

Prognosis of supravalve aortic stenosis in 81 patients in Liverpool (1960-1993)

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Abstract

Objective—To determine the prognosis of supravalve aortic stenosis into early adult life and the factors affecting this prognosis.

Design—81 patients with supravalve aortic stenosis were followed for a median duration of 8.3 (range 1 to 29) years.

Patients—40 patients (49.4%) had Williams' syndrome, 18 (22.2%) familial supravalve aortic stenosis, 18 (22.2%) sporadic supravalve aortic stenosis, and five (6.2%) other syndromes. Nineteen patients had additional levels of left ventricular outflow tract obstruction.

Results—47 patients (58%) underwent operation; 20% within a year of presentation. Multivariable analysis predicted that 88% of patients would undergo intervention within 30 years of follow up. The chance of intervention was increased by more severe aortic stenosis at presentation and the presence of multilevel obstruction in patients with sporadic supravalve aortic stenosis. Three deaths occurred before operation and 13 within a month of operation. Ten (62.5%) of the postoperative deaths were in patients with multilevel obstruction. Predicted survival 30 years after presentation was 66%. Risk factors for survival were age and severity of aortic stenosis at presentation. Multilevel obstruction did not emerge as a significant risk factor for death because of the high association with the severity of stenosis at presentation. 74% of survivors had mild or insignificant stenosis at follow up.

Conclusions—Long-term survival is related to age and the severity of aortic stenosis at presentation. Most patients will require intervention, and most survivors will have mild stenosis.

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Keywords: aortic stenosis; William's syndrome; familial supravalve aortic stenosis; prognosis

Supravalve aortic stenosis is the least common type of left ventricular outflow obstruction.¹ Most patients with this condition have Williams' syndrome or a positive family history,^{2,3} but about 25% of cases are sporadic.⁴ Progression with time has been demonstrated,^{2,5,6} but these reports contain relatively small numbers of patients. The aims of this

study were to determine the prognosis of patients with supravalve aortic stenosis from presentation into early adult life and define the factors influencing that prognosis.

Patients and methods

Eighty one patients (52 (64%) were male) with supravalve aortic stenosis who presented to the Royal Liverpool Children's Hospital between 1 January 1960 and 31 December 1992 were included. The severity of stenosis at presentation was determined from clinical data, together with echo/Doppler or cardiac catheterisation assessment if performed within a year of presentation. The criteria for assessing the severity of stenosis were the same as those used in a previous study.⁷ Patients with mild aortic stenosis had a short ejection systolic murmur and a normal electrocardiogram. A Doppler velocity of less than 3 m/s or a peak systolic gradient of less than 40 mm Hg across the left ventricular outflow tract at cardiac catheterisation was also used as evidence of mild stenosis. Patients with moderate stenosis had a long ejection systolic murmur and the electrocardiogram was normal or showed features of left ventricular hypertrophy. A Doppler velocity of 3-4.5 m/s or a peak systolic gradient of 40-80 mm Hg across the left ventricular outflow tract was also used as evidence of moderate stenosis. Patients with severe stenosis at presentation all had symptoms or left ventricular strain pattern on the electrocardiogram. The level of obstruction was determined from clinical, echocardiographic, angiographic, operative, and post-mortem information. Differentiation between localised and diffuse supravalve aortic stenosis was determined by aortic or left ventricular angiography in 52 patients, echocardiography in 24, and from operation notes in five in whom angiograms were not available. Survivors were traced to assess their current clinical status. Evaluation included clinical examination, electrocardiogram, and cross-sectional and Doppler echocardiography.

STATISTICAL ANALYSIS

Frequency data are presented as raw counts or percentages, and differences between groups were assessed using the χ^2 ⁸ or Fisher's exact test⁹ as appropriate. Continuously distributed data are given as medians with range, and group differences explored using the Wilcoxon's rank sum test.⁸ Seventy per cent confidence limits were used throughout. Time related analysis of death and first intervention

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Table 1 Age at presentation and incidence of associated conditions, and distribution of patients with supravulve aortic stenosis (SVAS) alone and those with multilevel obstruction

	No of patients	Median (range) age (months)
Williams' syndrome	40 (49.4)	16.7 (1.6-99.6)
Familial SVAS	18 (22.2)	6.9 (0.2-52.3)
Sporadic SVAS	18 (22.2)	28.6 (0.1-143.6)
Other syndromes*	5 (6.2)	3.9 (0.1-15.4)
SVAS alone	62 (76.5)	14.6 (0.2-118.5)
Multilevel obstruction	19 (23.5)	3.9 (0.1-143.6)

Values in parentheses are percentages. *Noonans (n = 2); Shones (n = 2); rubella (n = 1).

Table 2 Severity of aortic stenosis at presentation related to associated conditions, and the presence of supravulve aortic stenosis alone (SVAS) or multilevel obstruction

	Insignificant/mild stenosis	Moderate stenosis	Severe stenosis
Williams' syndrome	24	12	4
Familial SVAS	9	5	4
Sporadic SVAS	7	8	3
Other syndromes	1	3	1
SVAS alone	37	20	5
Multilevel obstruction	4	8	7

(surgery or balloon dilatation) after presentation (time zero) were performed actuarially¹⁰ and parametrically.¹¹ Multivariable analyses of demographic, clinical, institutional, and morphological variables (appendix) were made in the hazard function domain¹¹ and retained in the multivariable equation when the P value for the variable was < 0.1.

Results

The median age at presentation was 13.8 months with a range of 3 days to 12 years.

Table 3 Distribution of other cardiac lesions in patients with supravulve aortic stenosis (SVAS) related to associated conditions

	Williams' syndrome	Familial SVAS	Sporadic SVAS	Other syndromes
PPS (29.6)	16	3	5	
PVS (6.2)	2			3
VSD (4.9)	1‡	2	1	
Ao arch obst* ± VSD ± PDA (6.2)	1	1	3	2‡
Total	20 (50)	6 (33)	9 (50)	5 (100)

Values in parentheses are percentages. *One patient had aortic arch interruption. †Additional mitral valve disease. ‡Additional right ventricular outflow tract obstruction. Ao, aortic; obst, obstruction; PDA, patent arterial duct; PPS, peripheral pulmonary artery stenosis; PVS, pulmonary valve stenosis; VSD, ventricular septal defect.

Table 4 Incidence of surgery and reoperation related to associated conditions in the 47 patients who underwent operation, and relation of surgery to the presence of supravulve aortic stenosis (SVAS) alone or multilevel obstruction

	No operation (n = 34) (42.0)	1 operation (n = 39) (48.2)	2 operations (n = 7) (8.6)	3 operations (n = 1) (1.2)
Williams' syndrome	21	19		
Familial SVAS	7	9	2	
Sporadic SVAS	6	8	3	1
Other syndromes		3	2	
SVAS alone	34	27	1	
Multilevel obstruction		12	6	1

Values in parentheses are percentages.

Table 1 shows the incidence of conditions associated with supravulve aortic stenosis together with age at presentation. The age at presentation was lower in patients with familial supravulve aortic stenosis than in those with Williams' syndrome ($P < 0.02$) or sporadic supravulve aortic stenosis ($P < 0.05$). Nineteen patients had additional levels of left ventricular outflow obstruction (multilevel obstruction). Eight had aortic valve stenosis, and 11 had valve and subvalve obstruction. Diffuse supravulve aortic stenosis occurred in five patients (26.3%) with multilevel obstruction, and in only four patients (6.5%) with supravulve aortic stenosis alone ($P < 0.05$). There was no significant difference in the age at presentation in patients with supravulve aortic stenosis alone and those with multilevel obstruction (table 1). The incidence of multilevel obstruction was lower ($P < 0.001$) in patients with Williams' syndrome (two patients, 5.0%) and those with familial supravulve aortic stenosis (three patients, 16.7%) than in patients with sporadic supravulve aortic stenosis (nine patients, 50%) and those with other syndromes (five patients, 100%).

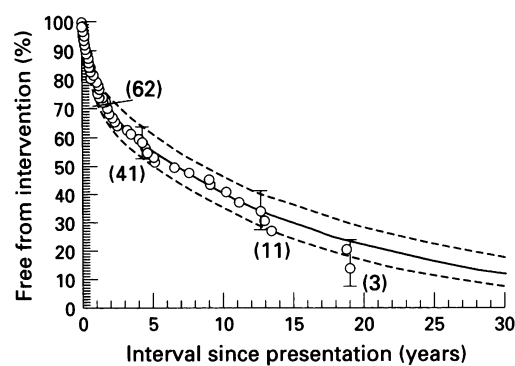
There was no difference in the distribution of severity of aortic stenosis at presentation related to the various associated conditions ($P = 0.12$). However, patients with more severe stenosis at presentation had an increased tendency ($P < 0.001$) to have multilevel obstruction (table 2). Other cardiovascular lesions were found in 40 patients (49.4%) (table 3). There was no difference in the incidence of other cardiac lesions in patients with supravulve aortic stenosis alone (n = 29; 46.8%) and those with multilevel obstruction (n = 11; 58%). With one exception, aortic arch obstruction occurred only in patients with multilevel obstruction. Aortic regurgitation was found at presentation in three patients (3.7%) who all had additional aortic valve stenosis.

The median duration of follow up in survivors was 8.3 (range 1-29) years. Nine patients were lost to follow up after a median duration of 11 (range 4.1-18.4) years. Aortic regurgitation was found in four patients with additional aortic valve stenosis at follow up. Infective endocarditis was not encountered.

INTERVENTION

Forty seven patients (58%) underwent operation for supravulve aortic stenosis (table 4). The median age at first operation was 4.9 (range 0.1-20.9) years and there was no difference in relation to the various associated conditions. All patients underwent cardiac catheterisation before surgery and the peak systolic gradient across the left ventricular outflow tract was a median of 72 (range 42-120) mm Hg. The peak systolic gradient was more than 50 mm Hg in all but four patients who had symptoms or evidence of left ventricular strain pattern on the electrocardiogram. Three patients underwent balloon dilatation of the left ventricular outflow tract. This was successful in only one patient with isolated supravulve steno-

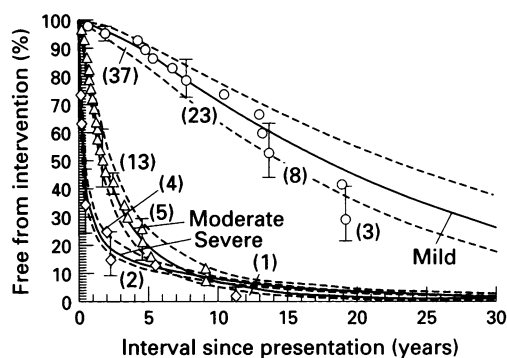
Figure 1 Freedom from first intervention after presentation in 81 patients with supravalve aortic stenosis. This graph contains two depictions. The first results from an actuarial (Kaplan-Meier) analysis in which each intervention (○) is positioned actuarially along the y axis and the time interval along the x axis. Bars represent 70% confidence intervals and the numbers in parentheses indicate the number of patients followed up at that interval after intervention. The second is a graphical representation of the solution to the equation (nomogram) resulting from the parametric analysis of freedom from intervention, in which a continuous point estimate (—) and the 70% confidence limits are shown. The table gives the time related depictions.



Interval (years)	Life table (%)	Predicted parametric (%)
1	80	81
10	43	39
15	27	29
20	13	23
25	13	16
20	13	12

sis who had previously had surgery. Some 20% of patients underwent intervention within a year of presentation. Actuarial and hazard analysis predicted that 88% of patients were likely to require relief of obstruction within 30 years of presentation (fig 1).

Multivariable analysis of potential risk factors (appendix) indicated that more severe aortic stenosis at presentation was the strongest determinant of the need for surgical



Aortic stenosis grade	Actual	Predicted	P value
Mild	13	14.2	0.69
Moderate	25	21.8	0.14
Severe	9	10.9	0.05

Figure 2 Freedom from intervention after presentation in 81 patients with supravalve aortic stenosis stratified by severity of aortic stenosis at presentation. Kaplan-Meier estimates of freedom from intervention are depicted as in fig 1 for patients with mild (○), moderate (△) and severe aortic stenosis (◇) at presentation. The predicted time related freedom from intervention for each group (—), obtained by averaging the predicted patient-specific freedom from first intervention estimates derived from the solution to the multivariable equation for each member of the group, and 70% confidence intervals (---) are shown. The table gives results from an internal validation of the multivariable equation in terms of the association between actual and predicted number of interventions for each stratum.

intervention. Figure 2 shows that most patients who presented with moderate or severe stenosis underwent operation within the first few years after presentation, while patients who presented with mild obstruction gradually progressed to require intervention over a number of years. Multivariable analysis also indicated that the presence of multilevel obstruction in patients with sporadic supravalve aortic stenosis was a significant ($P = 0.002$) risk factor for intervention. The presence of Noonan's syndrome also proved significant ($P < 0.05$) in an effort to explain the intervention experiences of the two patients with this condition as both had additional severe right ventricular outflow obstruction which contributed to their early management. Factors not significant in relation to intervention were the sex of the patient, syndromes other than Noonan's syndrome, and the presence of aortic regurgitation at presentation.

The reoperation rate was 17%. The incidence was higher ($P < 0.01$) in patients with multilevel obstruction than in those with supravalve aortic stenosis alone (table 4). The median duration between first and second operations was 4.6 (range 0.5–8.2) years, and this was similar in patients with the various associated conditions. Table 5 shows the results of surgery.

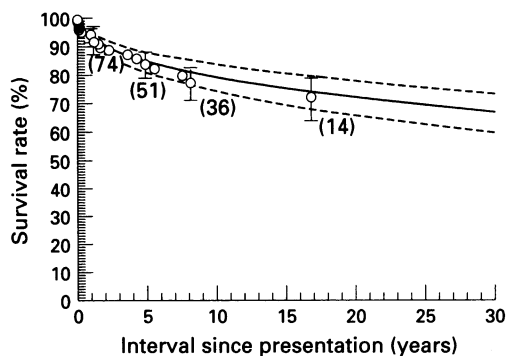
SURVIVAL

There were 16 deaths (19.8%) during the study period. Fourteen patients had severe aortic stenosis and two with Noonan's syndrome had additional severe pulmonary valve and peripheral pulmonary artery stenosis. The mortality was lower ($P < 0.001$) in patients with isolated supravalve aortic stenosis than in those with multilevel stenosis (table 5). Four patients with Williams' syndrome (10%), five with familial supravalve aortic stenosis (27.7%, three with sporadic supravalve aortic stenosis (16.7%), and four with other syndromes (80%) died. There were no sudden, unexpected deaths. Two patients with severe isolated supravalve aortic stenosis died before operation could be performed and one with Williams' syndrome and severe kyphoscoliosis declined surgery. Thirteen patients died within a month of operation. Three of these patients had severe isolated supravalve stenosis with profound left ventricular hypertrophy. Ten patients with multilevel obstruction died after operation. Six of these had supravalve, valve, and subvalve obstruction, one had

Table 5 Current clinical status after surgery in patients with supravalve aortic stenosis (SVAS) alone and in those with multilevel obstruction, and median age at initial operation

	SVAS alone	Multilevel obstruction
No stenosis	4	
Mild stenosis	13	4
Moderate stenosis	6	2
Hospital mortality (death \leq 30 days)	3	10
Lost to follow up	2	3
Median (range) age at first operation (months)	60.5 (9.4–250.9)	42.7 (0.8–229.4)

Figure 3 Survival after presentation in 81 patients with supravalue aortic stenosis. The general form of the depictions (actuarial and parametric) are as in fig 1, with death at any time after presentation (○) in terms of survival.

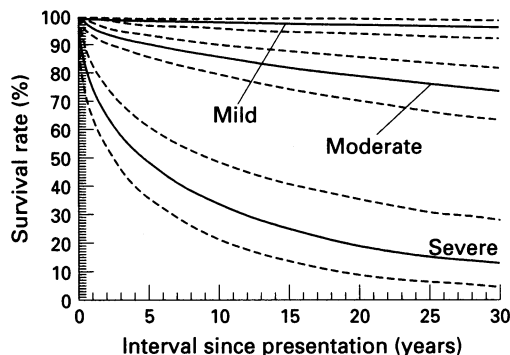


Interval (years)	Life table (%)	Predicted parametric (%)
1	95	93
10	77	79
15	77	65
20	71	71
25	71	69
30	71	66

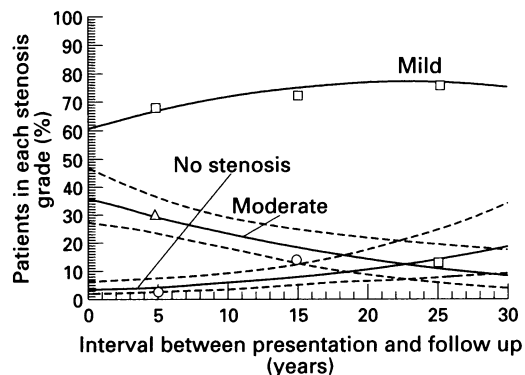
supravalue and valve stenosis, and three had additional surgery for right ventricular outflow tract obstruction. Four of the patients with multilevel obstruction died at reoperation and three of these operations included attempted aortic valve or root replacement. The operative mortality was lower ($P < 0.005$) in patients with supravalue aortic stenosis alone (10.7%) than in those with multilevel obstruction (53%).

An actuarial analysis of death at any time after presentation indicated that survival declined gradually over time (fig 3) to plateau at 71%, 17 years after presentation. Evidence from the parametric model suggests that the proportion of patients alive after 30 years of follow up is unlikely to differ much from this value. Multivariable analysis determined that risk factors for death were more severe aortic stenosis at presentation, younger age at presentation, and the presence of Noonan's syndrome (appendix). Multilevel obstruction did not emerge as a significant risk factor because

Figure 4 Graph showing risk adjusted time related survival after presentation with supravalue aortic stenosis according to severity of aortic stenosis. The depiction is a nomogram of a specific solution of the multivariable equation (appendix) where 1.15 years (13.8 months) is the value entered for age at presentation and no for presence of Noonan's syndrome.



Interval (years)	Mild (%)	Moderate (%)	Severe (%)
1	99.4	96.1	76.6
10	97.6	85.0	33.8
20	96.4	78.0	19.1
30	95.3	72.9	12.0



Distribution of aortic stenosis grade at follow up (%)

Interval (years)	No stenosis	Mild stenosis	Moderate stenosis
1	3	62	35
5	4	67	29
10	6	71	23
20	10	76	14
30	18	74	8

Figure 5 Relation of interval between presentation and follow up with the grade of aortic stenosis severity in the 65 surviving patients at last follow up evaluation. The actual proportions of patients with no (○), mild (□), or moderate (△) stenosis (appendix) at the mid-points of 10 year intervals are represented. Nomograms of the parametric predictions of the prevalences of stenosis grade (—) and 70% confidence intervals (- - -) are shown. The table gives percentage of patients in each aortic stenosis grade (total 100%) at each time interval.

of a close association with the severity of aortic stenosis at presentation. Factors insignificant in relation to survival were the sex of the patient, the presence of syndromes other than Noonan's syndrome, and the presence of aortic regurgitation at presentation. Figure 4 shows the clear separation in time related survival in patients with mild, moderate, and severe aortic stenosis at presentation when adjusted for the presence of the risk factors of age at presentation and Noonan's syndrome. The data in fig 4 indicate that 30 year survival is predicted to be 95.3% for such a patient presenting with mild stenosis, 72.9% for one with moderate stenosis, and 12.0% for one with severe stenosis.

FOLLOW UP

Figure 5 shows the distribution of the severity of aortic stenosis in survivors at follow up. With increasing duration of follow up, there was a reduction in the proportion of patients with moderate stenosis and an increase in the number with no stenosis. The proportion of patients with mild stenosis remained fairly

Table 6 Current status of patients with supravalue aortic stenosis (SVAS) alone and those with multilevel obstruction*

	SVAS alone	Multilevel obstruction
Mild stenosis	20 (32.2)	
Moderate stenosis	7 (11.3)	
Surgery and survived	23 (37.1)	6 (31.6)
Lost to follow up	6 (9.7)	3 (15.8)
Died	6 (9.7)	10 (52.6)

Values in parentheses are percentages. *Each patient appears once.

constant at between 60 and 75%. Table 6 shows the current clinical status of all patients.

Discussion

Supravalve aortic stenosis is a rare condition. Only careful follow up of patients over a long period provides an insight into its prognosis. This study comprised the largest group of patients followed from presentation. Most patients were traced and re-examined, and the duration of follow up in survivors allowed predictions of the prognosis into adult life.

INTERVENTION

Although only 47 patients (58%) underwent intervention during the study period, hazard analysis indicated that more patients are likely to undergo intervention the longer the duration of follow up (fig 1). Patients with other levels of left ventricular outflow tract obstruction have also shown progression with time,^{1,7,12} but this has not previously been confirmed in a large group of patients with supravalve aortic stenosis. The emergence of increasing severity of aortic stenosis at presentation as a risk factor for intervention, as found in this study, has also been documented in patients with other levels of left ventricular outflow tract obstruction.^{1,7} In general, the presence of multilevel obstruction was closely related to more severe aortic stenosis at presentation, but this was not the case in patients with sporadic supravalve aortic stenosis. Therefore, for the purposes of predicting the likely time intervention, the occurrence of multilevel obstruction in patients with sporadic supravalve aortic stenosis emerged as a significant risk factor, in addition to the information provided by the severity of aortic stenosis at presentation. Noonan's syndrome is a very rare association with supravalve aortic stenosis¹³ and the atypical nature of the two patients with this syndrome was confirmed in the requirement for additional interventions. These two patients had additional severe pulmonary valve stenosis and intervention was also combined with relief of this obstruction.

SURVIVAL

Mortality was highest in patients with multilevel obstruction and this indicates the serious nature of this particular condition. Difficulties in the management of patients with multilevel obstruction are reflected in the high postoperative mortality in this group. Hazard analysis predicted that 66% of the study group would be alive after 30 years of follow up, and multivariable analysis indicated that the severity of aortic stenosis at presentation significantly influenced survival. Figure 4 shows the predicted risk of premature death for patients with an identical distribution of risk factors—that is, risk adjusted, in all respects other than the severity of aortic stenosis. Therefore it represents the true effect of the severity of aortic stenosis at presentation on survival. A natural order emerged in terms of premature death with increasing severity of stenosis at presentation, which has also been found in patients

with other levels of left ventricular outflow tract obstruction.^{1,7}

The age of the patient at presentation was also shown to modify survival significantly, with younger patients having a poorer outcome. Similar findings have been documented in patients with other levels of left ventricular outflow tract obstruction.^{1,7,13} Patients with supravalve stenosis and Noonan's syndrome had a particularly poor survival record, probably because of their associated cardiac conditions. Patients with more than one level of left ventricular outflow tract obstruction are reported to have a worse prognosis than those with a single level of stenosis,^{14,15} but multivariable analysis has not previously been performed in relation to patients with supravalve aortic stenosis. Perhaps surprisingly, multilevel obstruction did not emerge as a significant risk factor for death. The severity of aortic stenosis at presentation was found to correlate closely with the presence of multilevel obstruction. The significantly higher mortality in patients with multilevel obstruction than in patients with supravalve aortic stenosis alone is thus accounted for by their differences in the severity of aortic stenosis at presentation.

Multilevel obstruction is more common in patients with supravalve aortic stenosis than in those aortic valve stenosis. It occurs in 20–45% of patients with supravalve aortic stenosis,^{4,16,17} whereas less than 10% of patients with aortic valve stenosis have other levels of obstruction.^{1,16,18} Diffuse supravalve stenosis is reported in 15–24% of patients,^{2,17,18} but was lower in the current study. These patients generally have a worse prognosis than those with localised obstruction,^{2,19,20} but again, diffuse stenosis did not emerge as a risk factor for death or intervention in this study due to a high degree of association with other identified risk factors.

FOLLOW UP

The proportion of patients with mild stenosis remained reasonable constant (fig 5). Although progression of stenosis occurred with time in patients who presented with mild stenosis, others who presented with moderate or severe stenosis underwent operation which resulted in mild residual stenosis at follow up. Other patients had complete relief of the obstruction, so the number of patients with no stenosis also increased with time. The decline in the proportion of patients with moderate stenosis with time results from intervention, as no patient improved without it.

CONDITIONS ASSOCIATED WITH SUPRAVALVE AORTIC STENOSIS

Patients with supravalve aortic stenosis commonly have associated conditions. Williams' syndrome was the most common condition associated with supravalve aortic stenosis and it occurred more frequently than previously reported.^{2,20,21} No patient with Williams' syndrome required reoperation. Patients with Williams' syndrome had a relatively good prognosis with a 10% mortality, as found in another study.⁶

Familial supravulve aortic stenosis occurred almost half as frequently as Williams' syndrome, with an incidence similar to that in other series.^{2,22} In a study by Johnson *et al*,²³ the mean age at presentation was 14 years. With the use of cross sectional and Doppler echocardiography,^{5,23} early diagnosis is possible. Patients in the current study presented at a younger age than those with Williams' syndrome, probably because the family history encouraged early cardiac assessment.

The incidence of sporadic supravulve aortic stenosis (22%) was a little lower than in other series,^{2,22} possibly because of careful clinical assessment for features of Williams' syndrome and a family history of supravulve aortic stenosis. The relatively older age at presentation in this group may have been because patients with Williams' syndrome or a family history were likely to undergo cardiac examination at a younger age. Reoperation was more common in patients with sporadic supravulve aortic stenosis. This reflects the significantly higher incidence of multilevel obstruction in patients with sporadic supravulve aortic stenosis than in with Williams' syndrome or familial supravulve aortic stenosis and inadequate relief of stenosis at initial operation.

Rubella syndrome is known to be associated with supravulve aortic stenosis,²⁴ and patients with Shone's syndrome have left ventricular outflow obstruction²⁵ which can include supravulve aortic stenosis. The association of Noonan's syndrome with supravulve aortic stenosis is extremely rare. The incidence of these syndromes was low but all had multilevel obstruction. In some ways they were not representative of patients with supravulve aortic stenosis. However, multilevel obstruction did occur in other patients with supravulve aortic stenosis, so it was considered that these patients should not be excluded. Patients with these syndromes presented at a young age, all had other cardiac lesions, and all required surgery for supravulve aortic stenosis. They had the highest mortality of any subgroup, which consisted entirely of early postoperative deaths. Noonan's syndrome emerged as a significant ($P < 0.02$) risk factor for intervention and death because of unsuccessful attempts to relieve the coexistent severe right ventricular outflow tract obstruction.

The incidence and distribution of other cardiac lesions was similar to that in other published series.^{6,17} The most common lesion was peripheral pulmonary artery stenosis, which occurred in patients with Williams' syndrome and those with the familial types of supravulve aortic stenosis, but was also found in patients with sporadic supravulve aortic stenosis. The higher incidence of aortic arch obstruction in patients with multilevel obstruction emphasises the diffuse nature of left ventricular outflow tract obstruction.

Infective endocarditis occurs in patients with supravulve aortic stenosis¹⁸ but was not encountered in this study. Sudden death did not occur in any patient in this study but it has been reported, in relation to severe supravulve

aortic stenosis and obstruction of coronary ostia in patients with mild stenosis.^{18,26}

Conclusions

Patients with severe supravulve aortic stenosis present early and undergo intervention at a young age. Patients who present with moderate or mild stenosis fare better, but most will require intervention. Most survivors will have mild stenosis.

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Appendix

VARIABLES ENTERED INTO MULTIVARIABLE ANALYSES OF FREEDOM FROM FIRST INTERVENTION AND DEATH AT ANY TIME

Demographic age at presentation (with transforms), sex. *Clinical* aortic stenosis severity at presentation (with transforms), presence of aortic regurgitation, presence of Noonan's, rubella, Shone's or Williams' syndrome, and familial supravalve aortic stenosis.

Institutional interval from first patient presenting to Royal Liverpool Children's Hospital to date of presentation (with transforms).

Morphology level of obstruction: diffuse or localised supravalve aortic stenosis. These factors were considered as isolated potential risk factors and as interactive terms (product of two potential risk factors).

FREEDOM FROM FIRST INTERVENTION AT ANY TIME AFTER PRESENTATION

Parameter estimates: single declining hazard phase $\mu_3 = 0.04210502$, $\tau = 1$, $a = 1$, $\gamma = 1$, $\eta = 0.651$.

Shaping parameter estimates and the regression

coefficients, standard deviations, and p values (in parentheses) of the multivariable risk factor equation: $\tau = 1$, $a = 1$, $\gamma = 1$, $\eta = 0.265$, intercept = 0.00055946, aortic stenosis severity at presentation - 1, multiplied by interval from first patient presenting to Royal Liverpool Children's Hospital to date of presentation¹ 0.010 (0.001) ($P \leq 0.0001$), presence of multilevel obstruction (in patients with sporadic supravalve aortic stenosis) 1.436 (0.389) ($P = 0.002$), presence of Noonan's syndrome 1.586 (0.703) ($P = 0.033$).

FREEDOM FROM DEATH AT ANY TIME AFTER PRESENTATION

Parameter estimates: single declining hazard phase $\mu_3 = 0.02312534$, $\tau = 1$, $a = 1$, $\gamma = 1$, $\eta = 0.488$.

Shaping parameter estimates and the regression coefficients, standard deviations, and p values (in parentheses) of the multivariable risk factor equation: $\tau = 1$, $a = 1$, $\gamma = 1$, $\eta = 0.610$, intercept = 0.00054268, aortic stenosis severity at presentation 1.899 (0.40) ($P \leq 0.0001$), age at presentation (natural logarithmic transform) -0.386 (0.12) ($P = 0.001$), presence of Noonan's syndrome 2.222 (0.89) ($P = 0.013$).

¹This variable was created for each patient in the study from the transformation of severity of aortic stenosis (by subtracting 1) and multiplying it with the interval from first patient to each patient's date of presentation, and was necessary to reflect the increasing probability of intervention with experience of the hospital in correcting supravalve aortic stenosis.