>Postoperative peak LVOT gradient, mm Hg</td>
</tr>
<tr>
<td>Preoperative aortic regurgitation, n (%)</td>
</tr>
<tr>
<td>Mild</td>
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<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Severe</td>
</tr>
</tbody>
</table>

Postoperative aortic regurgitation, n (%)

| None | 87 (27.8) | 18 (22.5) | 5 (26.3) |
| Mild | 208 (66.4) | 59 (73.8) | 13 (68.4) |
| Moderate | 18 (5.8) | 3 (3.8) | 1 (5.3) |
| Severe | 0 (0.0) | 0 (0.0) | 0 (0.0) |

Type of surgery, n (%) Isolated enucleation | 189 (60.4) | 31 (38.8) | 8 (42.1) |

Additional myectomy | 122 (39) | 43 (53.8) | 9 (47.4) |

Unknown | 2 (0.6) | 6 (7.5) | 2 (10.5) |

Concomitant surgery, n (%)*†

| Aortic valve bioprosthesis | 8 (2.5) | 7 (8.8) | 2 (10.5) |
| Aortic valve mechanical prosthesis | 10 (3.2) | 12 (15.1) | 8 (42.1) |
| Aortic valve repair | 18 (5.8) | 7 (8.8) | 2 (10.5) |
| Ross procedure | 2 (0.6) | 12 (15.0) | 2 (10.5) |
| Coarctation repair | 4 (1.3) | 0 (0.0) | 0 (0.0) |
| Supravalvular aortic repair | 3 (1.0) | 1 (1.3) | 1 (5.3) |
| Persistent ductus arteriosus ligation | 9 (2.9) | 0 (0.0) | 0 (0.0) |
| Mitral valve replacement or repair | 8 (2.5) | 3 (3.8) | 0 (0.0) |
| Ventricular septal defect closure | 46 (14.7) | 1 (1.3) | 0 (0.0) |
| Atrial septal defect closure | 6 (1.9) | 0 (0.0) | 0 (0.0) |
| Postoperative complications, n (%)† | 36 (3.2) | 8 (10) | 0 (0.0) |
| New left bundle-branch block | 33 (3.2) | 3 (3.8) | 1 (5.3) |
| New complete heart block requiring pacemaker | 12 (3.8) | 3 (3.8) | 2 (10.5) |
| Atrial fibrillation | 6 (1.9) | 2 (2.5) | 2 (10.5) |
| Heart failure | 3 (1.0) | 1 (1.3) | 0 (0.0) |
| Mortality | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| Neurological complication (stroke or neuropathy) | 1 (0.3) | 2 (2.5) | 0 (0.0) |

*LVOT indicates left ventricular outflow tract obstruction. Values are mean±SD when appropriate.

† Only available for 298 patients.

† Overlapping categories.
defect, no left ventricular hypertrophy). The cumulative survival of DSS patients after surgery was 97% at 20 years.

During follow-up, 34 patients (age, 29.9±15.1 years) were hospitalized for various reasons (0.61% per patient-year): heart failure (n=13), endocarditis (n=12), ventricular fibrillation followed by successful resuscitation (n=2), cardioversion for atrial fibrillation (n=5), stroke (n=1), and pericarditis (n=1).

Reoperations

During follow-up, 80 patients (25.6%) underwent at least 1 reoperation for recurrent DSS; 19 of these patients required a third operation (reoperation rate, 1.76% per patient-year; Table 2). The mean time interval between initial operation and reoperation was 12.0±7.6 years. Median intervention-free survival was 17 years (Figure 1A). Independent predictors for impaired intervention-free survival were female sex (hazard ratio, 1.531; 95% confidence interval, 1.018–2.302; Figure 1B), peak instantaneous LVOT gradient progression over time (hazard ratio, 1.454; 95% confidence interval, 1.308–1.616), preoperative peak instantaneous LVOT gradient ≥80 mmHg (hazard ratio, 1.016; 95% confidence interval, 1.004–1.028), and difference between preoperative and postoperative peak instantaneous LVOT gradients (hazard ratio, 1.021; 95% confidence interval, 1.007–1.035; Table I in the online-only Data Supplement).

Recurrence of LVOT Gradient Postoperatively

Postoperative peak instantaneous LVOT gradient was 15.1±14.1 mm Hg, which linearly increased over time at
a rate of 1.31±0.16 mm Hg/y (P=0.001). Independent risk factors for faster postoperative peak instantaneous LVOT gradient progression were increased age at the time of DSS diagnosis (P=0.048) and female sex (P=0.059 for trend; Figure 2). A higher preoperative LVOT gradient was associated with an overall higher residual postoperative peak instantaneous LVOT gradient (P<0.001) but did not significantly influence the postoperative peak instantaneous LVOT gradient progression rate (P=0.74). Peak instantaneous LVOT gradient progression rate was not influenced by type of surgery (enucleation with or without myectomy; P=0.85), age at the time of surgery (P=0.21), presence of associated CHD (P=0.12), or smoking (P=0.24; Table II in the online-only Data Supplement).

Progression of AR Postoperatively
Immediately postoperatively, mild AR was present in 68% of patients and moderate AR was seen in 5%; no patients exhibited severe AR. Over time, AR severity did not progress significantly in the total study population (P=0.76; Figure 3). However, ≈10% of patients progressed from having no AR to mild AR, and another 10% of patients developed moderate AR during the first 8 years after surgery (Figure 3). None of the patients progressed to severe AR. A preoperative peak instantaneous LVOT gradient ≥80 mm Hg was an independent risk factor for the development of moderate AR postoperatively (P=0.008; Figure 4). We could not identify any other factor that was significantly associated with postoperative development of mild AR or progressive AR (Table III in the online-only Data Supplement).

Discussion
In this multicenter study, we have analyzed data on a large cohort of adult patients who underwent surgical DSS resection with 13 years of postoperative follow-up (range, 1–31 years) to determine predictors for DSS recurrence, AR worsening, and reoperation. The results of the present study may be the basis for modification of the current strategies for management of DSS patients.

DSS Recurrence and Reoperations
In the total study population, postoperatively, the peak instantaneous LVOT gradient increased slowly but significantly over time at 1.3 mm Hg/y. This finding confirms a smaller study that previously reported a slight increase in postoperative gradient at late follow-up.27 Surprisingly, increased age at the time of diagnosis (>30 years of age) was a risk factor for faster postoperative LVOT gradient progression. This phenomenon might be explained by the fact that when DSS was discovered late in adulthood, patients were more likely to present with symptoms and thus might be in an advanced stage of the disease. Another hypothesis is that aging itself is related to faster postoperative progression.

In this study, we used reoperation as an objective clinically relevant outcome rather than recurrence only because of the lack of a universal definition for recurrence. We acknowledge that the indication for reoperation is also not concrete and universal. Our reoperation rate for recurrent DSS (1.8% per patient-year) was comparable to that in 2 other adult surgical series, which reported reoperation rates of 0.5% and 2.6% per patient-year.15,27 As reported in several studies in children with DSS, a higher peak instantaneous gradient across the LVOT at the final preoperative echocardiogram was an independent predictor for reoperation in our adult patient population.10,12,16,17,24

Testing various cutoff points, we found that a peak instantaneous LVOT gradient ≥80 mm Hg is most predictive of the need of reoperation. In addition, incomplete removal of the LVOT obstruction, reflected in a smaller difference between preoperative and postoperative gradients, was found to be a risk factor for reoperation. This has previously been demonstrated in several previous studies.12,15,20,22,26,37 Furthermore, as expected, LVOT gradient progression postoperatively is a strong predictor for reoperation. In addition to the echocardiographic parameters to monitor and predict LVOT gradient progression, perhaps biomarkers might be useful for identifying those with more rapidly progressing disease. Further research in this area is warranted.

Surprisingly, women carry a 1.5-times elevated risk for reoperation compared with men. In addition, female patients tended to have a more rapid postoperative LVOT gradient progression rate than male patients. These sex differences in reoperation and recurrence risk have not been reported previously. This phenomenon might be explained by the fact that women are likely to have a smaller LVOT. In our cohort, the LVOT diameter tended to be smaller in women compared with men, although not statistically significant. Perhaps pregnancy might have been a confounding factor, but unfortunately, we did not collect information about pregnancies during follow-up, and there is a lack of studies investigating the consequences of pregnancy in DSS patients. Furthermore, transcriptional regulation of genes related to myocardial hypertrophy and fibrosis might be sex dependent, as has been shown after aortic valve replacement for valvular aortic stenosis.38 Pathophysiological studies are required to explore the underlying mechanisms for these sex differences.
Isolated Enucleation Versus Additional Myectomy

Several hypotheses on DSS recurrence have been proposed. Recurrence may result from regeneration of tissue from the same region or from scar formation in the subvalvular area during healing.19,39 Furthermore, turbulence caused by incomplete removal of the LVOT obstruction has been postulated to promote fibrosis and subsequent restenosis.12 Although some previous studies have suggested that additional myectomy during the first operation reduces the incidence of recurrence, other authors have questioned this finding.8,16–27 Our results do not support the benefit of additional myectomy for either the risk of reoperation or LVOT gradient progression rate postoperatively. A tradeoff when aggressive surgical resection is performed to potentially lower the recurrence rate is the risk of a complete atrioventricular block, which was significantly higher in the patients who underwent additional myectomy compared with those who underwent isolated enucleation (8% versus 2%). In previous studies, the risk of a postoperative complete atioventricular block is typically 1% to 5% but might be up to 14% when a more aggressive surgical approach is performed.8,16–27 Our results do not support the benefit of additional myectomy for either the risk of reoperation or LVOT gradient progression rate postoperatively. A tradeoff when aggressive surgical resection is performed to potentially lower the recurrence rate is the risk of a complete atrioventricular block, which was significantly higher in the patients who underwent additional myectomy compared with those who underwent isolated enucleation (8% versus 2%). In previous studies, the risk of a postoperative complete atioventricular block is typically 1% to 5% but might be up to 14% when a more aggressive surgical approach is performed.8,16–27 Of course, the results of a myectomy and the risk of heart block are operator dependent, but this study included patients from 4 different centers over a time span of 30 years, making it impossible to study this factor adequately. Therefore, from our study, we conclude that an additional myectomy may be justified when a substantial degree of septal hypertrophy is detected but should be discouraged in most patients.

AR After DSS Surgery

Although most DSS patients exhibited mild (nonhemodynamically relevant) AR both preoperatively and postoperatively, our study shows that in most patients AR is not progressive over time. Approximately 10% of patients who did not have AR before surgery, however, developed mild AR relatively shortly after surgery. Furthermore, another 10% of patients progressed from mild to moderate AR, but progression to severe AR was very rare. We identified a preoperative peak instantaneous LVOT gradient ≥80 mm Hg as a risk factor for progressive AR after surgery. Previous studies in children with DSS have also demonstrated the association between a high preoperative LVOT gradient and progressive AR postoperatively.40,41 To prevent progressive AR postoperatively, it may be wise to reoperate before the peak LVOT gradient reaches 80 mm Hg. In conclusion, we agree with the statement made by Stassano et al27 that resection of the subaortic membrane cannot improve AR, but we disagree with their suggestion that resection can entirely "stabilize" the grade of regurgitation.

Clinical Implications

Postoperative long-term survival after surgical treatment of DSS is excellent and comparable to that of the normal population. The rate of reoperation is considerable (≈2%/y), and given the excellent survival of these young adult patients, most patients will require a reoperation for recurrent DSS at some point in their lifetime. Postoperatively, the peak instantaneous LVOT gradient progresses slowly but steadily over time in adults. Therefore, lifelong regular follow-up, including echocardiography, is required after surgery. However, because the LVOT progression is generally slow, follow-up can probably be limited to 2- to 4-year intervals in most patients. Women and patients >30 years of age at time of diagnosis are at risk for faster LVOT gradient progression after surgery and should thus be monitored more frequently. Of course, patients with decreased LV function or severe/progressive AR should also be followed up more frequently. Additional myectomy did not reduce DSS recurrence or reoperation risk and significantly increased the risk of a complete heart block. Therefore, myectomy should not be encouraged in most patients and should...
be performed only in case of marked LV hypertrophy. Postoperative AR is common but generally mild and nonprogressive over time in most patients. Patients with a preoperative Doppler-derived peak instantaneous LVOT gradient ≥80 mm Hg, however, are at increased risk of developing moderate AR, but progression to severe AR is rare.

**Study Limitations**

Several limitations of this study merit attention. This retrospective study included patients monitored in adult congenital clinics; therefore, referral bias may exist. One of the major study limitations was the fact that indications for (re)operation were not standardized because of the multicenter approach and broad time period. By using prospective databases to identify eligible patients and therefore also including deceased patients, we aimed to limit survival bias. Unfortunately, some echocardiographic parameters could not be retrieved for all patients, but this was dealt with through the use of the multiple imputation approach for missing values. The fact that echocardiography was not performed precisely every year was accounted for by the use of mixed-effects models that take different lengths of follow-up into account. Furthermore, by using the joint modeling approach, we allowed for the dependency and association between the longitudinal echocardiographic data and survival data. Ideally, our findings need to be validated by a large prospective cohort study.

The current European Society of Cardiology and American College of Cardiology/American Heart Association guidelines for adults with CHD do not provide specific recommendations for reinterventions in DSS patients. The Canadian guidelines state that a peak instantaneous LVOT gradient >50 mm Hg is an indication for reoperation when patients have symptoms. The timing of reoperation is a highly complex issue that should take various factors into account: the peak LVOT gradient, progression rate of the LVOT gradient, severity and progression of AR, left ventricular volume and function, presence of (exercised-induced) symptoms, and risk of sudden death. Unfortunately, the optimal timing of reoperation, when all these factors are combined, in adult patients with DSS cannot yet be derived from the present study.

**Conclusions**

Although survival is excellent after surgery for DSS, most patients will require a reoperation for recurrent DSS at some point during their lifetime. Postoperatively, the LVOT gradient progresses slowly and mild AR is common but nonprogressive over time in most patients. Myectomy should not be performed routinely because it does not reduce the risk of recurrence or reoperation and increases the risk of a complete heart block.

**Acknowledgments**

We would like to thank the medical teams, technicians, and sonographers at the participating centers.

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**Disclosures**

None.

**References**

Discrete subaortic stenosis is a narrowing of the left ventricular outflow tract just beneath the aortic valve. In childhood, discrete subaortic stenosis is known for its unpredictable and sometimes rapid hemodynamic progression. Furthermore, aortic regurgitation is present in 30% to 80% of patients. Because reoperation rates have been reported to be high (8%–34%), there is ongoing debate about the timing of surgical intervention and type of surgery. This is the first large study to evaluate factors for reoperation after relief of congenital heart disease.

Additional myectomy does not reduce the risk for reoperation but significantly increases the risk of a complete heart block. Therefore, myectomy should not be performed routinely.

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Surgical Outcome of Discrete Subaortic Stenosis in Adults: A Multicenter Study

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SUPPLEMENTAL MATERIAL

In this online supplement, coefficients with standard errors and p-values are provided for the covariates in the mixed-effects model.

**Main effect** = effect of a covariate on the outcome at baseline (intercept).

**Interaction effect** = effect of a covariate on the outcome in time (slope).

For the Cox regression models the hazard ratios and p-values are provided for each covariate.
**Supplemental Table 1. Hazard ratios from Cox regression models for intervention-free survival.**

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Hazard ratio</th>
<th>p-value</th>
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<tbody>
<tr>
<td></td>
<td>(95% confidence interval)</td>
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<tr>
<td><strong>Cox model with baseline covariates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Pre-operative peak instantaneous LVOT gradient ≥80 mmHg</td>
<td>1.016 (1.004 – 1.028)</td>
<td>0.011 *</td>
</tr>
<tr>
<td>- Difference between pre- and post-operative LVOT gradient (Delta)</td>
<td>1.021 (1.007 – 1.035)</td>
<td>0.002 *</td>
</tr>
<tr>
<td>- Type of surgery (enucleation +/- myectomy)</td>
<td>1.003 (0.980 – 1.027)</td>
<td>0.793</td>
</tr>
<tr>
<td>- Age at time of surgery</td>
<td>1.012 (0.977 – 1.048)</td>
<td>0.507</td>
</tr>
<tr>
<td>- Age at time of diagnosis</td>
<td>1.689 (0.752 – 3.794)</td>
<td>0.205</td>
</tr>
<tr>
<td>- Gender (female)</td>
<td>1.531 (1.018 – 2.302)</td>
<td>0.040 *</td>
</tr>
<tr>
<td>- History of prior intracardiac surgery</td>
<td>1.368 (0.901 – 2.076)</td>
<td>0.143</td>
</tr>
<tr>
<td>- Presence of associated CHD</td>
<td>1.095 (0.861 – 1.394)</td>
<td>0.459</td>
</tr>
<tr>
<td>- Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Joint model (with longitudinal LVOT gradient model)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Age at time of surgery</td>
<td>1.046 (1.044 – 1.048)</td>
<td>&lt;0.001 *</td>
</tr>
<tr>
<td>- Gender (female)</td>
<td>1.387 (0.840 – 2.290)</td>
<td>0.202</td>
</tr>
<tr>
<td>- Peak LVOT gradient progression over time</td>
<td>1.454 (1.308 – 1.616)</td>
<td>&lt;0.001 *</td>
</tr>
<tr>
<td><strong>Time-dependent Cox model (for AR over time)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Age at time of surgery</td>
<td>1.006 (0.987 – 1.025)</td>
<td>0.552</td>
</tr>
<tr>
<td>- Gender (female)</td>
<td>1.493 (0.999 – 1.967)</td>
<td>0.097</td>
</tr>
<tr>
<td>- Aortic regurgitation</td>
<td>(overall p=0.105)</td>
<td></td>
</tr>
<tr>
<td>o Mild AR</td>
<td>0.640 (0.050 – 1.330)</td>
<td>0.205</td>
</tr>
<tr>
<td>o Moderate AR</td>
<td>0.783 (0.121 – 1.445)</td>
<td>0.469</td>
</tr>
<tr>
<td>o Severe AR</td>
<td>1.441 (0.782 – 2.099)</td>
<td>0.277</td>
</tr>
</tbody>
</table>

AR = aortic regurgitation; LVOT = left ventricular outflow tract; CHD = congenital heart disease.

* p<0.05.
**Supplemental Table 2. LVOT gradient: estimated coefficients, standard errors and p-values from the linear mixed-effects model. To take into account that peak LVOT gradient values exhibited a slightly skewed shape of distribution, a square root transformation was applied.**

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Coefficient</th>
<th>Standard error</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>3.768</td>
<td>0.378</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time</td>
<td>0.136</td>
<td>0.042</td>
<td>0.001 *</td>
</tr>
</tbody>
</table>

**Main effect**

- Pre-operative peak instantaneous LVOT gradient 0.082 0.008 <0.001 *
- Difference between pre- and post-operative LVOT gradient (Delta) -0.082 0.008 <0.001 *
- Type of surgery (enucleation +/- myectomy) -0.143 0.193 0.458
- Age at time of surgery -0.030 0.009 0.001 *
- Age at time of diagnosis 0.015 0.011 0.183
- Gender (male) -0.487 0.190 0.010 *
- Presence of associated CHD -0.053 0.185 0.774
- Former smoking -0.241 0.352 0.494
- Current smoking -0.122 0.230 0.597

**Interaction effect**

- Pre-operative peak instantaneous LVOT gradient 0.000 0.001 0.738
- Difference between pre- and post-operative LVOT gradient (Delta) 0.000 0.001 0.532
- Type of surgery (enucleation +/- myectomy) -0.004 0.020 0.845
- Age at time of surgery -0.001 0.001 0.205
- Age at time of diagnosis 0.003 0.002 0.048 *
- Gender (male) -0.037 0.019 0.059 *
- Presence of associated CHD -0.030 0.019 0.118
- Former smoking 0.012 0.035 0.736
- Current smoking 0.029 0.024 0.235

LVOT = left ventricular outflow tract; CHD = congenital heart disease. * p<0.05.
**Supplemental Table 3. Aortic regurgitation: estimated coefficients, standard errors and p-values from the continuation ratio mixed-effects model.**

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Coefficient</th>
<th>Standard error</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>0.389</td>
<td>1.081</td>
<td>0.719</td>
</tr>
<tr>
<td>Time</td>
<td>0.027</td>
<td>0.090</td>
<td>0.764</td>
</tr>
</tbody>
</table>

**Main effect**

- Pre-operative peak instantaneous LVOT gradient  
  -0.050  
  0.019  
  0.008 *

- Difference between pre- and post-operative LVOT gradient (Delta)
  0.029  
  0.019  
  0.138

- Type of surgery (enucleation +/- myectomy)
  -0.272  
  0.467  
  0.560

- Age at time of surgery
  0.023  
  0.023  
  0.326

- Age at time of diagnosis
  -0.002  
  0.027  
  0.934

- Gender (male)
  -0.241  
  0.465  
  0.605

- Presence of associated CHD
  1.018  
  0.527  
  0.053

- Former smoking
  0.607  
  0.860  
  0.480

- Current smoking
  -0.100  
  0.555  
  0.858

**Interaction effect**

- Pre-operative peak instantaneous LVOT gradient
  -0.004  
  0.002  
  0.008 *

- Difference between pre- and post-operative LVOT gradient (Delta)
  0.003  
  0.002  
  0.112

- Type of surgery (enucleation +/- myectomy)
  -0.070  
  0.038  
  0.064

- Age at time of surgery
  -0.004  
  0.002  
  0.066

- Age at time of diagnosis
  0.002  
  0.003  
  0.434

- Gender (male)
  -0.004  
  0.036  
  0.914

- Presence of associated CHD
  -0.082  
  0.042  
  0.051

- Former smoking
  -0.052  
  0.059  
  0.378

- Current smoking
  0.038  
  0.043  
  0.377

LVOT = left ventricular outflow tract; CHD = congenital heart disease. * p<0.05.