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## Left Ventricular Outflow Obstruction

### Subaortic Stenosis, Bicuspid Aortic Valve, Supravalvar Aortic Stenosis, and Coarctation of the Aorta

Jamil Aboulhosn, MD; John S. Child, MD

Left ventricular outflow tract obstructions (LVOTOs) encompass a series of stenotic lesions starting in the anatomic left ventricular outflow tract (LVOT) and stretching to the descending portion of the aortic arch (Figure 1). Obstruction may be subvalvar, valvar, or supravalvar. These obstructions to forward flow may present alone or in concert, as in the frequent association of a bicuspid aortic valve with coarctation of the aorta. All of these lesions impose increased afterload on the left ventricle and, if severe and untreated, result in hypertrophy and eventual dilatation and failure of the left ventricle. LVOTOs are congenital in the vast majority of individuals younger than 50 years in the United States; some variants of subaortic obstruction are the exception. It is imperative to consider all patients with LVOTO at a high risk for developing infective endocarditis, and one should always institute appropriate measures for prophylaxis. The present article is intended as a contemporary review of the causes, manifestations, treatments, and outcomes of LVOTO; it will not address LVOTO in the pediatric population or genetic hypertrophic cardiomyopathy but will focus strictly on congenital malformations in the adult.

#### Subaortic Stenosis

Fixed subaortic stenosis (SAS) may be due to a discrete fibrous membrane (Figures 1 and 2), a muscular narrowing, or a combination of the 2. The obstruction may be focal, as in a discrete membrane, or more diffuse, resulting in a tunnel leading out of the left ventricle. The discrete form of fibromuscular SAS is most frequently encountered (90%), but the tunnel-type lesions are associated with a greater degree of stenosis.<sup>1</sup> Rarely, abnormal accessory mitral valve tissue or chords may cause SAS. SAS may be a congenital isolated lesion but may also be acquired. The prevalence of discrete SAS in adults with congenital heart disease is  $\approx 6.5\%$ ,<sup>2</sup> with a male to female ratio of 2:1. Familial clusters have been reported. Rosenquist et al<sup>3</sup> suggested a plausible explanation for both the initial lesion and the considerable rate of recurrence of SAS. They found that the distance between the mitral and aortic valves in patients with SAS is consistently increased. They hypothesized that the alteration in direction of blood flow near the crest of the interventricular septum

leads to differentiation of embryonic cells into a fibrotic tissue variant. A bicuspid aortic valve (BAV) is present in 23% of patients.<sup>1</sup> SAS may also present as part of a complex of obstructive lesions, as in Shone's complex, which frequently includes parachute mitral valve, mitral stenosis, BAV, and coarctation of the aorta. Thirty-seven percent of patients with SAS may also have concomitant ventricular septal defects (VSDs) of the perimembranous type.<sup>1</sup> Subvalvar obstruction has also been reported after surgical patch closure of malaligned VSDs and is thought to be secondary to fibrous tissue proliferation at sites of turbulent outflow.<sup>4</sup>

The physical examination findings of a patient with mild SAS are outlined in the Table. The ECG is usually normal. Transthoracic echocardiography with Doppler will often demonstrate a focal or diffuse narrowing of the LVOT (Figure 2) with color flow acceleration and a continuous-wave Doppler-derived estimated peak instantaneous systolic gradient that is  $<20$  mm Hg. In the absence of left ventricular hypertrophy, dilatation, or failure, intervention can be deferred, but there should be careful lifelong follow-up for symptoms and progression. Aortic regurgitation may result from damage to the valve by the turbulent systolic jet caused by SAS. The clinical course of SAS is generally progressive, with increasing obstruction and progression of aortic regurgitation in  $>80\%$  of untreated patients, but the degree of aortic regurgitation is mild in the majority of patients.<sup>5-9</sup> Membranes located immediately adjacent to the aortic valve or extending to the anterior leaflet of the mitral valve are more likely to lead to progressive obstruction as well as more likely to cause aortic valve damage with aortic regurgitation. Severe forms of SAS result in an increased gradient across the area of stenosis and are usually evidenced on physical examination by a harsh late-peaking systolic murmur, delayed and diminished peripheral pulses, and a displaced and sustained left ventricular systolic impulse (Table).<sup>10</sup> The ECG may demonstrate evidence of left ventricular hypertrophy and QRS left axis deviation that is indistinguishable from the findings in severe valvar aortic stenosis. Transthoracic and transesophageal echocardiography with Doppler are widely used for identifying and quantifying the severity of SAS. A continuous-wave Doppler-derived peak instantaneous gradi-

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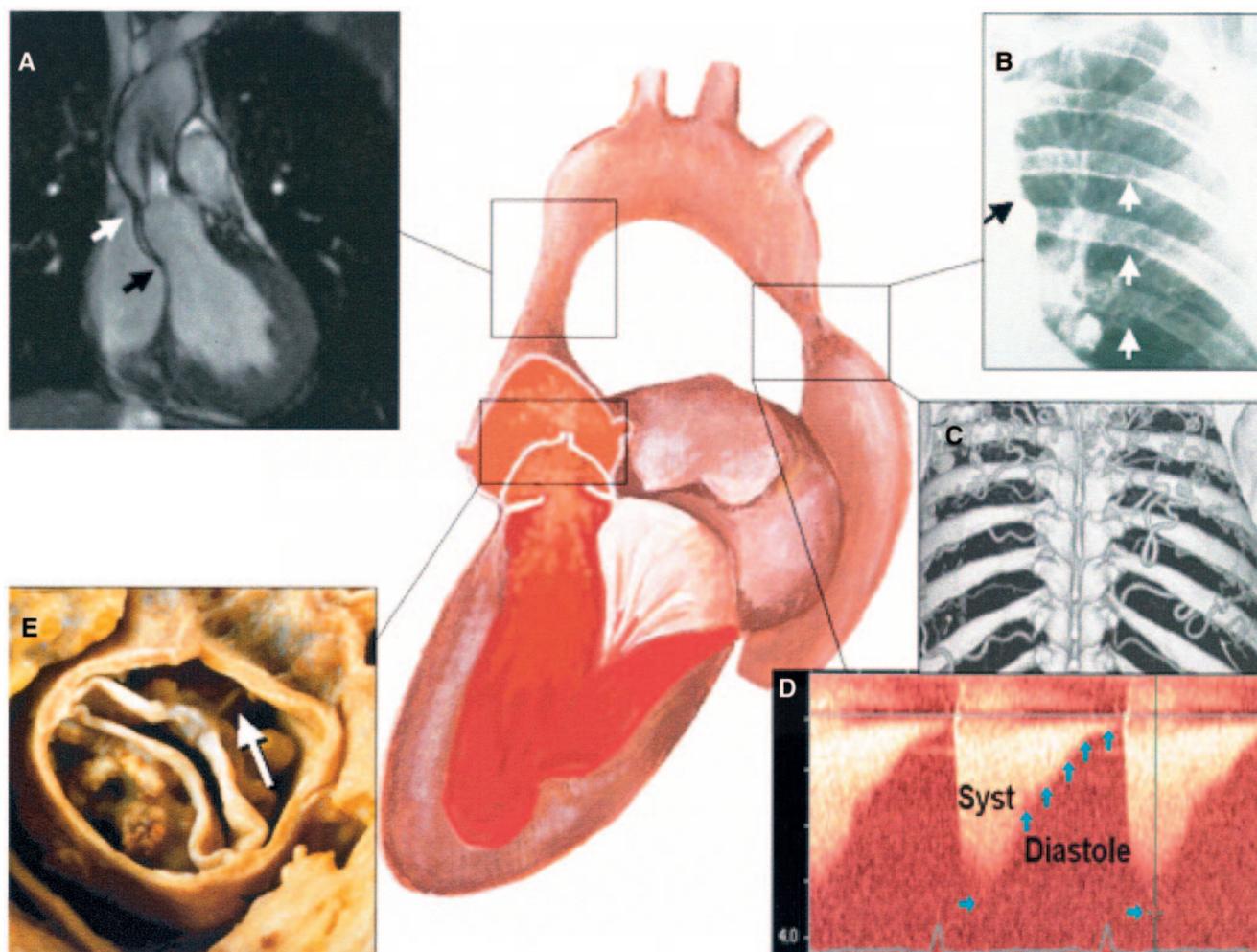
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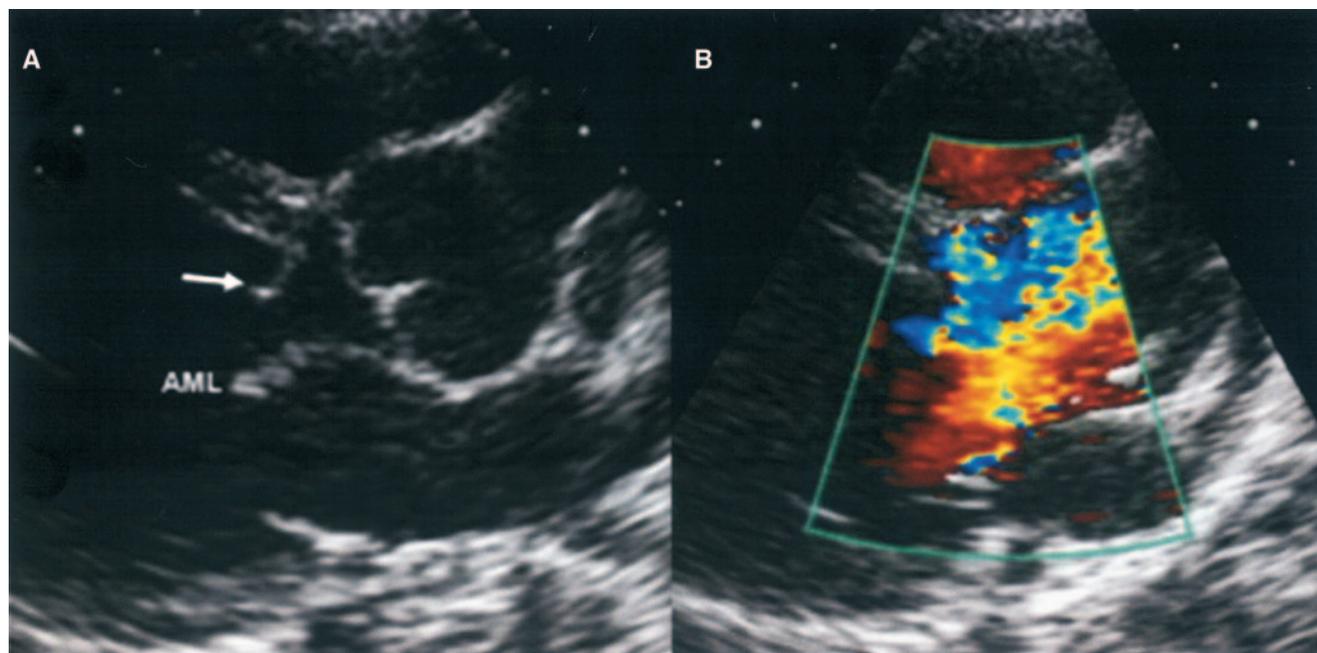


**Figure 1.** Artist's rendering of the LVOTO lesions in sequence as viewed from a superolateral orientation. A, Gradient echo cardiac MR image as viewed from the frontal projection demonstrating flow acceleration at a site of supravulvar aortic stenosis (white arrow) in a patient with Williams syndrome. The black arrow identifies the level of the unrestricted aortic valve. B, Classic radiological signs of coarctation of the aorta: rib notching (white arrows) as seen on a posteroanterior chest x-ray in a patient with coarctation of the aorta. The rib notching is caused by erosion of the inferior rib margins by dilated pulsatile posterior intercostals collateral arteries. The black arrow points to the Figure 3 silhouette that is created by the combination of a dilated left subclavian artery above and a convex dilated descending aorta below the site of coarctation. C, Three-dimensional reconstruction of a cardiac CT angiogram as viewed from the posteroanterior projection, demonstrating a plethora of dilated intercostal collateral arteries in a patient with coarctation of the aorta. D, Continuous-wave Doppler signal through the site of coarctation with a systolic flow velocity of 3.4 m/s (Syst) and a peak pressure gradient of 46 mm Hg. Horizontal arrows point to the peak of the systolic velocity profile. The vertical arrows point to the "diastolic tail," a diastolic pressure gradient at the site of coarctation leading to nearly continuous flow, indicating significant coarctation of the aorta. E, Autopsy specimen of a calcified and stenotic bicuspid aortic valve. The white arrow points to the false raphe. There is fusion of the left and right coronary cusps.

ent of  $\geq 50$  mm Hg is considered severe and portends a poor prognosis if left untreated.<sup>11</sup> Invasive cardiac catheterization is usually unnecessary unless echocardiography is equivocal. Magnetic resonance (MR) imaging can also be used to clarify anatomy and quantify flow velocity.

The primary hemodynamic effect on the left ventricle is one of increased afterload, resulting in increased intracavitary pressure and wall stress. In accordance with La Place's law, the ventricle hypertrophies in an attempt to reduce wall stress. Patients may present with one of the triad of symptoms associated with severe valvar aortic stenosis: angina, heart failure, or syncope. Because of the small number of patients reviewed in available case series, the prognostic significance of these symptoms has not been confirmed in patients with

SAS but can be reasonably inferred from available outcomes data in patients with valvar aortic stenosis.<sup>12</sup> However, in a series of 75 pediatric and adult patients who underwent surgical SAS resection at University of California at Los Angeles (UCLA), the severity of presenting symptoms did not correlate with the preoperative LVOT gradient but did correlate with the presence of a VSD in 54% of symptomatic patients.<sup>1</sup> Patients with SAS are at a high risk for developing infective endocarditis, which frequently involves the aortic valve<sup>13,14</sup> and often leads to aortic regurgitation. The aortic valve is in harm's way even in the absence of endocarditis. The high-velocity systolic jet collides with the aortic valve leaflets and results in damage, scarring, leaflet redundancy, and prolapse that makes the valve more likely to fail and more



**Figure 2.** A, Transthoracic echocardiogram in the parasternal long-axis orientation demonstrating a discrete subaortic membrane (white arrow) during diastole. The anterior mitral leaflet is labeled (AML). B, Color-flow Doppler in systole demonstrating flow acceleration at the subaortic membrane well below the level of the aortic valve.

susceptible to clot and vegetation formation. Once the Doppler-derived LVOT gradient reaches  $\geq 50$  mm Hg, there is an increased risk of moderate to severe aortic regurgitation.<sup>15</sup> Some degree of aortic regurgitation occurs in  $>50\%$  of patients with SAS, and moderate or severe aortic regurgitation occurs in 12% of patients.<sup>1</sup> Surprisingly, BAVs in the presence of SAS are not more prone to regurgitation than tricuspid aortic valves. The degree of SAS may be underestimated by the pressure gradient in the presence of depressed left ventricular function or a nonrestrictive VSD that allows left to right shunting to the pulmonary arterial circulation.

Surgical resection is the intervention of choice for treatment of SAS and is usually done via a transaortic approach. Surgical mortality is low, and complications are generally minimal.<sup>16</sup> Patients with a resting catheter-determined or

Doppler-derived estimated peak instantaneous pressure gradient of  $\geq 50$  mm Hg have severe SAS and should undergo operative resection of SAS.<sup>11</sup> Surgical intervention should be considered in patients with lower gradients (peak instantaneous pressure gradient  $<50$  mm Hg) if there is left ventricular systolic dysfunction, moderate/severe aortic regurgitation, or a VSD. Development of symptoms attributable to SAS (angina, dyspnea, or syncope/presyncope) with or immediately after exertion should prompt surgical intervention. Asymptomatic patients planning to become pregnant or wishing to participate in competitive sports should be considered for SAS resection if the gradient is  $\geq 30$  mm Hg. Surgical management consists of discrete membrane excision and/or blunt dissection in focal SAS with focal septal myectomy. Tunnel-type SAS is more surgically challenging

#### Characteristic Physical Examination Findings in LVOTO

Diagnosis	Mild/Moderate Stenosis	Severe Stenosis
SAS	1-2/6 MSM at LUSB/RUSB, may radiate to carotids, nonsustained/nondisplaced LV impulse. EDM at LLSB in patients with AR.	$>3/6$ late-peaking MSM at LUSB/RUSB radiating to carotids. LV impulse laterally displaced and sustained. Diminished and delayed arterial pulses. S4 gallop is common. EDM at LLSB in patients with AR.
BAV	1-2/6 MSM at LUSB/RUSB, may radiate to carotids. ES heard at apex/LLSB if age $<40$ years. Nonsustained/nondisplaced LV impulse. EDM at LLSB in patients with AR.	$>3/6$ late-peaking MSM at LUSB/RUSB radiating to carotids. LV impulse laterally displaced and sustained. Diminished and delayed arterial pulses. No ES. S4 gallop is common. EDM at LLSB in patients with AR.
SVAS	1-2/6 MSM at RUSB, often radiates to carotids. Nonsustained/nondisplaced LV impulse.	$>3/6$ late-peaking MSM at RUSB radiating to carotids. LV impulse laterally displaced and sustained. S4 gallop is common.
Aortic coarctation	Absent or mild brachial to femoral pulse delay. 0-1/6 paraspinal MSM may be present.	Significantly decreased/absent and delayed femoral pulses. $>2/6$ paraspinal MSM or continuous murmur. Atrophy of lower extremity musculature compared with upper extremity.

MSM indicates midsystolic murmur; EDM, early diastolic murmur; AR, aortic regurgitation; LUSB, left upper sternal border; LLSB, left lower sternal border; RUSB, right upper sternal border; LV, left ventricle; ES, ejection sound; and S4, fourth heart sound.

and often necessitates concomitant myectomy or application of the Konno-Rastan procedure to reconstruct the LVOT.<sup>1,17,18</sup> Concomitant repair of the aortic valve is performed if aortic regurgitation severity is more than mild. SAS recurs in up to 37% of cases after surgical resection.<sup>1</sup> In this series, tunnel-type SAS recurred in 71% of patients versus a 14.7% recurrence rate for discrete SAS over 6 years of follow-up. Even discrete SAS was far more likely to recur, however, if the resting preoperative gradient was >40 mm Hg. The presence of an immediate postoperative gradient of >10 mm Hg led to progressive recurrent SAS in 75% of patients; therefore, considerable attention must be paid by a qualified surgeon to the excision of all abnormal tissue to include myectomy of the base of the membrane and removal of the membrane from the anterior mitral leaflet. Time to recurrence depends on SAS type; the tunnel-type lesions recur earlier than the discrete lesions.

Progressive aortic regurgitation may develop despite relief of SAS and absence of or surgical repair of aortic regurgitation. Persistently turbulent flow patterns in the LVOT after SAS resection may continue to cause valve damage. In the surgical series by Brauner et al,<sup>1</sup> a higher preoperative LVOT gradient predicted late progression of aortic regurgitation. Other investigators have reported less postoperative aortic regurgitation in patients who underwent SAS resection at a young age or had a low LVOT gradient.<sup>19–21</sup> It is reasonable to consider surgery at the time of diagnosis even in patients with low gradients if late outcome can be safely improved by this strategy. However, this early aggressive approach should be weighed against the significant incidence of recurrent obstructive lesions even in patients with low LVOT gradients.<sup>8,22,23</sup> Therefore, although surgical resection is the treatment of choice for this disease, the optimal timing for surgery can be elusive. Percutaneous balloon dilation of a fixed focal stenosis causes short-term improvement in the gradient and may be considered for palliation of SAS.<sup>22,24</sup> The long-term effects of percutaneous balloon intervention for SAS are uncertain.

### Bicuspid Aortic Valve

BAV is one of the most common congenital cardiovascular malformations, with an estimated incidence of 1% to 2%.<sup>25</sup> An echocardiographic survey of primary school children demonstrated a BAV prevalence of 0.75% in males and 0.24% in females.<sup>26</sup> The true prevalence of BAV in newborns was determined in a recent study of 1075 neonates screened by echocardiography.<sup>27</sup> BAV was identified in a prevalence of 4.6 per 1000 live births. The prevalence of BAV by sex was 7.1/1000 in male neonates and 1.9/1000 in female neonates. BAV is sometimes inherited, and family clusters have been studied. Inheritance patterns are autosomal dominant with variable penetrance.<sup>28,29</sup> Prevalence among asymptomatic family members of patients with BAV was 37% by echocardiographic screening. First-degree relatives of patients with various types of LVOTO are at an increased risk of having BAV compared with the general population.<sup>30</sup>

BAVs arise from abnormal valvulogenesis and cusp formation, resulting in the formation of 1 smaller cusp and 1 larger cusp. Variants range from a nearly trileaflet bicommissural valve with mild cuspal inequality to a unicuspid unicommissural valve.

The aortic root tissue structure is invariably abnormal. The histology of the ascending aortic wall is similar to that of the Marfan syndrome.<sup>31</sup> Medial disease is present, as are varying degrees of abnormality of the smooth muscle, extracellular matrix, elastin, and collagen.<sup>25,31–33</sup> Although aortic dilatation above a stenotic BAV has previously been attributed to “poststenotic” turbulence, several studies have clearly demonstrated that dilatation and histological abnormalities of the ascending aorta in BAV occur irrespective of the degree of valvar stenosis or regurgitation.<sup>31,34</sup> Dilatation of the ascending aorta may be the result of a number of factors including the disruption of the extracellular matrix by upregulation of matrix metalloproteinase-2 that is triggered by an inherent deficiency of fibrillin 1.<sup>25,35–39</sup> Moreover, premature smooth muscle cell apoptosis leads to upregulation of matrix metalloproteinase-2.<sup>40</sup> BAV is likely a genetic disorder, and multiple genes have been implicated. Endothelium-derived nitric oxide synthase has also been implicated because mice deficient in this gene frequently develop BAV.<sup>41</sup> Mutations in the signaling and transcriptional regulator *NOTCH1* result in developmental aortic valve abnormalities and severe valve calcification in affected families.<sup>42</sup> Another potential candidate is the ubiquitin fusion degradation 1-like gene, which is highly expressed in the cardiac outflow tract during embryogenesis and is downregulated in patients with BAV.<sup>43</sup>

BAV disease is gradually progressive in the majority of cases. Severe cuspal inequality or a unicuspid valve portend a poor unoperated prognosis with accelerated stenosis at an early age.<sup>44,45</sup> This is in part due to the small orifice area, decreased cusp flexibility, and excessive wall stress on the valvar apparatus during systole.<sup>46–48</sup> A normally functioning BAV is characterized by abnormal folding and creasing throughout the cardiac cycle, extended areas of valve contact, turbulent flow, and restricted motion.<sup>49</sup> These stresses lead to valve damage, scarring, calcification, and resultant stenosis and regurgitation. Turbulent flow into the ascending aorta, when added to the aforementioned intrinsic medial abnormalities, contributes to progressive dilatation and an increased likelihood of rupture or dissection.<sup>49,50</sup> The histopathology of a BAV includes inflammation, fibrosis, calcification, neoangiogenesis, and bone formation.<sup>25,36,44,45,51–54</sup> Atherosclerotic changes have been identified in BAV and are similar to those seen with calcific degenerative stenosis of trileaflet aortic valves. Moreover, the presence of dyslipidemia appears to be associated with accelerated progression of BAV stenosis.<sup>55,56</sup>

Aortic stenosis is the most common complication of BAV. The physical examination findings in patients with BAV are similar to those with SAS and are listed in the Table. However, patients with a mobile BAV have an ejection sound after the first heart sound best heard at the apex. This ejection sound is present until valve calcification restricts mobility. A midsystolic murmur is present whose harshness and time to peak correlate with degree of stenosis (Table). Concomitant aortic regurgitation results in an early diastolic murmur; when well heard at the right midsternal border, it suggests the presence of a dilated ascending aorta. Evidence of echocardiographic sclerosis can be seen as early as the second decade

of life.<sup>57</sup> Thickening and calcification often occur in the fourth decade and are readily identified by echocardiography, computed tomography (CT), and MR imaging (Figure 3A). Only 15% of patients with BAV have a normally functioning valve in the fifth decade.<sup>44</sup> Two thirds of patients with BAV eventually develop aortic stenosis; patients with BAV make up >50% of cases with clinically significant aortic stenosis.<sup>44,45,58</sup> Moreover, a BAV predisposes patients to the development of aortic regurgitation. Progression to aortic stenosis and aortic regurgitation is fastest in BAV with a posteroanterior cusp relationship.<sup>57</sup> Progression of aortic regurgitation may occur via several mechanisms and in most cases is directly correlated with the degree of aortic root and annular dilatation (although the aortic valve does not have a "true" annulus).<sup>59</sup> Other mechanisms include leaflet prolapse, degeneration, and retraction, each accelerated by infective endocarditis. Infection may cause leaflet destruction and perforation along with intimal dissection leading to a sudden worsening of aortic regurgitation; acute severe left ventricular volume overload is poorly tolerated hemodynamically and may be a surgical emergency. Aortic dissection is an infrequent but dreaded complication. Aorto-cervicocephalic arterial dissections, usually involving an aneurysmal right brachiocephalic artery, can occur and may be familial.<sup>60</sup> Asymptomatic patients with a peak transvalvar systolic velocity of  $\geq 4$  m/s are likely to develop symptoms related to stenosis (dyspnea, chest pain, syncope) within 5 years.<sup>61</sup>

The ascending aorta has been reported to gradually dilate at a mean 0.9 mm/y (Figure 3B).<sup>62</sup> The risk of dissection in patients with BAV is estimated to be 5 to 9 times that of the general population<sup>63,64</sup> and is highest in cases with concomitant coarctation. Unfortunately, aortic valve repair or replacement has not prevented progressive root dilatation.<sup>65</sup> Surgery to repair or replace the aortic root should be considered when the root diameter is  $>5$  cm or if the rate of increase in diameter is  $>0.5$  cm/y. Yearly imaging of the aortic root and ascending aorta is indicated in patients with a dilated aortic root ( $\geq 4$  cm). We perform yearly transthoracic echocardiography and have increasingly utilized CT and MR angiography over the past decade to quantify extent of dilatation and as the primary imaging modality when the aortic root or ascending aorta cannot be assessed accurately by echocardiography.

There are currently no proven medical therapies that alter the course of aortic stenosis, regurgitation, or aneurysmal root dilation.  $\beta$ -Blockers may retard the progression of ascending aortic dilation and thus are a reasonable therapy to institute, although this positive effect has only been demonstrated in Marfan syndrome.  $\beta$ -Blockers should be avoided in patients with severe aortic regurgitation. Patients with aortic regurgitation may benefit from angiotensin-converting enzyme inhibitors, hydralazine, or calcium channel blockers.<sup>66–69</sup> However, a recent randomized prospective trial of enalapril or nifedipine versus placebo in severe aortic regurgitation revealed no differences in regurgitant volume, left ventricular size, or ejection fraction over 7 years of follow-up.<sup>70</sup> Although none of these medications have been tested specifically in a population with BAV, the possible beneficial effects on delaying progression of aortic regurgitation and

maintaining ventricular volume and function may be reasonably applied to patients with BAV who are hypertensive. Atherosclerosis may play a role in BAV sclerosis and stenosis, as has been demonstrated in calcific trileaflet aortic stenosis. Statins have shown promise in delaying progression; however, in a recent large prospective randomized trial, they did not halt the progression of or cause the regression of stenosis in advanced calcific aortic valve disease.<sup>71</sup> One critique of this trial is that patients were selected only if they had evidence of calcium deposition on the aortic valve, and thus one cannot conclude that statins have no effect in delaying progression to stenosis of a noncalcified BAV. Clearly, further prospective, randomized, multicenter clinical trials are required to answer this question. Our practice at UCLA is to prescribe low-dose aspirin to patients with BAV in the hope of possibly delaying inflammatory progression of stenosis. When the public health burden of this disease is considered, any benign therapy with the potential to reduce progression of aortic valve and root disease would have immense global benefits.

Once severe aortic valve stenosis is symptomatic, surgical or percutaneous interventions should be performed.<sup>72</sup> Because stenosis is secondary to bicuspid commissural fusion, balloon valvuloplasty may safely decrease the gradient and improve symptoms in those without a calcified valve.<sup>73,74</sup> Surgical repair or replacement is indicated for patients with severe stenosis (peak instantaneous Doppler velocity of  $\geq 4$  m/s) who are symptomatic or have left ventricular systolic dysfunction. Surgery should also be considered in those with less severe stenosis who have concomitant moderate or severe aortic valve regurgitation or a dilated ascending aorta ( $\geq 45$  mm).<sup>72</sup> Asymptomatic patients with severe BAV stenosis who desire to become pregnant or to exercise more vigorously should also be considered for surgery. Severe aortic regurgitation, if associated with symptoms, severe aortic root enlargement, or left ventricular dilation and dysfunction, should be surgically corrected. Various surgical techniques have been used to repair or replace the aortic valve. Older surgical valvuloplasty techniques often resulted in recurrent stenosis or worsening regurgitation. Current valve repair has shown promising results and should be considered if the valve is not calcified.<sup>75</sup> If valve replacement is needed, bioprosthetic valves are generally preferred in patients older than 65 years, women of child-bearing age wishing to avoid warfarin, or patients refusing to take or allergic to warfarin. These valves function well for 1 to 2 decades, then generally deteriorate and require replacement because of stenosis or regurgitation. Mechanical prostheses have superior durability in patients who can tolerate warfarin. The Ross procedure has been used in patients with BAV.<sup>76</sup> This procedure involves excision of the diseased aortic valve and aortic root with subsequent placement of a pulmonary autograft in the aortic position with reimplantation of the coronary arteries into the "neo-aorta" (previously the patient's pulmonary trunk). An aortic homograft is usually placed in the pulmonary position. This surgical technique is especially favored in patients with infective endocarditis. After the Ross procedure, patients are at risk for developing neo-aortic dilatation, progressive aortic regurgitation, neopulmonary

homograft regurgitation, or myocardial ischemia. Aortic root repair or replacement with coronary artery reimplantation should be considered in patients with a dilated aortic root.

### Supravalvar Aortic Stenosis

Supravalvar aortic stenosis (SVAS) is the rarest lesion of the LVOTs. The defining feature is a focal or diffuse narrowing starting at the sinotubular junction and often involving the entire ascending aorta with rare involvement of the aortic arch and peripheral arterial system.<sup>77,78</sup> SVAS is frequently associated with Williams-Beuren syndrome, a multisystem disorder with an autosomal dominant inheritance pattern that occurs in 1 of 20 000 births.<sup>79</sup> Affected patients are developmentally delayed and have SVAS 71% of the time; pulmonary artery stenosis and mitral valve prolapse are common associated findings.<sup>80</sup> Besides its association with Williams syndrome, SVAS occurs in an autosomal inherited form and in a rare sporadic form. In all 3 types, the underlying cause has been identified as a mutation of the elastin gene on chromosome 7q11.23.<sup>81–83</sup> In patients with Williams syndrome, the mutation of the elastin gene is accompanied by deletion or disruption of several neighboring genes that accounts for the multisystem involvement in this syndrome. Sporadic or inherited forms of isolated SVAS are caused by point mutations or loss of function translocations specifically within the elastin gene. The main histological feature in SVAS is the reduction in and disorganization of elastin fibers within the aortic media.<sup>84</sup> An increased number of hypertrophied smooth muscle cells and increased collagen content within the media have also been described. The reduced and disorganized elastin fibers translate into reduced elasticity and increased shear stress within the ascending aorta, which provokes smooth muscle hypertrophy and increased collagen deposition leading to SVAS.

The physical examination signs of SVAS are outlined in the Table. The diagnosis of SVAS can be made by multiple imaging modalities. In our experience, MR and CT angiography provide excellent visualization of the ascending aorta and aortic arch and should be used to delineate the extent of SVAS (Figure 1A). Cardiac catheterization and invasive angiography have traditionally been used for diagnosis and quantification of severity of SVAS. Transthoracic Doppler echocardiography is useful in deriving peak instantaneous and mean pressure gradients.<sup>85</sup> Moreover, the full extent of the ascending aorta is difficult to visualize in adults with transthoracic echocardiography; transesophageal echocardiography is superior. Aortic valve abnormalities occur in 50% of patients, most commonly a BAV.<sup>86</sup> Fatigue stress and shear forces are increased on the aortic valve leaflets in the setting of a poorly distensible sinotubular junction and result in leaflet thickening and damage.<sup>87</sup> Resultant aortic valve dysfunction, stenosis, regurgitation, or a combination of both is the most frequent reason for reoperation and may predict decreased long-term survival.<sup>88,89</sup> Subaortic stenosis occurs in 16% of cases and may contribute to aortic valve damage.<sup>88</sup> Impaired coronary perfusion has been reported and is usually due to varying degrees of aortic valve leaflet adhesion to the narrowed sinotubular junction that restricts diastolic filling of the coronary arteries.<sup>90</sup> The left coronary sinus is most

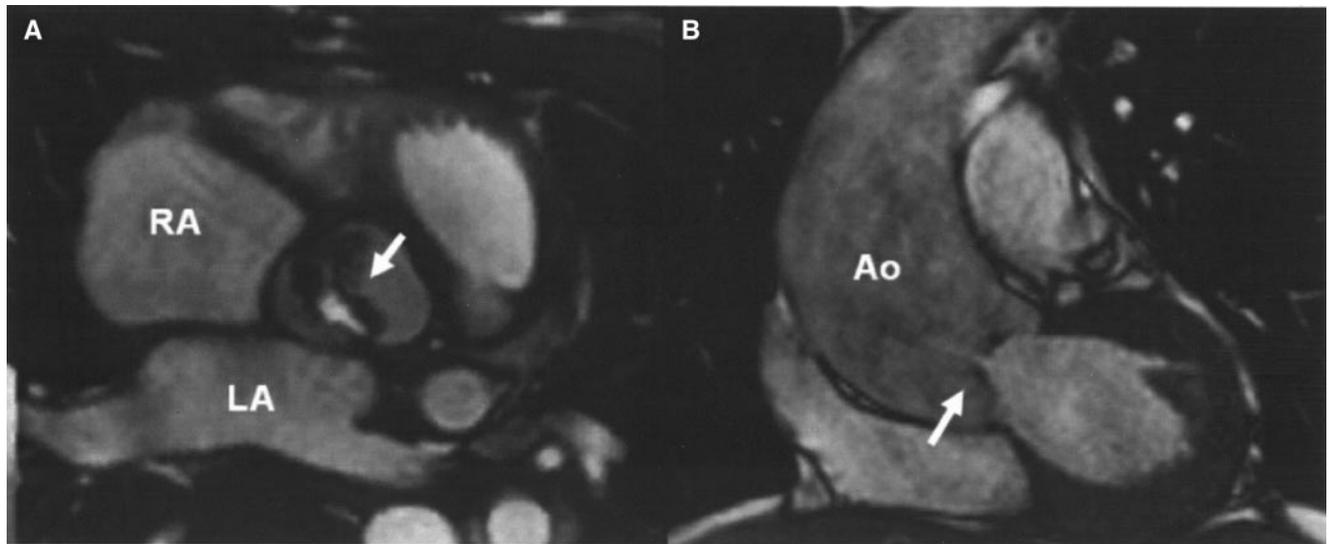
frequently involved.<sup>91</sup> Myocardial ischemia may also be the result of perfusion mismatch due to increased myocardial mass and intramyocardial pressure; this mechanism may play a role in the symptomatology and long-term outcome of all forms of LVOTO described in this review.<sup>92</sup> Furthermore, the coronary arteries are subjected to elevated systolic pressures in SVAS, which leads to dilatation, tortuosity, and accelerated atherosclerosis.<sup>93</sup> Limited data are available on the natural history of SVAS. Sinotubular stenosis increases as does the pressure gradient across the SVAS, in part as a result of the failure of the affected sinotubular junction to grow over time.<sup>94</sup>

Surgical enlargement of the narrowed sinotubular region and adjacent ascending aorta is recommended with symptoms (angina, dyspnea, syncope) or a mean pressure gradient of  $\geq 50$  mm Hg. Relief of obstruction can be achieved by excision of a focal stenosis with end-to-end anastomosis of the ascending aorta, patch enlargement of the sinotubular junction, or more complex aortoplasty involving patch placement into  $\geq 2$  sinuses of Valsalva. The Ross procedure has also been used to replace the aortic root in patients with concomitant aortic valve disease.<sup>95</sup> Some authors have advocated aortic valvuloplasty or valve repair in patients with SVAS and BAV regardless of the presence of stenosis or regurgitation.<sup>86</sup> Balloon angioplasty of SVAS is not useful.

### Coarctation of the Aorta

Morgagni is credited in 1760 with the first description (autopsy) of an aortic coarctation. Coarctation of the aorta usually presents as a discrete narrowing in the region of the ligamentum arteriosum, especially in the newly diagnosed adult.<sup>96,97</sup> More diffuse forms of the disease may involve the arch or isthmus to varying degrees. Coarctation of the aorta occurs in 7% of patients with congenital heart disease, and there is a slight male predominance of 1.5:1. Coarctation is a diffuse arteriopathy even in the absence of a BAV. Cystic changes in the aortic media with fragmentation of elastin and increased collagen deposition have been described in the paracoarctation segment and the ascending aorta.<sup>98</sup> The descending aorta immediately distal to the segment of coarctation is frequently aneurysmal. A BAV is present in 22% to 42% of cases.<sup>96,97</sup> Intracranial aneurysms, usually of the circle of Willis, have been detected in up to 10% of patients.<sup>99</sup> Other less common associations are ventricular septal defects and Shone's complex (multiple LVOTO and parachute mitral valve). Patients with Turner syndrome (XO) frequently present with coarctation of the aorta and a BAV.

Adult unoperated patients almost invariably present with systemic arterial hypertension measured in the upper extremities. A patient with systemic arterial hypertension should have upper and lower extremity arterial blood pressures measured on physical examination. A normal patient should have an increase of 5 to 10 mm Hg in systolic blood pressure in the lower extremities compared with the upper extremities. Absence of this increase or presence of a decrease in systolic blood pressure in the lower extremities should prompt further investigation to rule out coarctation of the aorta. Moreover, we strongly recommend that all patients with systemic hypertension should have a brachial and femoral pulse timing



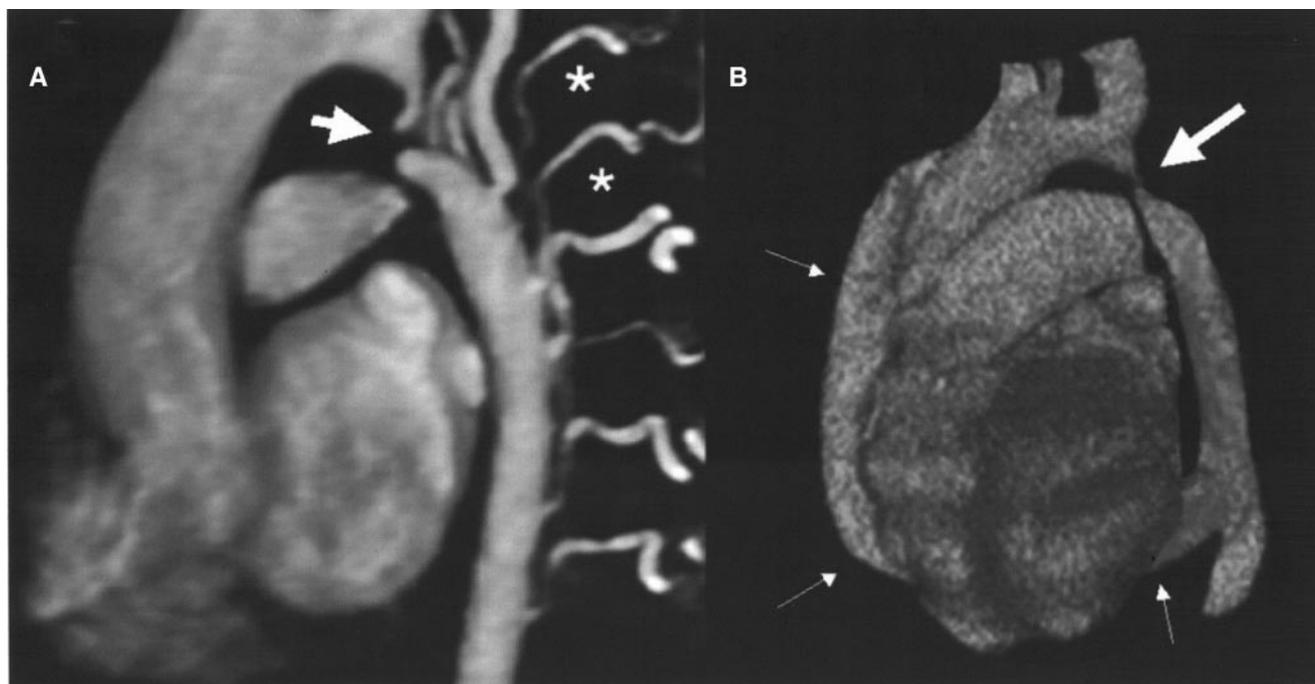
**Figure 3.** A, Gradient echo cardiac MR image axial cut at the level of a calcified stenotic bicuspid aortic valve (white arrow) during systole. The calcium appears black and is predominantly deposited at the leaflet tips. There is fusion of the right and left coronary cusps. The right atrium (RA) and left atrium (LA) are labeled. B, Frontal projection of the same patient. Note the systolic doming despite calcification of this aortic valve (white arrow) and the severely dilated ascending aorta (Ao) with characteristic effacement of the sinotubular junction. Note that the dilated ascending aorta tends to normalize proximal to the innominate artery.

and amplitude evaluation on physical examination; this can easily be done by palpating the brachial and femoral pulses simultaneously. One should be careful to palpate both brachial arteries for this determination because of the occasional involvement of the left subclavian artery in the segment of coarctation or the occasional takeoff of the right subclavian artery beyond the left subclavian artery at the site of coarctation. Presence of a delay or decrease in amplitude of the femoral pulse should prompt further investigation. Auscultation over the left upper back will often reveal a parascapular systolic or continuous murmur (depending on the number and degree of collaterals). Patients with a coexistent BAV will have an ejection sound and midsystolic murmur at the apex and base, respectively. Characteristic rib notching is often present on chest x-ray or CT and is indicative of extensive arterial collateral formation bypassing the area of coarctation; a characteristic “3” sign is often also seen on chest x-ray (Figure 1B, 1C).

The initial imaging and hemodynamic evaluation in suspected aortic coarctation is transthoracic Doppler echocardiography. Evaluation for coarctation anatomy is best done via the suprasternal notch view and should include continuous-wave Doppler assessment of the distal aortic arch and isthmus. A hemodynamically significant coarctation will have a typical continuous-wave Doppler profile demonstrating continuing antegrade flow tapering off during diastole<sup>100–102</sup> (Figure 1D). In addition to evaluation for coarctation gradient and anatomy, echocardiography should also be used to rule out commonly associated lesions such as BAV and dilation of the ascending aorta. What defines a “significant” coarctation? An accepted definition is a peak-to-peak catheter-determined gradient of 20 mm Hg across the narrowed segment.<sup>103</sup> Comparison of this with gradients derived by Doppler echocardiographic maximum and mean velocity is problematic. At the Ahmanson/UCLA Adult Congenital

Heart Disease Center, our practice has been to determine both resting and exercise continuous-wave Doppler velocities across the site of coarctation. A  $\geq 20$  mm Hg peak instantaneous gradient at rest or on provocation with exercise may be indicative of a significant coarctation. Moreover, we rely heavily on the presence of the previously described diastolic antegrade flow as a marker of hemodynamic significance (Figure 1D). Recall that in the presence of an extensive bypassing collateral network, the systolic and diastolic gradients are less reliable, and more accurate anatomic imaging is needed (Figure 1C). Moreover, in patients with repaired coarctation without significant narrowing, a gradient may develop in the absence of significant narrowing because of a lack of compliance at the anastomotic site because flow to the descending aorta increases with leg exercises. MR and CT angiography of the chest with 3-dimensional reconstruction clearly demonstrate the degree and extent of coarctation and collateral formation (Figure 4A); we highly recommend the routine use of either of these modalities to fully evaluate the thoracic aorta and intracranial vessels in patients with coarctation.

Unoperated patients survive an average of 35 years with a 75% mortality noted by 46 years of age.<sup>97,104</sup> In Campbell’s<sup>104</sup> necropsy study of 304 unoperated patients with coarctation of the aorta, 25.5% of patients died from congestive heart failure, 21% had rupture of the aorta, 18% died of endocarditis complications, and 11.5% died of intracranial hemorrhage. Campbell<sup>104</sup> and Reifenshtein et al<sup>97</sup> noted that the majority of deaths from aortic rupture and endocarditis occurred in the second and third decades, from heart failure in the third to fifth decades, and from bacterial endocarditis in the first 5 decades. The grave prognosis of unoperated coarctation of the aorta spurred efforts to develop surgical treatments for this condition. Blalock and Park<sup>105</sup> used a divided left subclavian artery to bypass a discrete coarctation



**Figure 4.** A, MR angiogram of a patient with complete interruption of the aorta (white arrow) as viewed from the lateral orientation. Note the extensive collateral network (\*) of intercostals arteries bypassing the site of interruption. B, Three-dimensional surface rendered reconstruction of a 64-slice CT angiogram of the same patient in the same orientation after surgical placement of a prosthetic conduit from the proximal aortic arch to the descending aorta (small white arrows) bypassing the site of complete interruption (large white arrow). The extensive collateral network was still present but has been selectively “sculpted out” during postprocessing of the image.

in animal experiments as early as 1944. In 1944, Crafoord and Nylin<sup>106</sup> performed the first coarctation repair in a human being with excision of the narrowed segment and end-to-end anastomosis of the paracoarctation aorta. This procedure rapidly gained worldwide popularity and is the preferred method for initial repair. Blalock’s left subclavian turn-down was reserved for cases in which end-to-end anastomosis was not feasible. Subsequent modifications in surgical technique include the use of prosthetic overlay grafts, subclavian patch aortoplasty, and prosthetic tube grafts from the ascending to the descending aorta in patients with complete interruption (Figure 4A, 4B). When an aneurysm of the paracoarctation aorta is present, resection of the aneurysm along with the coarctation is performed, and continuity is usually established with the use of an interposed tubular Dacron graft. Postrepair paraplegia is rare but is more common in cases that require extensive aneurysm resection. Percutaneous balloon angioplasty with or without stenting for primary coarctation has gained popularity and has displayed encouraging results. Results from a series of 422 native and 548 recurrent coarctation patients who all underwent balloon angioplasty demonstrated that older age, recurrent obstruction, and higher pressure gradients were markers of a suboptimal outcome.<sup>107</sup> A recent 10-year follow-up report of children with either surgery or balloon angioplasty showed no differences in resting blood pressure, coarctation gradient, exercise performance, MR imaging measurements of the aortic arch, or need for repeat interventions between treatment strategies.<sup>108</sup> However, there was a higher incidence of aneurysm formation (35% versus 0%) and a greater difference in blood pressure

between the right and left legs with exercise with angioplasty. Only 50% of angioplasty subjects remained free of both aneurysm formation and repeat intervention compared with 87.5% of surgical subjects. For discrete stenoses, balloon angioplasty may be used as a primary intervention but is less suitable for long-segment or tortuous forms of coarctation. Stent implantation greatly decreases the risk of aneurysm formation and has excellent long-term outcomes in both native and recurrent coarctation. Less than 1% of patients require redilation of the stented segment.<sup>109,110</sup> Surgery remains the gold standard, but these promising results for endovascular interventions are highly compelling.

Patients with successfully treated coarctation often continue to have systemic arterial hypertension both at rest and with exercise despite the absence of any residual coarctation.<sup>111–114</sup> Various potential mechanisms have been identified, including resetting of the renin-angiotensin system, impaired small-resistance-vessel reactivity, and abnormal aortic distensibility.<sup>115–123</sup> Coarctation repair after the age of 14 years is associated with more hypertension and decreased survival, whereas surgical repair before 3 years of age is associated with an increased incidence of recoarctation.<sup>124</sup> Understandably, patients with hypertension after late repair are at an increased risk for developing heart failure, accelerated atherosclerosis, stroke, and progressive aortic disease. Nearly half of the patients will have a bicuspid aortic valve, which should be monitored frequently for stenosis and/or regurgitation. Pregnancy in coarctation of the aorta continues to be a concern, but major cardiovascular complications are infrequent.<sup>124</sup>

## Disclosures

None.

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