Pathology of coronary arteries, myocardium, and great arteries in supravulvular aortic stenosis

Report of five cases with implications for surgical treatment

Among five patients with supravulvular aortic stenosis in whom autopsy tissues were available, all were male, 1½ to 39 years old (mean 10 years, median 3 years), and the four children had Williams-Beuren syndrome (two familial, two sporadic). Medial thickening and dysplasia (disorganization) characterized the aortic sinotubular junction of three patients with discrete disease and the entire ascending aorta and arch branches of the two with diffuse disease. Medial dysplasia also involved the pulmonary arteries in each case, but less severely than the aorta. Dysplasia of coronary arteries was observed in all five hearts and was more obstructive proximally than distally, in cases with diffuse than discrete aortic disease, and in the adult than in the two children with discrete supravulvular aortic stenosis. All major epicardial arteries were involved, without predilection for any particular vessel. In contrast to the great arteries, coronary artery dysplasia involved all three layers, not just the media. To varying degrees, vessels showed intimal hyperplasia, fibrosis, and disorganization (dysplasia); disruption and loss of the internal elastic membrane, with indistinct intimal-medial junctions; medial hypertrophy and dysplasia; and adventitial fibroelastosis. In severe cases, the microscopic structure resembled that of the ductus arteriosus. Acute intramedial dissections were observed in the ascending aorta and distal right coronary artery in one patient each. Chronic microfocal ischemic fibrosis was identified in the subendocardium and papillary muscles of the left ventricle in four patients, and the adult patient also had an acute myocardial infarction. In summary, these findings emphasize the extraaortic extent of supravulvular aortic stenosis and the development of ischemic heart disease even in childhood. The presence of severe coronary obstruction in the adult with discrete aortic disease suggests that chronic high pulsatile coronary blood pressure may favor the proliferation of dysplastic tissue. Early surgical intervention may minimize the degree of proliferation, as well as allow regression of left ventricular hypertrophy, thereby lessening the risk of myocardial ischemia and aortic dissection. (J THORAC CARDIOVASC SURG 1994;108:21-8)

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Congenital supravulvular aortic stenosis represents a developmental complex that is characterized by localized or diffuse narrowing of the ascending aortic lumen com-

mencing at the sinotubular junction (Fig. 1). Additional manifestations of the complex include stenoses in the pulmonary arteries and proximal aortic arch vessels, aortic valve dysplasia, and coronary ostial stenoses.¹⁻⁵ In a recent review of the Mayo Clinic experience with the surgical treatment for supravulvular aortic stenosis, ostial and distal coronary arterial lesions and myocardial scarring were described from the autopsy reports from patients who died.⁶ These findings prompted us to perform a detailed histologic investigation of the coronary arteries, myocardium, and great arteries in supravulvular aortic stenosis.

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Received for publication Oct. 1, 1993.

Accepted for publication Dec. 8, 1993.

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0022-5223/94 \$3.00 + 0 12/1/54002

Fig. 1. Schematic diagram of discrete and diffuse forms of supravalvular aortic stenosis.

Table I. Pathologic features of five patients with supravalvular aortic stenosis

Case No.	Age (yr)	Year of autopsy	Williams-Beuren syndrome	SVAS type	Grade of dysplasia			Other cardiac lesions
					Asc Ao	Arch branch	PA	
1	2	1978	Familial	Diffuse	3	3	2	Dissection (Asc Ao)
2	3	1959	Sporadic	Diffuse	2	2	2	Dysplastic MV
3	1½	1983	Familial	Discrete	2	0	1	Left coronary ostial stenosis, dysplastic MV, PDA
4	5	1980	Sporadic	Discrete	1	0	1	Dysplastic AV, left SVC, others*
5	39	1985	No	Discrete	3	0	2	Bicuspid AV

Asc Ao, Ascending aorta; Arch branch, aortic arch branches; AV, aortic valve; MV, mitral valve; PDA, patent ductus arteriosus; PA, pulmonary arteries; SVAS, supravalvular aortic stenosis; SVC, superior vena cava.

*Aplastic left parathyroids and left lobe of thymus, horseshoe kidney, and hypospadias.

Patients and methods

From the tissue registry of the Mayo Clinic, five hearts with supravalvular aortic stenosis were identified and reviewed by a cardiac pathologist (W.D.E.). The histologic findings in one heart (Table I, case 2) have been reported previously.⁴ Multiple sections were taken for microscopic examination from the left main coronary artery and from the proximal, middle, and distal regions of the left anterior descending, left circumflex, and right coronary arteries. In addition, in each specimen, myocardial samples were obtained from the antero-septal, anterolateral, and inferior walls of the left ventricle, including both mitral papillary muscles. Sections from the ascending aorta, aortic arch vessels, descending thoracic aorta, main pulmonary artery, and right and left pulmonary arteries were also processed for evaluation of arterial dysplasia or other abnormalities.

Tissues were processed routinely for examination with a light microscope, and sections were stained with hematoxylin and eosin. In addition, all arteries were stained with elastic-van Gieson, and myocardium was stained with trichrome. Coronary artery obstruction was graded on the basis of the percent of

luminal narrowing in cross-sectional area, in 25% increments for grades 1 through 4. Aortic medial dysplasia and myocardial fibrosis were graded semiquantitatively as absent (grade 0) or as mild, moderate, or severe (grades 1 through 3). Moreover, for each specimen, we reviewed the patient's clinical chart and autopsy report and recorded the age, gender, and clinical diagnoses.

Results

Clinical features. All five patients were male. The mean age at the time of death was 10 years (range 1½ to 39 years, median 3 years). The four children had Williams-Beuren syndrome, two familial and two sporadic (see Table I). Additional patient data including the year of autopsy, the type of supravalvular aortic stenosis, and associated cardiovascular and noncardiovascular lesions are summarized in Table I.

Three patients had the discrete form of supravalvular

Fig. 2. Gross pathology of supravulvar aortic stenosis. **A** and **B**, Discrete form shows external constriction (**A**, arrows) and internal thickening at level of aortic sinotubular junction (**B**, *). Note focal fusion of aortic cusp to junctional ridge (arrow). **C**, Diffuse form exhibits marked thickening of aortic wall and walls of brachiocephalic branches. *Asc Ao*, Ascending aorta; *AS*, aortic sinus; *LV*, left ventricle; *PT*, pulmonary trunk; *SVC*, superior vena cava.

Table II. Microscopic grades of coronary artery stenosis and myocardial fibrosis in five male patients with supravulvar aortic stenosis

Case No.	Age (yr)	SVAS type	Grade of stenosis				Grade of LV fibrosis	
			LMA	LAD	LCx	RCA	Pap muscle	Subendo
1	2	Diffuse	3	3	3	3	2	2
2	3	Diffuse	3	1	2	2	2	1
3	1½	Discrete	1	1	1	3	1	1
4	5	Discrete	1	1	1	1	0	0
5	39	Discrete	3	4	3	4	3	3

LAD, Left anterior descending coronary artery; *LCx*, left circumflex coronary artery; *LMA*, left main coronary artery; *Pap muscle*, mitral papillary muscles; *RCA*, right coronary artery; *Subendo*, subendocardial myocardium; *SVAS*, supravulvar aortic stenosis.

aortic stenosis (Fig. 2). Two of these had a history of sudden death, one during repair of hypospadias (case 4) and the other spontaneously (case 3). Patient 5 died of an acute myocardial infarction on the first day after aortic

valve replacement and mitral valvuloplasty, and 9 years after enlargement of the ascending aorta with a teardrop-shaped pericardial patch and decalcification of a focally calcified bicuspid aortic valve.

Fig. 3. Photomicrographs of coronary arteries in supravulvar aortic stenosis. **A.** Normal coronary artery, for comparison. **B.** Distinct intima (*Int*), media (*Med*), and adventitia (*Adv*), with thickening of all three layers. **C.** Severe luminal obstruction caused by wall thickening, with loss of internal elastic membrane, loss of distinction between intima and media, and disorganized (dysplastic) intimal-medial proliferation. **D.** Severe stenosis caused by dysplasia and atherosclerosis in 39-year-old man. **E.** Transition from three distinct arterial layers (*right*) into thickened and disorganized wall with loss of distinction between intima and media (*left*). **F.** Arterial dysplasia associated with focal acute intimal tear (*) and minor intramedial dissection (*arrow*). (Elastic-van Gieson; **A**, $\times 35$; **B** and **C**, $\times 30$; **D**, $\times 15$; **E**, $\times 60$; **F**, $\times 20$.)

Fig. 4. Photomicrograph of myocardium in supralvalvular aortic stenosis with coronary artery obstruction. Chronic ischemic changes include replacement fibrosis (*left*) and sarcoplasmic vacuolization of myocytes (*right*) from mitral papillary muscle. (Hematoxylin and eosin; $\times 200$.)

The remaining two patients (cases 1 and 2) both had Williams-Beuren syndrome and the diffuse form of supralvalvular aortic stenosis; both died intraoperatively of heart failure, one during insertion of a left ventricular-supraceliac aortic valved conduit and the other during enlargement of the ascending aorta with a teardrop-shaped Teflon patch. In both specimens, the ascending aorta, aortic arch, and proximal aortic arch vessels were diffusely thickened and their lumina were markedly narrowed (see Fig. 2).

Pathologic features. Coronary arterial lesions were categorized as congenital or acquired. Congenital lesions consisted of intimal hyperplasia ($n = 5$), intimal fibrosis ($n = 4$), indistinct intimal-medial junction with loss of internal elastic lamina ($n = 5$), medial hypertrophy ($n = 5$), medial disorganization with “woven” fibroelastic pattern ($n = 5$), and adventitial fibroelastosis ($n = 5$) (Fig. 3). In severe cases, this constellation of lesions resulted in a thickened arterial wall that appeared similar in structure to the ductus arteriosus.

In the coronary arteries of the four youngest patients (aged $1\frac{1}{2}$ to 5 years, mean 3 years), there were varying degrees of intimal hyperplasia, intimal fibrosis, and medial hypertrophy. Generally, the grade of luminal narrowing (Table II) was greater in the proximal segments than in the distal segments. In the $1\frac{1}{2}$ -year-old patient with left ostial narrowing caused by focal adherence of the left aortic cusp to the supralvalvular ridge, a lesser degree of intimal hyperplasia and intimal fibrosis was present in the left than in the right coronary system. The heart of the 39-year-old patient showed severe intimal hyperplasia and focal calcific atherosclerosis of the coronary arteries;

in addition, there was a dissection of the distal right coronary artery (see Fig. 3).

All cases exhibited left ventricular hypertrophy. Ischemic myocardial lesions consisted of fibrosis of the anterolateral ($n = 4$) and posteromedial ($n = 4$) papillary muscles, with or without focal calcification, and microfocal fibrosis of the left ventricular subendocardium ($n = 4$) (Fig. 4). In the heart of the 39-year-old patient, an acute myocardial infarction without coronary thrombosis was superimposed on moderate to severe focal subendocardial fibrosis. In one heart (case 4), no ischemic myocardial injury was present, but mild lymphocytic myocarditis with focal myocyte necrosis was evident.

The ascending aorta, aortic arch, main pulmonary artery, and left and right pulmonary arteries showed mild to moderate medial dysplasia ($n = 5$) and medial fibrosis ($n = 3$). Dysplastic vessels were characterized by medial thickening, with haphazard (nonparallel) arrangement of smooth muscle cells, increased collagen deposition, and markedly decreased elastin content (Fig. 5). In the two specimens with the diffuse form of supralvalvular aortic stenosis, the proximal aortic arch vessels were also dysplastic. Except for medial thickening in the two cases of diffuse supralvalvular aortic stenosis, no differences in the histologic findings were detected between cases with or without Williams-Beuren syndrome. The descending thoracic aorta was normal (cases 1 to 4) (Fig. 5) or showed mild focal dysplasia (case 5). In one heart (case 1), a localized dissection of the ascending aorta was associated with acute luminal narrowing without external rupture.

Fig. 5. Photomicrograph of ascending aorta in supravulvular aortic stenosis. **A**, Marked disorganization and loss of elastic elements. **B**, Normal tissue, from distal portion of descending thoracic aorta in same patient, for comparison (Elastic-van Gieson; $\times 260$.)

Discussion

In patients with supravulvular aortic stenosis, blood flow to the aortic sinuses and coronary ostia may be obstructed because of adhesion of the valve cusps to the stenotic supravulvular ridge.⁵⁻¹¹ Left ostial stenosis caused by this mechanism was observed in one of the specimens in the present series. In the absence of such ostial obstruction, the coronary arteries are exposed to both an elevated systolic pressure and a high pulse pressure, which represent appreciable distending forces that may lead to dilatation and tortuosity. In our recently reported series of 80 patients with supravulvular aortic stenosis, dilatation of the right coronary artery was found

in 29% of the patients and dilatation of the left coronary artery in 20%.⁶ As in other series, the higher incidence of dilatation of the right versus the left coronary artery was due to the higher prevalence of left ostial stenosis.^{6, 8-11}

Other secondary structural changes in the coronary arteries that are caused by high systolic pressure in the aortic root include intimal hyperplasia and atherosclerosis. The high smooth muscle content of the media of the coronary artery (as opposed, for instance, to the media of the internal mammary artery, which is mainly elastic) may predispose to these early occurring and progressive processes.^{12, 13} The spectrum of coronary artery disease in supravulvular aortic stenosis, as observed

in the current series, may be explained by the difference in exposure time among the cases. An additional potential complication of the high pressure to which the coronary arteries are exposed is focal dissection of the arterial wall, as occurred in the 39-year-old patient in the present series.

Data from this study illustrate the prevalence of ischemic heart disease among patients with supravulvar aortic stenosis. With coexistent left ventricular hypertrophy, lesions of myocardial ischemia often begin to develop in early childhood.

In patients with supravulvar aortic stenosis as part of the Williams-Beuren syndrome, the most common associated anomalies consist of stenoses in the proximal aortic arch vessels and pulmonary arteries.^{1-3, 5} In the present study, stenoses of the innominate, left common carotid, and left subclavian arteries were observed in two patients with the Williams-Beuren syndrome and the diffuse form of supravulvar aortic stenosis. Proximal and distal pulmonary artery stenoses, extending beyond the first lobar branches, were found in the specimens of all four patients with the Williams-Beuren syndrome. Severe flow disturbance distal to the obstructing ridge at the sinotubular junction may cause dissection of the dysplastic aortic wall, as was seen in a 2-year-old boy in the present series.

In addition, supravulvar aortic stenosis has been reported to be associated with abnormalities of the mitral valve. Becker and colleagues¹⁴ reported on three patients who had uniform thickening of the mitral valve and protrusion of the mitral valve toward the left atrium. The thickening was caused by an increase in fibrous tissue, and two of their three patients also had fibrous chordal thickening. Similar findings have been reported by others.^{5, 15} In our series, two patients with Williams-Beuren syndrome had mitral valve abnormalities consisting of thickening of both leaflets and the attached chordae tendineae.

On the basis of the pathologic findings in the coronary arteries, myocardium, and ascending aorta as presented in this study, we recommend operative treatment of supravulvar aortic stenosis in early childhood, to prevent accelerated coronary artery disease, its detrimental ischemic effects on the myocardium, and dissection of the ascending aorta or coronary arteries. Our experience^{6, 10} and that of others¹⁶⁻¹⁸ indicate that enlargement of the aortic root with a teardrop-shaped or pantaloon-shaped patch leads to excellent long-term results. Alternatively, patching of the three aortic sinuses¹⁹ or circular excision of the stenosis at the level of the sinotubular junction followed by end-to-end anastomosis of the ascending aorta to the aortic root²⁰ may restore a more anatomic configuration to the aortic root, but long-term results

are not available. In diffuse supravulvar aortic stenosis, the entire ascending aorta should be enlarged with a patch, often with extension into the aortic arch and one or more of the proximal aortic arch vessels.⁶ Alternatively, a conduit may be inserted from the ascending to descending aorta with side branches to stenotic arch vessels.⁶

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