Risk factors for reoperation after relief of congenital subaortic stenosis

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Abstract

Background: Congenital subaortic stenosis entails a lesion spectrum, ranging from an isolated obstructive membrane, to complex tunnel narrowing of the left outflow associated with other cardiac defects. We review our experience with this anomaly, and analyze risk factors leading to restenosis requiring reoperation. Methods: From 1994 to 2006, 58 children (median age 4.3 years, range 7 days—13.7 years) underwent primary relief of subaortic stenosis. Patients were divided into simple lesions (n = 43) or complex stenosis (n = 15) associated with other major cardiac defects. Age, pre- and postoperative gradient over the left outflow, associated aortic or mitral valve insufficiency, chromosomal anomalies, arteria lusoria, and operative technique (membrane resection (22) vs associated myectomy (34) vs Konno (2)) were analyzed as risk factors for reoperation (Kaplan–Meier, Cox regression). Results: There was no operative mortality. Median follow-up spanned 2.7 years (range 0.1—10), with one late death at 4 months. Reoperation was required for recurrent stenosis in 11 patients (19%) at 2.6 years (range 0.3—7.5) after initial surgery. Risk factors for reoperation included complex subaortic stenosis (p = 0.003), younger age (p = 0.012), postoperative residual gradient (p = 0.019), and the presence of an arteria lusoria (p = 0.014). For simple lesions, no variable achieved significance for stenosis recurrence. Conclusions: Surgical relief of congenital subaortic stenosis, even with complex defects, yields excellent results. Reoperation is not infrequent, and should be anticipated with younger age at operation, complex defects, residual postoperative gradient, and an arteria lusoria. Myectomy concomitant to membrane resection, even in simple lesions, does not provide enhanced freedom from reoperation, and should be tailored to anatomic findings.

Keywords: Congenital; Subaortic stenosis; Reoperation

1. Introduction

Subaortic stenosis is a relatively rare congenital heart defect, representing 1–2% of all congenital anomalies. The lesion entails a spectrum, ranging from an isolated discrete subaortic membrane in up to 70% of cases [1], to its diffuse form with tunnel-like near obliteration of the left ventricular outflow tract (LVOT), which is more commonly associated with other complex congenital heart defects. Although the immediate surgical results are satisfactory, even in the presence of associated complex defects, recurrence of left ventricular outflow tract stenosis is frequent, but the reasons are not fully understood. Also, the fate of pre-existing aortic valve insufficiency (AI) or its occurrence after successful surgery is controversial. We reviewed our surgical results in the recent era, and analyzed the data for eventual risk factors leading to restenosis requiring reoperation.

2. Materials and methods

Permission to proceed with a retrospective review of anonymous patient data was approved by our hospital ethics committee, and patient/parent written consent was waived. Between 1994 and 2006, 58 consecutive children (median age 4.3 years, range 7 days—13.7 years) underwent primary relief of subaortic stenosis. Patients presented either with simple lesions (n = 43), namely an isolated subaortic membrane, with at most an associated mild unoperated coarctation of the aorta (n = 1), an atrial septal defect (ASD; n = 5) or ventricular septal defect (VSD; n = 11). The group with
associated major cardiac defects (n = 15) represented the complex spectrum of the lesion. Details of associated lesions for both simple and complex groups are given in Table 1. Prior repair of coarctation of the aorta had been performed in 9 patients (16%), 6 of which were in the simple group, and 3 in the complex group. Patients developing LVOT obstruction following complete repair of atrio-ventricular septal defect or after ventricular septal defect closure were excluded. Patient demographics of age, pre- and immediate post-operative gradients over the left outflow as measured by transthoracic Duplex echocardiography in millimetres of Mercury (mmHg), associated aortic or mitral valve insufficiency (grade I—IV), chromosomal abnormalities, and an associated arteria lusoria were studied. Preoperative aortic valve insufficiency was graded I—IV: 24 patients had no insufficiency, 8 had grade I, 23 grade II, 2 grade III, and 1 grade IV insufficiency. Patients presenting with mitral valve insufficiency included none (n = 46), grade I (n = 2), grade II (n = 5), grade III (n = 3) and grade IV (n = 2). Associated chromosomal abnormalities were present in 9 patients (16%), and included 22q11 deletion syndrome (n = 3), trisomy 21 (n = 2), Biedl-Bardet syndrome (n = 2), Noonan syndrome (n = 1), and Williams-Beuren syndrome (n = 1). Operative technique was taken into consideration, namely a simple membrane resection (n = 22), with concomitant myectomy (n = 34), or a Konno repair (n = 2).

Surgery was performed with cardiopulmonary bypass, moderate hypothermia (28—32 ºC), left ventricular venting, aortic cross-clamp and cold antegrade blood cardioplegia. After a longitudinal aortotomy extending into the non-coronary cusp of the aortic valve, transaortic valve membrane excision was performed using a combination of blunt and sharp dissection. An effort was made to remove all pathological tissue, including that encroaching on the aortic and mitral valves. When necessary, concomitant wedge myectomy was performed of the interventricular septum, so as to properly visualize the left ventricular apex from within. In the simple group, concomitant myectomy was performed in 24/43 patients, and in the complex group, it was required in all but 2 neonates where the interventricular septum was judged too thin to allow muscle excision. Two other patients in the complex group with tunnel-like stenosis underwent a primary modified Konno-Vouhé procedure with an aortic valve-sparing technique. The aortotomy was closed, and eventual associated defects were addressed during rewarming, followed by discontinuation from bypass. With associated complex cardiac defects, deeper cooling to 26 ºC was applied.

2.1. Statistical analysis

The endpoint of the study was the time to first reoperation. As potential risk factors, we considered preoperative pressure gradient (continuous), immediate postoperative pressure gradient (continuous), age (continuous), aortic valve insufficiency (grade 0—I vs grade II—IV), mitral valve insufficiency (grade 0 vs grade larger than 0), chromosomal anomalies (absent vs present), surgical technique (isolated membrane resection vs concomitant myectomy), arteria lusoria (absent vs present), and subaortic stenosis (simple vs complex). Strength of association and statistical significance between a risk factor and the endpoint were assessed using a hazard ratio and Cox regression. For the binary risk factors (such as surgical technique or subaortic stenosis), Kaplan—Meier curves were calculated. A p-value smaller than 0.05 was considered statistically significant. Initially, the entire cohort was analyzed (n = 58), and a Kaplan—Meier freedom from reoperation curve was calculated to distinguish between the complex and simple groups (Fig. 2). As the two groups are otherwise anatomically and physiologically different, the analysis as described above was repeated considering each group separately (simple; n = 43 and complex; n = 15). Note that in cases where no event occurred in small subgroups, it was technically not possible to estimate a hazard ratio using Cox regression (see Table 2).

3. Results

Preoperative systolic pressure gradients across the left ventricular outflow tract ranged from 5 to 120 mmHg

Table 1
Associated cardiovascular anomalies in both groups (n = 58)

<table>
<thead>
<tr>
<th>Defect</th>
<th>Simple (n = 43)</th>
<th>Complex (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular septal defect</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Coarctation</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Interrupted aortic arch</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Hypoplastic aortic arch</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Shone’s complex</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Arteria lusoria</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 2
Cox regression with hazard ratios (95% confidence intervals) of potential risk factors after analyzing the two groups simple and complex separately

<table>
<thead>
<tr>
<th></th>
<th>All (n = 58)</th>
<th>Simple (n = 43)</th>
<th>Complex (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple vs complex</td>
<td>HR: 6.7 (1.9—23.9); p = 0.003</td>
<td>HR: 0.6 (0.1—3.7); p = 0.60</td>
<td>HR: 5.5 (0.6—48.3); p = 0.12</td>
</tr>
<tr>
<td>Membrane resection vs myocardium</td>
<td>HR: 1.7 (0.5—5.9); p = 0.40</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Arteria lusoria vs none</td>
<td>HR: 5.7 (1.4—22.7); p = 0.014</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Age at surgery (years)</td>
<td>HR: 0.70 (0.53—0.93); p = 0.012</td>
<td>HR: 0.76 (0.56—1.05); p = 0.10</td>
<td>HR: 0.7 (0.32—1.52); p = 0.37</td>
</tr>
<tr>
<td>Chromosomal defects vs none</td>
<td>HR: 2.1 (0.6—7.2); p = 0.26</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mitral valve insufficiency</td>
<td>HR: 0.4 (0.05—2.9); p = 0.34</td>
<td>HR: 0.9 (0.1—8.1); p = 0.92</td>
<td>NA</td>
</tr>
<tr>
<td>Aortic valve insufficiency</td>
<td>HR: 0.4 (0.1—1.6); p = 0.19</td>
<td>HR: 1.0 (0.2—6.3); p = 1.0</td>
<td>NA</td>
</tr>
<tr>
<td>Preoperative gradient (per mmHg)</td>
<td>HR: 1.004 (0.98—1.029); p = 0.73</td>
<td>HR: 0.999 (0.965—1.034); p = 0.94</td>
<td>HR: 1.001 (0.961—1.043); p = 0.96</td>
</tr>
<tr>
<td>Postoperative gradient (per mmHg)</td>
<td>HR: 1.052 (1.008—1.098); p = 0.019</td>
<td>HR: 1.011 (0.927—1.103); p = 0.80</td>
<td>HR: 1.022 (0.964—1.083); p = 0.46</td>
</tr>
</tbody>
</table>

HR: hazard ratio, NA: not applicable.
(median 52 mmHg), and diminished to a median of 25 mmHg postoperatively (range 0–67 mmHg) as shown in Fig. 1.

There was no operative mortality. Median follow-up spanned 2.7 years (range 0.1–10), with one late death at 4 months. The late death followed a second reoperation in a patient with type B interrupted aortic arch, a hypoplastic aortic annulus, and subaortic stenosis. After an initial neonatal complete repair for IAA, VSD closure, fenestrated ASD closure and subaortic membrane resection with myectomy, the child required a first reoperation after two and a half months for a Konno septoplasty with commissurotomy of the bicuspid aortic valve. Finally, at 4 months, the patient required a second reoperation for a trileaflet reconstruction of the aortic valve and annular enlargement, followed by extracorporeal membrane oxygenation (ECMO). The infant died after 3 days of ECMO support from multi-organ failure.

One major postoperative complication included complete heart block requiring a pacemaker in one patient (1.7%). Reoperation was required for recurrent stenosis in 11 patients (19%) at 2.6 years (range 0.3–7.5) after initial surgery. The gradients measured across the left outflow tract indicating the need for reoperation ranged from 32 to 99 mmHg (mean 69 mmHg). Five reoperations were necessary in the simple group (5/43; 12%) and 6 in the complex group (6/15; 40%). Kaplan–Meier estimates of freedom from reoperation at 5 years were 92% for the simple group, and only 32% for the complex group ($p = 0.003$; Fig. 2). Reoperation consisted of repeat membrane resection, with concomitant myectomy in all but two cases, and was achieved without mortality. In two patients, the reoperation consisted of a modified Konno procedure with aortic valve tricuspidization and enlargement annuloplasty. After reoperation, gradients dropped to a mean of 19 mmHg (range 0–80 mmHg). Two patients needed a second reoperation, one of which survived without further restenosis at last follow-up, and the other died as described above.

The statistical relationship between various risk factors and time to first reoperation were analyzed using Cox regression. For the entire cohort, negative findings included preoperative pressure gradient across the LVOT (hazard ratio 1.004 per mmHg; $p = 0.73$), aortic valve insufficiency (hazard ratio 0.4; $p = 0.19$), mitral valve insufficiency (hazard ratio 0.4; $p = 0.34$), chromosomal anomalies (hazard ratio 2.1; $p = 0.26$), and surgical technique (isolated membrane resection vs concomitant myectomy (hazard ratio 1.7; $p = 0.40$). Risk factors for reoperation included complex defects (hazard ratio 6.7; $p = 0.003$; Fig. 2), immediate postoperative gradient (per mmHg; hazard ratio 1.052; $p = 0.003$).
are poorly understood [6], mainly because the etiology of this lesion is still obscure, and it is still uncertain if the defect is congenital, or acquired [2,4,7,8], since many patients develop stenosis at a later stage in life [3,9]. With complex stenosis and associated cardiac defects, the lesion appears very early on, so that a congenital nature seems plausible. The prognosis of surgical repair is probably more related to the morphologic type and complexity of subaortic stenosis and probably to associated defects, although recurrence of subaortic stenosis is even more of a concern, due to common associated multilevel obstruction and limitation of blood flow through the left outflow tract.

When analyzing the group as a whole, we found complex forms of subaortic stenosis, including tunnel-like stenosis, hypoplastic aortic annulus, mitral stenosis, and hypoplastic arch with coarctation, associated with other intracardiac defects, to be a risk factor for reoperation (hazard ratio 6.7; \( p = 0.003 \)). Similar to our findings, Serraf et al. found tunnel-like stenosis associated with Shone’s complex to be a univariate risk factor for operative mortality and recurrence rate [2]. Similarly, the presence of an arteria lusoria (aberrant right subclavian artery) was a risk factor for reoperation (hazard ratio 5.7; \( p = 0.014 \)). Not surprisingly, all four patients with this anomaly were in the complex group, three of which required a reoperation. In these patients with duct-dependent systemic circulations, perfusion to the descending aorta distributes flow to the left subclavian artery and the aberrant right subclavian artery, and therefore antegrade flow through the aortic valve feeds only the remaining two carotid vessels. In this situation, the steal from antegrade proximal left-sided flow, compared to that with normal upper extremity vascular anatomy, potentially leads to underdevelopment of left-sided structures and multi-level stenosis, including the mitral valve, the left ventricle itself, the subaortic area, the aortic valve, and the ascending aorta and arch, giving the physiological substrate to Shone’s complex. The presence of an arteria lusoria is more a surrogate of hypoplastic left-sided structures and hindrance of left-sided forward flow. Probably due to the small sample size, the presence of an arteria lusoria was not a risk factor for reoperation in the complex lesions group, whereas there was only one patient with this anomaly in the simple group who had no reoperation, therefore it was technically not possible to perform the Cox regression in the simple group.

Considering the entire cohort, we found early age at operation to be an independent risk factor for reoperation (hazard ratio of 0.7 per year; \( p = 0.012 \)). In patients with isolated membrane subaortic stenosis, age at initial surgery was not an independent risk factor for reoperation (hazard ratio = 0.76; \( p = 0.10 \)). The relatively short time of median follow-up in our series may explain this finding, and longer follow-up could reveal progressive recurrence of the disease. Partially concurring with our findings are the results of Serraf et al. who found that an age younger than 5 years at initial surgery was a univariate risk factor for recurrence, although this was not confirmed in their multivariate analysis [2].

4. Discussion

Surgical results for the relief of isolated congenital subaortic stenosis are excellent in the short to mid-term, although recurrence is a concern and indicates long-term follow-up [2]. Recurrence of subaortic stenosis requiring reoperation is reported between 0 [3] and 28% [2,4,5], reflecting also our results (19%). The reasons for recurrence are poorly understood [6], mainly because the etiology of this lesion is still obscure, and it is still uncertain if the defect is congenital, or acquired [2,4,7,8], since many patients develop stenosis at a later stage in life [3,9]. With complex stenosis and associated cardiac defects, the lesion appears very early on, so that a congenital nature seems plausible. The prognosis of surgical repair is probably more related to the morphologic type and complexity of subaortic stenosis and probably to associated defects, although recurrence of subaortic stenosis is even more of a concern, due to common associated multilevel obstruction and limitation of blood flow through the left outflow tract.
left ventricular-aorta junction [2,13]. Some authors have found that a more aggressive approach is necessary, with systemic deep septal myectomy, thereby reducing the risk of recurrence and reoperation in their experience [3,4,10,14,15].

Although a genetic predisposition to subaortic stenosis has been postulated by some [16,17], partly due to abnormal aorto-septal geometry with a wider angle leading to gradient across the left outflow tract [4,18,19]. It may also each syndrome may have skewed the results otherwise. It is difficult to interpret, as there were five different syndromes grouped to risk of recurrence, neither when considering the entire cohort together, nor when analyzing the subgroups simple and complex defects separately. This finding is difficult to interpret, as there were five different syndromes grouped together as one variable, and larger numbers of patients in each syndrome may have skewed the results otherwise.

Aortic valve insufficiency may already be present at the time of operation, and in infants and children constitutes a surgical indication per se even in the absence of a significant gradient across the left outflow tract [4,18,19]. It may also appear years after successful surgery for subaortic stenosis [2,3,5], and in adult patients, appears to be even more prominent after surgical intervention, when compared to unoperated patients [9,20]. The latter authors conclude that in adults, 'prevention' of aortic regurgitation is not a criterion for surgery in patients with significant obstruction of the left outflow tract. We found no influence of gradient or preoperative AI on the occurrence of late aortic valve insufficiency, a finding also confirmed by other groups [2,10]. Also, Rohlicek et al. found that surgery had no influence on preexisting AI, or the occurrence of new AI after successful surgery, suggesting that surgery has little impact on the fate of the aortic valve [5]. Contrary to our findings, other authors report preoperative gradients to correlate with postoperative mild/moderate aortic valve insufficiency [3,5].

Limitations to the study are inherent to the retrospective nature of data retrieval. Also, the median follow-up time is relatively short, and stronger inferences could be made with longer follow-up, namely with regards to potential recurrence of subaortic stenosis and potentially a larger subgroup of patients eventually requiring reoperation.

In summary, excellent immediate surgical results are the rule with subaortic membrane resection, even with associated complex cardiac defects. Recurrence of LVOT obstruction is a frequent finding and gives reason for ongoing concern and close follow-up of patients with this lesion. Complex subaortic stenosis with associated cardiac defects is a risk factor for reoperation, compared to more simple forms of isolated membrane-type lesions. Systematic myectomy concomitant to simple membrane resection does not decrease the rate of stenosis recurrence, either in isolated membrane lesions or in complex forms of tunnel-like obstruction where it is indicated, and should be tailored to individual anatomic findings.

References