Cardiac outcomes in adults with supravalvar aortic stenosis

Greutmann, Matthias ; Tobler, Daniel ; Sharma, Nakul Chander ; Vonder Muhll, Isabelle ; Mebus, Siegrun ; Kaemmerer, Harald ; Schuler, Pia K ; Deanfield, John E ; Beauchesne, Luc ; Salehian, Omid ; Hoffmann, Andreas ; Golovatyuk, Vasilisa ; Oechslin, Erwin N ; Silversides, Candice K

Abstract: AIMS: Supravalvar aortic stenosis is a rare form of left ventricular outflow tract obstruction that is often progressive in childhood. Little data are available on outcomes in the adult population. Our aim was to define cardiac outcomes in adults with supravalvar aortic stenosis. METHODS AND RESULTS: This is a multicentre retrospective study of cardiac outcomes in adults (18 years) with supravalvar aortic stenosis. We examined: (i) adverse cardiac events (cardiovascular death, myocardial infarction, stroke, heart failure, sustained arrhythmias, and infective endocarditis) and (ii) the need for cardiac surgery in adulthood. One hundred and thirteen adults (median age at first visit 19 years; 55% with Williams-Beuren syndrome; 67% with surgical repair in childhood) were identified. Adults without Williams-Beuren syndrome had more severe supravalvar aortic stenosis and more often associated left ventricular outflow tract obstructions ($P < 0.001$). In contrast, mitral valve regurgitation was more common in patients with Williams-Beuren syndrome. Eighty-five per cent of adults (96/113) had serial follow-up information (median follow-up 6.0 years). Of these patients, 13% (12/96) had an adverse cardiac event and 13% (12/96) had cardiac operations (7 valve repair or replacements, 4 supravalvar aortic stenosis repairs, 1 other). Cardiac surgery was more common in adults without Williams-Beuren syndrome ($P = 0.007$). Progression of supravalvar aortic stenosis during adulthood was rare. CONCLUSION: Adults with supravalvar aortic stenosis remain at risk for cardiac complications and reoperations, while progression of supravalvar aortic stenosis in adulthood is rare. Valve surgery is the most common indication for cardiac surgery in adulthood.

DOI: https://doi.org/10.1093/eurheartj/ehs206

Cardiac outcomes in adults with supravalvar aortic stenosis

Matthias Greutmann, MD *† , Daniel Tobler, MD *‡, Nakul Chander Sharma, MD §, Isabelle VonderMuhll, MD §, Siegrun Mebus, MD ‖, Harald Kaemmerer, MD ‖, Pia Schuler, MD ¶, John E. Deanfield, MD ¶, Luc Beauchesne, MD #, Omid Salehian, MD **, Andreas Hoffmann, MD ‡, Vasilisa Golovatyuk †, Erwin N. Oechslin, MD ‡‡, Candice K. Silversides, MD ‡‡

*these authors contributed equally to the study design, data interpretation and manuscript preparation

Affiliations:
† Adult Congenital Heart Disease Program, University Hospital, Zurich, Switzerland
‡ Adult Congenital Heart Disease Clinic, University Hospital, Basel, Switzerland
§ Northern Alberta Adult Congenital Heart Clinic, University of Alberta Hospital, Edmonton, Canada
‖ German Heart Centre Munich, Technical University Munich, Congenital Heart Disease Clinic, Munich, Germany
¶ Grown Up Congenital Heart Disease Unit, The Heart Hospital, London, United Kingdom
# Ottawa Heart Institute Adult Congenital Heart Disease Clinic, University of Ottawa, Canada
** McMaster University Adult Congenital Cardiac Clinic, McMaster University, Hamilton, Canada
‡‡ Toronto Congenital Cardiac Center for Adults, Peter Munk Cardiac Centre/Toronto General Hospital, and University of Toronto, Canada

Conflicts of interest: None
Relationship to industry: None

Address for correspondence
Matthias Greutmann, MD, University hospital of Zurich, Raemistrasse 100, 8091 Zurich, Switzerland. Tel.: ++41 44 255 3883, Fax: ++41 44 255 8701, Email: Matthias.Greutmann@usz.ch

Word counts: Abstract: 244 words, entire manuscript: 5243 words

Abstract

Aims: Supravalvar aortic stenosis is a rare form of left ventricular outflow tract obstruction that is often progressive in childhood. Little data is available on outcomes in the adult population. Our aim was to define cardiac outcomes in adults with supravalvar aortic stenosis.

Methods and Results: This is a multicenter retrospective study of cardiac outcomes in adults (≥18 years) with supravalvar aortic stenosis. We examined: a) adverse cardiac events (cardiovascular death, myocardial infarction, stroke, heart failure, sustained arrhythmias and infective endocarditis) and b) the need for cardiac surgery in adulthood. One hundred and thirteen adults [median age at first visit 19 years; 55% with Williams-Beuren syndrome; 67% with surgical repair in childhood] were identified. Adults without Williams-Beuren Syndrome had more severe supravalvar aortic stenosis and more often associated left ventricular outflow tract obstructions ($p<0.001$). In contrast, mitral valve regurgitation was more common in patients with Williams-Beuren syndrome. Eighty-five percent of adults (96/113) had serial follow-up information (median follow-up 6.0 years). Of these patients, 13% (12/96) had an adverse cardiac event and 13% (12/96) had cardiac operations (7 valve repair or replacements, 4 supravalvar aortic stenosis repairs, 1 other). Cardiac surgery was more common in adults without Williams-Beuren syndrome ($p=0.007$). Progression of supravalvar aortic stenosis during adulthood was rare.

Conclusion: Adults with supravalvar aortic stenosis remain at risk for cardiac complications and reoperations, while progression of supravalvar aortic stenosis in adulthood is rare. Valve surgery is the most common indication for cardiac surgery in adulthood.

Key words: Congenital heart disease, Supravalvar aortic stenosis, Williams Beuren syndrome

Supravalvar aortic stenosis is a rare form of left ventricular outflow tract obstruction. While it may be associated with the Williams-Beuren syndrome, [1] it can also occur as familial disease without features of Williams-Beuren syndrome, in conjunction with other forms of obstructive left ventricular outflow tract lesions or as an isolated lesion. The supravalvar lesion may involve the entire aortic root, the coronary arteries and/or the aortic valve [2, 3] and in children it is felt to be a progressive disease, [4-6] perhaps related to an inadequate growth of the supravalvar aortic root and the sinotubular junction. [4] Children with supravalvar aortic stenosis often have early intervention as the supravalvar stenosis is known to be progressive. [7-11] The clinical course beyond childhood, in the operated and unoperated adult, is not well studied. [8, 11, 12] Therefore, the aim of this study was to examine late cardiovascular events in adults with supravalvar aortic stenosis and to identify features associated with increased risk for late cardiovascular complications. The secondary objective was to investigate progression of the supravalvar obstruction during adulthood.

Methods

Study Design and Study Cohort

This was a multicenter retrospective study of unoperated and repaired adults (≥ 18 years of age) with a diagnosis of supravalvar aortic stenosis. Adults with an outpatient visit at one of the participating tertiary adult congenital cardiac clinics were included. The following centers participated in the study: Toronto Congenital Cardiac Center for Adults, University Health Network, University of Toronto, Toronto, Canada; Northern Alberta Adult Congenital Heart Clinic, University of Alberta Hospital, Edmonton, Canada; McMaster University Adult Congenital Cardiac Clinic, McMaster University, Hamilton, Canada; Ottawa Heart Institute Adult Congenital Heart Disease Clinic, University of Ottawa, Canada; German Heart Centre Munich,

Technical University Munich, Congenital Heart Disease Clinic, Munich, Germany; Grown Up Congenital Heart Disease Unit, The Heart Hospital, London, United Kingdom; Adult Congenital Heart Disease Clinic, University Hospital, Basel, Switzerland and Adult Congenital Heart Disease Program, University Hospital, Zurich, Switzerland. The study was approved by the institutional ethics boards.

The diagnosis of supravalvar aortic stenosis was documented by cardiac catheterization, echocardiography, or magnetic resonance imaging. Supravalvar aortic stenosis was classified as localized when it was limited to the sinotubular junction and the proximal ascending aorta. It was classified as diffuse when the narrowing was less circumscript and also involved the ascending aorta beyond the proximal portion extending to the aortic arch or the descending aorta. Classification was left to the discretion of the treating physician. Patients were excluded if an echocardiogram was not available as part of their initial assessment.

Outcomes of Interest

When available, serial clinical and echocardiographic data after the initial presentation to the adult clinic was collected. The primary outcomes of interest were: a) adverse cardiovascular events in adulthood and b) the need for cardiac surgery in adulthood. Adverse cardiovascular events were defined as cardiovascular death (specified as sudden or not sudden), sustained (>30 seconds) supraventricular or ventricular arrhythmias, acute coronary syndromes, cerebrovascular events, new onset heart failure or infective endocarditis. Secondary outcomes included: a) postoperative complications related to prior surgery of supravalvar stenosis including aneurysms or pseudoaneurysms at the site of previous patch repair, b) echocardiographic evidence of recurrent stenosis at the supravalvar level and c) progression of supravalvar aortic stenosis in adulthood.

Data Collection

Baseline clinical, electrocardiographic and echocardiographic data were obtained by chart review. Baseline clinical variables at the first clinic visit included: age at first visit, gender,

diagnosis of Williams-Beuren syndrome, details pertaining to other congenital cardiac lesions specifically those associated with left ventricular outflow tract obstruction, type of supravalvar aortic stenosis at diagnosis, history of systemic arterial hypertension, New York Heart Association functional class, medical therapy and surgical and non-surgical interventions in childhood. Electrocardiographic characteristics included type of rhythm, presence of bundle branch block and QRS-duration.

Echocardiographic variables included the supravalvar aortic gradients, presence and severity of other left ventricular outflow tract lesions, nature and severity of concomitant valvular lesions, right ventricular outflow tract obstruction and left ventricular systolic function. Residual supravalvar aortic stenosis was defined as a peak systolic velocity > 2 meters/second (peak systolic gradient of > 16 mmHg) at the sinotubular junction of the ascending aorta. Significant mitral valve disease was defined as moderate or severe regurgitation and/or stenosis (mean diastolic gradient of more than 5 mmHg). Significant aortic valve disease was defined as moderate or severe aortic regurgitation and/or stenosis (peak systolic velocity > 3m/s).[13] To examine echocardiographic progression of the supravalvar stenosis, we examined the supravalvar gradient at three time points (when available); the last visit in childhood, the first visit in adulthood and the last visit in adulthood. Progression of supravalvar stenosis was defined as an increase in the peak systolic pressure gradient at the sinotubular junction of the ascending aorta of > 10 mmHg during the serial echocardiograms.

Statistical Analysis

The statistical analysis was performed using SPSS Version 18 (SPSS Inc., Chicago, IL). Continuous variables are reported as either mean +/- SD or median or interquartile range (IQR) (25^{th} and 75^{th} percentiles) as appropriate. Kaplan-Meier plots were used to depict survival free from adverse cardiovascular events and cardiac surgery in adulthood and stratified according to the absence or presence of Williams-Beuren syndrome. A Cox proportional hazard model was used to identify determinants of adverse cardiac outcomes and the need for cardiac surgery in

adulthood. Significance of changes in peak supravalvar systolic gradients between the first clinic visit in adulthood and the last clinic visit were determined using the Wilcoxon Signed Rank test. A p-value <0.05 (two-sided) was considered to be significant.

Results

Baseline Characteristics

A total of 113 patients with supravalvar aortic stenosis were identified. Sixty-two patients (55%) with supravalvar aortic stenosis had the Williams-Beuren syndrome. Other baseline characteristics are presented in Table 1A and 1B. Patients without Williams-Beuren syndrome more commonly had other left-sided outflow tract obstructive lesions (22/51 (43%) versus 2/62 (3%), $p < 0.0001$) including aortic valve stenosis (14 patients), subvalvar aortic stenosis (6 patients) and coarctation of the aorta (12 patients). Only 2 patients (2%), both without Williams-Beuren syndrome, had a parachute mitral valve (Shone's complex, defined as the presence of multiple levels of left ventricular outflow tract obstruction and left ventricular inflow obstruction). Seventy-six patients (67%) had undergone surgical repair of supravalvar aortic stenosis in childhood. The median age at operation was 7.1 years (IQR 1.4-11.2). Of those 37 patients who had no operation for supravalvar aortic stenosis in childhood, 32 (87%) had Williams-Beuren-Syndrome. Those who underwent surgical repair of supravalvar aortic stenosis in childhood were more likely to have other left ventricular outflow tract obstructions (29% versus 5%, $p = 0.004$), were more likely to have moderate or severe aortic valve regurgitation at first visit in adulthood (15% versus 0%, $p = 0.015$) and were less likely to have residual supravalvar aortic stenosis at first visit in adulthood (36% versus 65%, $p = 0.003$). Right bundle branch block at first visit in adulthood was more common in patients with surgery for supravalvar aortic stenosis in childhood (15% vs. 3%, $p = 0.057$).

Adults with Williams-Beuren syndrome were less likely to have additional left ventricular outflow tract obstruction. Those without the diagnosis of Williams-Beuren syndrome appeared to have more severe forms of supravalvar aortic stenosis and more complex left-sided outflow tract disease. In childhood, they more commonly had undergone surgical repair of supravalvar aortic stenosis (90% versus 48%, $p < 0.001$) and more often had undergone multiple surgical procedures (57% versus 15%, $p<0.0001$). At first assessment in the adult clinic, they were more likely to have significant supravalvar aortic stenosis (41% versus 5%, $p < 0.001$), more likely to have aortic valve stenosis or regurgitation (33% versus 3%, $p < 0.0001$) and more commonly had a complete right bundle branch block on their electrocardiogram (18% versus 5%, $p = 0.028$). Presentation with a right bundle branch block on the electrocardiogram was more common in patients who had multiple cardiac operations in childhood (26% versus 3%, $p < 0.0001$).

In contrast, mitral valve regurgitation was more common in adults with Williams-Beuren syndrome. Moderate or severe mitral valve regurgitation at first assessment in the adult clinic was present in 4 patients (4%); all of whom had Williams-Beuren syndrome. Significant mitral stenosis at first presentation in the adult clinic was present in 3 patients. One of the adults with significant mitral stenosis had Williams-Beuren syndrome and mitral valve repair at age 17. The other two patients were non-syndromic and had dysplastic mitral valves. Three patients had mild right ventricular outflow tract obstruction (peak gradients of 33 mmHg, 35 mmHg and 40 mmHg, respectively).

Adverse Cardiovascular Events in Adults

Serial clinical follow-up information was available in 85% (96/113) of patients. Of those 17 patients who had only one clinic visit in adulthood, all had been seen for the first time in the adult clinic within the last 3 years and were scheduled for regular follow-up visits in the future. Sixteen patients had just transitioned from pediatric care and were less than 20 years old at first

visit in adulthood. Baseline characteristics of patients with clinical follow-up did not differ from patients without follow up.

The median follow-up duration was 6.0 years (IQR 2.1-11.4, range 0.1-30.0) after the initial clinic presentation. The median age at last follow up was 27.3 years (range 18.2-57.9). For those patients who had surgical resection of supravalvar aortic stenosis in childhood, the mean follow-up interval after surgery was 20.7 ± 8.4 years (maximum 42 years).

During the follow-up period, 12 patients (13%) experienced a total of 20 cardiovascular complications (Table 2). The 2 deaths were associated with heart failure in the setting of severe mitral regurgitation. Kaplan-Meier survival curves for late adverse cardiovascular events and reoperation are shown in Figure 1.

At first clinic visit in adulthood, patients with cardiovascular complications had higher left ventricular mass (124 ± 27 g/m^2 versus 90 ± 31 g/m^2, p = 0.003) and lower left ventricular fractional shortening (30 ± 8% versus 40 ± 8%, p = 0.001) compared to those without complications, while left ventricular ejection fraction was not significantly different (61 ± 4% versus 63 ± 7%, p = 0.42).

For patients with new onset heart failure during follow-up compared to those without, baseline left ventricular ejection fraction was not different (59 ± 3% versus 63 ± 7%, p = 0.20). Of the 7 patients who developed clinical heart failure, 3 had moderate to severe mitral regurgitation, 1 had severe tricuspid regurgitation, 1 had severe aortic regurgitation and 1 had severe supravalvar aortic stenosis. Three patients had an abnormal left ventricular ejection fraction, including one patient requiring support by a left ventricular assist device. In all patients with abnormal left ventricular ejection fraction, the coronary arteries were documented to be normal by angiography. Determinants of adverse cardiovascular events in adulthood are shown in Table 3.

Patients without Williams-Beuren syndrome who experienced an adverse cardiovascular event more often had additional levels of left ventricular outflow tract obstructions compared to

those without an event but this did not reach statistical significance (20% versus 0%, p = 0.083). The rate of reoperations was not different in patients without Williams-Beuren syndrome with or without additional levels of left ventricular outflow tract obstruction (20% versus 19%, p = 1.0). Surgical repair of supravalvar aortic stenosis in childhood was not associated with cardiovascular complications during follow-up in adulthood (HR 5.5, 95%CI 0.7-42.9, p = 0.10).

During follow-up 6 patients (6%) newly developed echocardiographic evidence of moderate or severe mitral regurgitation; 4/6 (67%) fulfilled diagnostic criteria for mitral valve prolapse. All of the patients with progressive mitral regurgitation had Williams-Beuren syndrome. This accounts for 12% of all patients with Williams-Beuren syndrome for which follow-up data was available. Two of these patients developed atrial fibrillation and one patient later died from heart failure.

Cardiac Surgery in Adults

Twelve patients (13%) underwent cardiac surgery during the follow-up period (Table 2). Of the 12 reoperations, 6 (50%) were related to aortic valve disease, including one patient with percutaneous pulmonary valve replacement after previous Ross procedure for aortic valve stenosis. Only 2 patients with reoperations had Williams-Beuren syndrome. Both underwent surgical repair of supravalvar aortic stenosis (1 native stenosis and 1 re-stenosis after surgical repair in childhood).

At their first clinic visit in the adult clinic 51 patients (45%) had unrepaired or recurrent supravalvar aortic stenosis, including 7 patients with a peak systolic gradient ≥ 50 mmHg. Four of the 7 patients with significant gradients (≥ 50 mmHg) at first visit to the adult clinic underwent cardiac repair soon after presentation, while the other 3 patients with significant supravalvar aortic stenosis gradients are still under observation. Patients with cardiac surgery in adulthood had higher left ventricular mass at first clinic visit in adulthood compared to those without (117 ± 35 g/m2 versus 91 ± 31 g/m2, p = 0.019), but left ventricular ejection fractions were not significantly different (65 ± 11% versus 63 ± 6%, p = 0.43). Determinants of the need for cardiac

surgery in adulthood are shown in Table 4. In contrast to determinants for adverse cardiovascular events, neither mitral valve disease at first clinic visit (p=0.739) nor reoperation for supravalvar aortic stenosis in childhood (p=1.000) were associated with cardiovascular surgery during follow up in adulthood. As for cardiovascular complications, left ventricular mass was a determinant for reoperations, but not fractional left ventricular shortening or left ventricular ejection fraction. Surgical repair of supravalvar aortic stenosis in childhood was not a significant determinant of cardiac operations during follow-up in adulthood (HR 5.2, 95%CI 0.7-40.2, p = 0.12).

Other Postoperative Complications Related To Prior Surgery Of Supravalvar Stenosis

There were no adults with pseudoaneurysms or aneurysms at the site of previous patch repair. At their first clinic visit in the adult clinic, 3 patients had an enlarged aortic root (maximum 4.5cm) and 1 patient had a dilated proximal ascending aorta (4.7cm) after a Ross-operation. During follow-up, 3 additional patients developed dilatation of the proximal ascending aorta (maximum diameter 4.6cm); 2 in the setting of a bicuspid aortic valve.

Progression of Supravalvar Aortic Stenosis

Of 51 patients with supravalvar aortic stenosis (native stenosis or re-stenosis) at first clinic visit in the adult clinic, 4 underwent surgical repair shortly after presentation. Of the remaining 47 patients, serial echocardiograms were available in 75% of the patients (n=35). Figure 2 shows the serial supravalvar gradients over time. On average, the supravalvar gradients changed little during follow up [median gradient at first clinic visit in adulthood 28 mmHg (IQR 21-47) versus median gradient at last follow up in the adult clinic 24 mmHg (IQR 16-40), p = 0.046]. Of those patients without residual supravalvar aortic stenosis at first clinic visit in the adult clinic, none had a significant increase in peak supravalvar gradients on serial echocardiographic follow-up. As illustrated in Figure 2, three patients (9%) had serial increases in the peak supravalvar systolic gradient (increase from 20 to 35 mmHg, 50 to 70 mmHg and from 70 to 90 mmHg) over a follow-up period of 2.5, 13.7 and 7.0 years. All three patients remained asymptomatic and none experienced cardiovascular complications. The patient with a peak

systolic gradient of 90 mmHg at last clinic visit declined surgical repair. The patient with an increase in peak pressure gradient from 50 to 70 mmHg over a follow-up period of 13.7 years had serial cardiac magnetic resonance imaging at last follow-up and 12 years earlier with morphologically unchanged findings and a minimal supravalvar aortic diameter of 15 mmHg. No additional imaging was available in the 2 other patients.

Discussion

Patients with supravalvar aortic stenosis presenting to adult congenital cardiac clinics represent a heterogeneous population. Although supravalvar aortic stenosis can be associated with Williams-Beuren syndrome, almost half of all adults in our series had either an isolated form of supravalvar aortic stenosis or supravalvar aortic stenosis in conjunction with other left ventricular outflow tract obstructive lesions. The associated valvular cardiac lesions are common and are important determinants of long-term outcomes in the adult.

Adverse Cardiovascular Events

Adverse cardiovascular events occurred in more than 1/10 young adults (median age 28 years) with supravalvar aortic stenosis, primarily due to arrhythmias (both atrial and ventricular) and heart failure. Similar to other surgically repaired congenital lesions, multiple operations and subsequent scar tissue may act as a source of reentry circuits and increase the propensity toward arrhythmias. [14] Supravalvar aortic stenosis was not the primary determinant of late complications. In contrast to the manifestations reported in the pediatric series, mitral valve disease (regurgitation or stenosis) is an important determinant of cardiac complications in the adult. Williams-Beuren syndrome is caused by 7q11.23 deletion and although this region contains a number of genes, the elastin gene is felt to be the gene responsible for the clinical findings.[1] The involvement of the mitral valve, particularly mitral valve prolapse or regurgitation, in a condition affecting elastin fibers is not surprising. Indeed, despite a relatively short follow-up period,

progressive mitral regurgitation was identified in a number of these patients.[15] Our findings underscore the need to focus on concomitant valvar cardiac lesions, particular mitral valve lesions for optimal long-term care of these patients. Clinical and echocardiographic surveillance in adults with supravalvar aortic stenosis, even those without overt valvar heart disease, is important.

In children with supravalvar stenosis, acute coronary syndromes and sudden cardiac death are well documented outcomes. [16] In our series, one patient had an aborted sudden death which occurred in the setting of severe residual supravalvar aortic stenosis, with normal coronary arteries. No adults presented with acute coronary syndromes. In children, ostial coronary artery lesions are typically caused by abnormal growth of the aortic root. [2] While coronary events might have been detected in a larger cohort of patients or during a longer follow up period, it may be that the case that the mechanism responsible for coronary artery obstruction in children is not present in the adult population. Nonetheless, as this population ages, acquired atherosclerotic coronary artery disease may become more important. [17] Residual supravalvar aortic stenosis may accelerate coronary atherosclerosis as in these patients the offset of the coronary arteries is proximal to the anatomic narrowing and thus, even in patients without systemic hypertension, coronary arteries face an increased systolic pressure. Long-term cohort studies will be needed to better define late coronary outcomes in these patients.

Cardiac Surgery

Cardiac surgery during adulthood was required in approximately 1/10 young adults (median age 23 years) in this study. Cardiac surgeries varied significantly; one third of the adults required surgery for severe recurrent or native supravalvar aortic stenosis and the remainder required surgery for other indications, including left and right-sided valve disease. Cardiac surgery was more common in patients without Williams-Beuren syndrome, likely because of a higher frequency of associated aortic valve lesions in these patients. In our cohort, the presence of complete right bundle branch block was also associated with cardiac operations during adulthood.

We presume that this finding might be a reflection of more previous cardiac surgery in patients with right bundle branch block and although statistically significant it is less clinically meaningful. Not surprisingly, a high gradient across the ascending aorta was a strong predictor for cardiac surgery. Continued surveillance for concomitant valve disease, in any position, is important.

Progression of Supravalvar Aortic Stenosis

Progression of supravalvar aortic stenosis may occur in the adult population, but it is less common than in children. In most adults, systolic gradients remain stable. This contrasts some studies in children with supravalvar aortic stenosis, in whom stenosis was progressive in up to 80%. [4] Differences in the behavior of supravalvar obstruction in children and adults may be explained by the different nature of left ventricular outflow tract obstruction in these patients. Supravalvar narrowing is typically the consequence of differential growth of the aortic root during somatic growth and is not the result of degenerative tissue changes or progressive tissue ingrowth or hyperplasia. [4] Therefore it seems plausible that lesions are often progressive during childhood but remain stable, once growth of the aortic root is completed.

Limitations

This study inherits all limitations of a retrospective design. We could not ensure standardized clinical and genetic testing for Williams-Beuren syndrome. The diagnosis of this syndrome was obtained from available clinic reports and the screening process for Williams-Beuren syndrome in patients with supravalvar aortic stenosis may differ between sites. Information on more contemporary genetic testing was not performed or available.

There are also limitations with respect to echocardiography. Measurements of left ventricular ejection fraction, left ventricular fractional shortening and left ventricular muscle mass index were not available in all patients. No established criteria and thresholds exist for the definition of supravalvar aortic stenosis and its progression by means of Doppler echocardiography. In fact, some groups defined presence and progression as morphologic

narrowing at the supravalvar level, without hemodynamic criteria.[8] Because no specific criteria are available, the echocardiographic cut-offs used in this study are therefore arbitrary. Furthermore, echocardiographic Doppler-gradients may over- or underestimate the severity of supravalvar aortic stenosis depending on many factors including the left ventricular systolic function and the nature of stenosis (tubular versus discrete).

Our study population was relatively young and therefore, with ageing of this population, the frequency of complications and the need for operation may increase. Despite the multicenter efforts of this study, the number of identified patients with this diagnosis remains small. To better define outcomes and risk factors, prospective multicenter registries will be needed to identify predictors for long-term outcomes in patients with this rare cardiac condition.

Conclusions

Adults with supravalvar aortic stenosis remain at risk for cardiac complications in adulthood.. Adverse cardiovascular events are associated with valve disease, particularly the mitral valve. Surgery may be needed in some adults with supravalvar aortic stenosis, but surgical interventions are more commonly required for valve lesions and not resection of recurrent supravalvar aortic stenosis.

References

1. Ewart AK, Morris CA, Atkinson D*, et al.* Hemizygosity at the elastin locus in a developmental disorder, Williams syndrome. Nat Genet 1993;**5**(1):11-6.
2. Stamm C, Li J, Ho SY*, et al.* The aortic root in supravalvular aortic stenosis: the potential surgical relevance of morphologic findings. J Thorac Cardiovasc Surg 1997;**114**(1):16-24.
3. Thistlethwaite PA, Madani MM, Kriett JM*, et al.* Surgical management of congenital obstruction of the left main coronary artery with supravalvular aortic stenosis. J Thorac Cardiovasc Surg 2000;**120**(6):1040-6.
4. Wren C, Oslizlok P, Bull C. Natural history of supravalvular aortic stenosis and pulmonary artery stenosis. J Am Coll Cardiol 1990;**15**(7):1625-30.
5. Giddins NG, Finley JP, Nanton MA*, et al.* The natural course of supravalvar aortic stenosis and peripheral pulmonary artery stenosis in Williams's syndrome. Br Heart J 1989;**62**(4):315-9.
6. Wessel A, Pankau R, Kececioglu D*, et al.* Three decades of follow-up of aortic and pulmonary vascular lesions in the Williams-Beuren syndrome. Am J Med Genet 1994;**52**(3):297-301.
7. van Son JA, Danielson GK, Puga FJ*, et al.* Supravalvular aortic stenosis. Long-term results of surgical treatment. J Thorac Cardiovasc Surg 1994;**107**(1):103-14; discussion 114-5.
8. Hickey EJ, Jung G, Williams WG*, et al.* Congenital supravalvular aortic stenosis: defining surgical and nonsurgical outcomes. Ann Thorac Surg 2008;**86**(6):1919-27; discussion 1927.
9. Delius RE, Steinberg JB, L'Ecuyer T*, et al.* Long-term follow-up of extended aortoplasty for supravalvular aortic stenosis. J Thorac Cardiovasc Surg 1995;**109**(1):155-62; discussion 162-3.
10. Scott DJ, Campbell DN, Clarke DR*, et al.* Twenty-year surgical experience with congenital supravalvar aortic stenosis. Ann Thorac Surg 2009;**87**(5):1501-7; discussion 1507-8.

11. Kitchiner D, Jackson M, Walsh K*, et al.* Prognosis of supravalve aortic stenosis in 81 patients in Liverpool (1960-1993). Heart 1996;**75**(4):396-402.
12. Collins RT, 2nd, Kaplan P, Somes GW*, et al.* Long-term outcomes of patients with cardiovascular abnormalities and williams syndrome. Am J Cardiol 2010;**105**(6):874-8.
13. Bonow RO, Carabello BA, Chatterjee K*, et al.* 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation 2008;**118**(15):e523-661.
14. Bouchardy J, Therrien J, Pilote L*, et al.* Atrial arrhythmias in adults with congenital heart disease. Circulation 2009;**120**(17):1679-86.
15. Nasuti JF, Zhang PJ, Feldman MD*, et al.* Fibrillin and other matrix proteins in mitral valve prolapse syndrome. Ann Thorac Surg 2004;**77**(2):532-6.
16. Wessel A, Gravenhorst V, Buchhorn R*, et al.* Risk of sudden death in the Williams-Beuren syndrome. Am J Med Genet A 2004;**127A**(3):234-7.
17. Yalonetsky S, Horlick EM, Osten MD*, et al.* Clinical characteristics of coronary artery disease in adults with congenital heart defects. Int J Cardiol 2011 Jul 30. http://dx.doi.org/10.1016/j.ijcard.2011.07.021

Legends

Figure 1: Survival free of cardiovascular complication and reoperation

Kaplan-Meier plots demonstrating survival free of cardiovascular complications and reoperation during follow-up in adults stratified according in those with and without Williams-Beuren syndrome (WBS)

Figure 2: Serial peak systolic gradients at supravalvar aortic level

Systolic peak gradients at supravalvar aortic level at last pediatric cardiology visit, first visit in the adult clinic and last visit in the adult clinic: Each line represents an individual patient with residual stenosis at first clinic visit in the adult clinic. Red lines mark the 3 patients with an increase in systolic gradients > 10mmHg during follow-up in adulthood.

Table 1A: **Clinical baseline characteristics of study patients**

Characteristics	**N=113**
Demographics	**N (%)**
Males	77 (68)
Age at first visit in adulthood (years)	20.3 ± 4.3
Williams-Beuren syndrome	62 (55)
Cardiac Anatomy	
Diffuse form of supravalvar aortic stenosis	16 (14)
Involvement of coronary arteries	4 (4)
Documented renal artery stenosis	8 (7)
Documented involvement of aortic branches other than renal arteries	4 (4)
Involvement of other levels of left ventricular outflow tract obstruction	24 (21)
Shone's complex	2 (2)
Surgical history	
Surgical repair of supravalvar aortic stenosis in childhood	76 (67)
Age at repair (years)	7.5 (IQR 1.7-11.4)
Additional procedures at the time of repair	30 (27)
More than one cardiac surgery during childhood	38 (34)
Reoperation for supravalvar aortic stenosis in childhood	11 (10)
Reoperation for other cardiac lesions in childhood	19 (17)
Clinical findings at first visit in adulthood	
Arterial hypertension	29 (26)
New York Heart Association functional class ≥ 2	9 (8)
Cardiac medications	36 (33)
Beta-blockers	12 (11)
Calcium channel blocker	6 (5)
Angiotensin-converting enzyme (ACE) inhibitors	17 (15)
Angiotensin II receptor antagonists	1 (1)
Diuretics	6 (5)

Table 1B: **Electrocardiographic and echocardiographic baseline characteristics at first clinic visit in adulthood**

Characteristics	N=113*
Electrocardiography at first visit in adulthood	
Sinus rhythm at presentation in adulthood	111 (98)
Complete left bundle branch block	4 (4)
Complete right bundle branch block	12 (11)
Echocardiography at first visit in adulthood	
Native or residual supravalvar aortic stenosis (peak gradient ≥ 16 mmHg)	51 (45)
Peak systolic gradient across supravalvar aortic stenosis	27 (IQR 20-45)
Supravalvar aortic stenosis with peak gradient ≥ 50 mmHg	7 (6)
Aortic valve disease	
Bicuspid aortic valve	17 (15)
Aortic stenosis with peak systolic velocity > 3m/s	11 (10)
More than mild aortic regurgitation	11 (10)
Subvalvar aortic stenosis	2 (2)
Coarctation of the aorta with peak systolic gradient ≥ 20 mmHg	12 (11)
Mitral valve disease	
Any mitral valve disease	18 (16)
Mitral valve prolapse	14 (12)
Mitral stenosis (mean gradient ≥ 5 mmHg)	3 (3)
More than mild mitral regurgitation	4 (4)
Right ventricular outflow tract obstruction	3 (3)
Left ventricular ejection fraction (%)*	64 ± 7
Left ventricular fractional shortening (%)	39 ± 8
Left ventricular muscle mass, indexed to body surface area (g/m^2)	93 ± 32

* Left ventricular ejection fraction was reported to be normal in 110 patients (97%), numeric values were available in 72 patients (64%). Measurements of left ventricular fractional shortening were available in 93/113 patients (82%). Measurements of left ventricular muscle mass index were available in 83/113 patients (73%)

Table 2: Cardiovascular outcomes during adulthood in patients with supravalvar aortic stenosis

	N=96	Comments
Adverse Cardiovascular Events		
Any adverse cardiovascular event	20	Median age 28 years (range 19-51)
Cardiovascular death	2	Both deaths were secondary to heart failure
Arrhythmias	8	
Atrial flutter or atrial fibrillation	7	Two patients had paroxysmal atrial flutter / fibrillation in combination with sustained ventricular tachycardia
Sustained ventricular tachycardia	3	One patient had an aborted sudden cardiac death
New onset heart failure	7	
Ischemic stroke	1	
Endocarditis	2	Two patients had aortic valve endocarditis
Cardiac Surgery		
Any Cardiac Surgery	12	Median age 23 years (range 19-52)
Procedures for supravalvar aortic stenosis		
Intervention for restenosis after childhood surgery*	3	
Intervention for newly diagnosed severe supravalvar aortic stenosis	1	
Aortic valve procedures		
Prosthetic aortic valve replacement	2	
Konno procedure	1	
Bentall operation	1	
Combined aortic and mitral valve procedures		
Aortic valve and mitral valve replacement	1	
Procedures for right sided heart valves		
Tricuspid valve repair	1	
Percutaneous pulmonary valve replacement	1	
Other procedures		
Implantation of left ventricular assist device	1	

* Including 1 patient who underwent percutaneous stenting of supravalvar aortic stenosis

Cardiovascular events and operations are not mutually exclusive

Table 3 Determinants of adverse cardiovascular events during adulthood in patients with supravalvar aortic stenosis

	Hazard Ratio	95% Confidence Interval	P Value
Univariate analysis			
Anatomic variables			
Diffuse form of supravalvar aortic stenosis	7.9	2.3 - 27.6	0.001
Involvement of aortic branches other than renal arteries	3.1	0.9 - 11.5	0.089
Clinical variables			
No diagnosis of Williams-Beuren syndrome	1.7	0.5 - 5.4	0.373
Reoperation for supravalvar aortic stenosis in childhood	3.9	1.0 - 15.0	0.051
Multiple cardiac operations in childhood	6.1	1.6 - 22.6	0.007
NYHA functional class ≥ 2	9.5	2.5 - 35.5	0.001
Beta-Blocker	4.0	1.0 - 15.7	0.044
ACE inhibitor	4.2	1.2 - 14.9	0.027
Electrocardiographic variables			
Right bundle branch block	7.3	2.0 - 25.8	0.002
Echocardiographic variables			
Any residual supravalvar aortic stenosis at first clinic visit in adulthood	1.3	0.4 - 4.5	0.643
Peak systolic gradient of supravalvar aortic stenosis > 50 mmHg	1.2	0.2 - 9.7	0.842
Any hemodynamically significant mitral valve disease*	7.8	1.6 - 37.4	0.011
More than mild mitral regurgitation	7.8	1.0 - 62.8	0.053
Mitral stenosis	6.2	0.8 – 49.7	0.086
Left ventricular fractional shortening	0.872	0.802-0.948	0.001
Left ventricular ejection fraction	0,956	0.844-1.082	0.48
Left ventricular muscle mass index	1.028	1.010-1.046	0.002

*more than mild mitral regurgitation or mitral stenosis with mean diastolic pressure gradient > 5 mmHg

Table 4. Determinants of cardiac surgery during adulthood in patients with supravalvar aortic stenosis

	Hazards Ratio	95% Confidence Interval	P Value
Univariate analysis			
Anatomic variables			
Diffuse form of supravalvar aortic stenosis	3.5	0.9 - 13.5	0.075
Clinical variables			
No diagnosis of Williams-Beuren syndrome	6.4	1.4 - 29.6	0.017
Reoperation for supravalvar aortic stenosis in childhood	1.0	0.1-7.7	1.0
Multiple cardiac operations in childhood	3.8	1.1 - 12.5	0.030
NYHA functional class ≥ 2	6.3	1.6 - 25.7	0.010
ECG variables			
Right bundle branch block	5.1	1.5 - 16.9	0.008
Echocardiographic variables			
Peak systolic gradient of supravalvar aortic stenosis > 50 mmHg	5.2	1.4 - 19.8	0.015
More than mild aortic regurgitation	3.2	0.9 - 11.0	0.070
Any hemodynamically significant aortic valve disease*	2.8	0.8 - 9.1	0.097
Any significant mitral valve disease at first visit in adulthood	0.7	0.1-5.6	0.739
Left ventricular fractional shortening	0.956	0.881-1.036	0.269
Left ventricular ejection fraction	1.068	0.971-1.175	0.174
Left ventricular muscle mass index	1.019	1.003-1.035	0.018

* Aortic stenosis with peak systolic velocity > 3m/s and/or more than mild aortic regurgitation