Ascending Aortic Dilatation Associated With Bicuspid Aortic Valve
Pathophysiology, Molecular Biology, and Clinical Implications

Thomas M. Tadros, MD, MPH; Michael D. Klein, MD; Oz M. Shapira, MD

Ascending aortic dilatation occurs more frequently and at a younger age in patients with bicuspid aortic valves (BAV) than it does in patients with normal trileaflet aortic valves (TAV). The clinical significance of the correlation between BAV and dilatation of the ascending aorta is based on 2 factors. First, BAV is the most common congenital cardiac abnormality, occurring in 0.46% to 1.37% of the population.1-4 Second, aortic dilatation has a propensity for dissection and rupture, making it a potentially lethal disease. Ascending aortic dilatation with BAV warrants frequent monitoring, with possible early prophylactic surgical intervention to prevent dissection or rupture. The purpose of this article is to review the etiology and natural history and to make suggestions regarding management of the disease on the basis of the limited data available.

Pathophysiology

Differential for Etiology of Ascending Aortic Aneurysms

Most ascending aortic aneurysms have unknown etiology and are classified as idiopathic.5 In contrast to aneurysms of the descending aorta, ascending aortic aneurysms are not commonly a result of atherosclerosis.6,7 Among heritable connective tissue disorders such as Marfan syndrome and Ehlers-Danlos syndrome, ascending aortic aneurysms are a clinical component of the syndrome. BAV disease, also a heritable disorder, is known to have an increased risk of ascending aortic aneurysm as well. Marfan syndrome and BAV aortic disease share common histopathological findings, including medial degeneration, increased matrix metalloproteinase (MMP) activity, and decreased fibrillin-1 in the aortic wall.8

Anatomic Boundaries of BAV Disease

Development of a BAV is part of a larger spectrum of structural developmental abnormalities involving the great vessels. The aortic valve and ascending aorta share a common embryonic origin: they both develop from neural crest cells.9-12 The vascular smooth muscle cells (VSMCs) that undergo apoptosis in the media of the ascending aorta are of neural crest origin.13 The pulmonary trunk demonstrates histopathological changes similar to those of the ascending aorta in BAV patients.14,15 The strong association between BAV and coarctation of aorta, both with and without Turner syndrome, may indicate that BAV disease involves the ascending aorta and aortic arch extending to the ligamentum arteriosum, where most coarctations occur.16,17 BAV disease may also affect anatomy of the coronary ostia. Studies have shown a 29% to 57% incidence of left coronary arterial dominance associated with BAV,18,19 as well as case reports of BAV with a single coronary artery.20,21 Figure 1 demonstrates the anatomic boundaries of BAV disease.

Genetics

The pattern of inheritance of BAV is autosomal dominant with incomplete penetrance.22,23 However, the male predominance (male-to-female ratio ≥3:1.54) as well as association of BAV with Turner syndrome (45X chromosomal pattern)24 suggests an X-linked etiology. A heritability study found no X-linkage but did find linkage to chromosomal regions 5q, 13q, and 18q.25 Mutations in the NOTCH1 gene (chromosome 9q) lead to signaling abnormalities that may be responsible not only for development of a bileaflet aortic valve but also accelerated valvular calcium deposition.26,27 Another possible etiology is downregulation of the ubiquitin fusion degradation 1-like (UFD1L) gene on chromosome 22; this gene is highly expressed in the cardiac outflow tract during embryogenesis.28 Deletions within chromosome 22q11.2 resulting in DiGeorge syndrome and velocardiofacial syndrome have demonstrated concomitant BAV.29 Mutations in the ACTA2 gene (chromosome 10q), which encodes VSMC α-actin, are associated with familial thoracic aortic aneurysms and BAV.30 Murine studies showed that mice lacking the gene encoding endothelium-derived nitric oxide synthase are prone to development of BAV; BAV developed in 5 of 12 endothelium-derived nitric oxide synthase knockout mice compared with 0 of 26 controls.31 In humans, endothelium-derived nitric oxide synthase expression is lower in ascending aortas with BAV versus TAV.32 Endothelial nitric oxide plays a role in valve and vascular formation during embryogenesis, as well as vascular remodeling after development. Although...
BAV aortas have histopathological findings similar to those of Marfan syndrome aortas, the underlying genetic abnormality of Marfan syndrome—mutation in the FBN1 gene that encodes fibrillin-1—is not found with BAV disease. Genomewide association studies may reveal other genes involved with BAV disease.

Medial Degeneration
Gsell coined the term medionecrosis in 1928, and the following year Erdheim defined the 3 main histopathological features of what was formerly called cystic medial necrosis: noninflammatory loss of VSMCs, fragmentation of elastic fibers, and increased basophilic ground substance within cell-depleted areas of the ascending aortic media. The basophilic ground substance, composed of proteoglycan, is the medium through which neural crest cells migrate during embryonic development. The term cystic medial necrosis is a misnomer. The cysts are actually noncystic medial structural faults, and necrosis is rarely seen. The total thickness of the aortic media is the same for BAV and TAV aortas, but the distance between the elastic lamellae is greater with BAV, and the lamellae themselves are thinner and more fragmented (Figure 2). More recent evidence regarding elastin loss and fragmentation is conflicting. Several BAV studies show noninflammatory loss of VSMCs, as described by Erdheim, with similar degrees of VSMC apoptosis in Marfan aortas and preserved density of VSMCs in idiopathic ascending aortic aneurysms. Even nondilated BAV aortas have higher rates of VSMC apoptosis, particularly at the convexity, suggesting an underlying pathology in BAV aortas even before dilatation occurs. The convexity of the aorta is particularly affected by medial degeneration, demonstrating less collagen, greater elastic fragmentation, and fewer VSMCs. Differential expression of Bcl-2, a mediator of apoptosis, has been demonstrated in BAV aortas and may play a role in VSMC apoptosis.

VSMCs are responsible for both physiological and pathological remodeling of the aortic media. They produce extracellular matrix proteins of the aortic media, including collagen, elastin, laminin, proteoglycan, fibrillin, fibronectin, and tenasin. Defective protein transport from VSMCs to the extracellular matrix may be partly responsible for the structural abnormalities in both BAV and Marfan aortas. One study demonstrated intracellular accumulation of fibrillin, fibronectin, and tenasin in VSMCs; reduced extracellular matrix protein distribution; and degradation of elastic lamellae. The protein transport defect may have a dual role in pathogenesis, leading to both lack of maintenance of the extracellular protein matrix and increased apoptosis of the VSMCs in which the proteins accumulate. This mechanism would tie together the constellation of histopathological findings of medial degeneration in BAV aortas.

Deficiency of Fibrillin-1
Fibrillin-1 is a glycoprotein that helps to maintain the structural integrity of the aortic wall and valve leaflets by tethering VSMCs to a matrix of elastin and collagen. Deficiency of fibrillin-1 leads to VSMC detachment from elastin and collagen, inducing apoptosis and loss of structural integ-

Figure 1. Schematic diagram of the anatomic boundaries of BAV disease. The structures involved in BAV disease (highlighted in pink) include the aortic valve; aortic annulus (not labeled); sinuses of Valsalva; sinotubular junction; ascending aorta; aortic arch; pulmonary trunk; and coronary ostia.

Figure 2. Histopathological cross sections of aortic media demonstrating normal elastic lamellae in a control sample (A) vs degraded elastic lamellae associated with BAV disease (B). Stained with Alcian blue and Verhoeff van Gieson. Magnification ×250. Reprinted from Nataatmadja et al, with permission from Lippincott Williams & Wilkins. Copyright 2003, American Heart Association.
Increased Activity of MMPs

Tissue samples from ascending aortic aneurysms with BAV have increased activity\textsuperscript{43,45} and expression\textsuperscript{46–48} of proteolytic enzymes known as MMPs compared with aneurysms from patients with TAV. MMPs are a family of proteases that maintain the homeostasis of connective tissue. The main type found in the ascending aorta is gelatinases (gelatinase A [MMP-2] and gelatinase B [MMP-9]), which degrade type IV collagen and partially degrade elastin and fibrillar collagen.\textsuperscript{49} MMP-2 and MMP-9 are synthesized by a number of cells, including VSMCs, in response to hemodynamic changes and various disease states.\textsuperscript{50} Their activity is kept under tight control by a number of factors. Tissue inhibitors of metalloproteinase (TIMP), of which TIMP-1 is the most common in the aorta, are synthesized by VSMCs and fibroblasts and act by forming irreversible bonds with MMPs.\textsuperscript{49,50}

Protein kinase C is an upstream regulator of MMPs, and differential expression of protein kinase C isoforms in ascending aortic aneurysms with BAV versus TAV and nonaneurysmal controls has been demonstrated.\textsuperscript{51}

Tissue samples from aneurysms with BAV demonstrate increased expression of MMP-2\textsuperscript{46} and ratio of MMP-2/TIMP-1,\textsuperscript{52} whereas aneurysms with TAV have increased MMP-13 (a collagenase) and decreased TIMP-2.\textsuperscript{46} Marfan aneurysm tissue shows increased expression of MMP-12 (an elastase) and TIMP-2 and decreased MMP-2 and TIMP-3.\textsuperscript{53} Comparison among studies reveals conflicting patterns of MMP and TIMP expression, possibly secondary to small numbers of participants and differing sites of aortic tissue sampling. Nonetheless, particular patterns of MMP and TIMP expression and activity in BAV, Marfan, and idiopathic aneurysm tissue may indicate that different mechanisms of aortic pathophysiology occur depending on the underlying etiology of aortic disease (Table 1).

Hemodynamic Changes

Increased tensile and shear stresses play a role in pathogenesis of BAV aortic disease. Tensile stress or wall tension is exerted perpendicularly to the aortic wall and is evenly distributed along the circumference of the aorta. Tensile stress increases in correlation with increased aortic radius according to La Place’s Law. Shear stress, a product of blood viscosity and velocity, exerts force in parallel to the aortic wall by way of friction on the endothelial surface, with cellular signaling cascades resulting in increased expression of MMPs and growth factors that affect matrix degradation and VSMC apoptosis.\textsuperscript{54} Shear stress is exerted focally, and turbulent blood flow through BAVs, even those with no stenosis or regurgitation, causes an uneven burden of force on the convex wall of the ascending aorta.\textsuperscript{55}

Regurgitant BAVs have higher stroke volumes leading to higher wall tension in the ascending aorta. Severity of aortic regurgitation correlates with degree of aortic root dilatation.\textsuperscript{56,57} There may be a bimodal effect, with increasing root dilatation leading to poor leaflet coaptation and thus more regurgitation. Stenotic BAVs create a high-velocity jet that increases shear stress on the anterolateral portion of the ascending aorta.\textsuperscript{58} Evidence for a correlation between severity of aortic stenosis and degree of aortic dilatation is conflicting.\textsuperscript{57,59,60}
However, with 37 mm used as the upper limit of normal, this defines aneurysm as a vessel diameter 1.5 times normal. 

Uncertain at what threshold the ascending aorta should be (Figure 4), even in BAV patients with normal valve function (ie, no aortic stenosis or regurgitation). Furthermore, in those BAV patients with valve dysfunction (aortic stenosis, regurgitation, or both), valve dysfunction alone does not account for the degree of aortic dilatation. The prevalence of ascending aortic dilatation among those with BAV ranges according to study population, threshold used to define dilatation in each study, and region of aorta. Prevalence ranges from 7.5% to 59% at the annulus; 16% to 78% at the sinus of Valsalva; 15% to 79% at the sinotubular junction; and 35% to 68% at the proximal ascending aorta. Prevalence increases with age, beginning in childhood and continuing throughout life. A study of prevalence by age quintile showed dilatation in 56% of those aged <30 years old, up to 88% of those aged >80 years old.

### Natural History of Ascending Aortic Dilatation With BAV

#### Rate of Dilatation

Rate of growth of ascending aortas with BAV ranges among studies, from ~0.2 to 1.9 mm per year. Some individuals in these studies showed either no growth or a decrease in aortic diameter over time, exemplifying that estimation of dilatation rate is difficult to make for a number of reasons: variability in image readings, short follow-up periods and small sample sizes in some studies, and selection bias. Not unique to BAV disease is that rate of aortic dilatation is exponential; larger aortas have faster expansion rates.

One study demonstrated that expansion rate was ~2.1 mm/y for those with an initial diameter of 35 to 40 mm and 5.6 mm/y for aneurysms ~60 mm. Both pediatric and adult studies have demonstrated significantly faster aortic dilatation with BAV versus TAV. Other studies have shown that age at presentation of aortic dilatation was significantly younger with BAV versus TAV (mean, 49 versus 61 to 64 years old).

#### Aortic Dissection and Rupture

Aortic diameter is a significant predictor of dissection and rupture, particularly when the ascending aorta reaches 6 cm. From a database of 1600 thoracic aneurysms and dissections, those >6 cm had annual rates of rupture, dissection, and aorta-related death of 3.6%, 3.7%, and 10.8%, respectively; the cumulative rate of any of those events was 14.1%, more than double the rate of adverse events for aneurysms between 5 and 6 cm (6.5%). The mean and median ascending aortic diameters at time of dissection or rupture were 5.9 and 6.0 cm, respectively.

BAV-associated ascending aortic aneurysms dissect and rupture at a size range comparable to that of aneurysms due to other etiologies. In 1 study of 40 BAV patients with dissection, the mean aortic diameter was 6.0 ± 1.5 cm (range, 3.0 to 10.8 cm) at time of dissection.

Among 220 ascending aortic dissections in another study, those associated with connective tissue disorders (n = 94) had aortic diameters similar to those without connective tissue disorders (mean, 41.8 versus 41.3 mm, respectively); the proportion of dissections occurring in normal-sized or only mildly dilated aortas was actually higher in the group without connective tissue disease. Similarly, from the International Registry of Acute Aortic Dissections, the proportion of dissections occurring at

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**Table 1. Abnormalities Associated With BAV Disease**

<table>
<thead>
<tr>
<th>Genetics</th>
<th>Result</th>
</tr>
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<tbody>
<tr>
<td>NOTCH1 mutation</td>
<td>Disrupted intercellular signaling during aortic valve development</td>
</tr>
<tr>
<td>UFD1L downregulation</td>
<td>Abnormal development of the cardiac outflow tract</td>
</tr>
<tr>
<td>ACTA2 mutation</td>
<td>Decreased VSMC actin α2 production</td>
</tr>
<tr>
<td>eNOS mutation</td>
<td>Abnormal valve and vascular development</td>
</tr>
<tr>
<td>Chromosomal linkage detected on 5q, 13q, 18q, 22q</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Histopathology and immunohistochemistry

- Medial degeneration
  - VSMC apoptosis: Decreased production of extracellular matrix proteins
  - Elastin fragmentation: Loss of structural support and elasticity
  - Differential expression of Bcl-2: Increased VSMC apoptosis
  - Fibrillin-1 deficiency: Detachment of VSMCs from elastin and collagen matrix
  - Differential expression of MMPs and TIMPs: Increased degradation of collagen and elastin
  - Differential expression of PKC: Uregulation of MMPs
  - Decreased expression of eNOS: Abnormal regulation of vascular remodeling

eNOS indicates endothelial nitric oxide synthase; PKC, protein kinase C; and N/A, not applicable.

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**Prevalence of Ascending Aortic Dilatation With BAV**

A normal diameter for the ascending aorta has been defined as 20 to 37 mm. Advancing age, male sex, and indexes of larger body size (ie, height, weight, body surface area, and body mass index) correlate with larger aortic diameters. Blood pressure has a marginal effect on diameter. It is uncertain at what threshold the ascending aorta should be considered an aneurysm. The Society for Vascular Surgery defines aneurysm as a vessel diameter 1.5 times normal. However, with 37 mm used as the upper limit of normal, this definition would imply that an ascending aorta would have to be >5.5 cm to be considered aneurysmal. A lower threshold, perhaps ~4.5 cm, may be more appropriate. Aortic dilatation is defined by a diameter >1.1 times normal on the basis of age, sex, and body surface area. The incidence of ascending aortic dilatation in the general population has been increasing over the past 3 decades, partly because of the larger aging population as well as the frequency of incidental findings since the advent of computerized tomography (CT) and 2-dimensional echocardiography in the 1970s and 1980s, respectively.

In persons with BAV, the aortic root and ascending aorta are significantly larger than those in persons with TAV (Figure 4). Even in BAV patients with normal valve function (ie, no aortic stenosis or regurgitation), Furthermore, in those BAV patients with valve dysfunction (aortic
smaller sizes (<5.5 cm) was actually higher in those without BAV disease or Marfan syndrome.87

The increased risk of dissection and rupture associated with BAV is due to the higher prevalence and rate of aortic dilatation, which occurs at a significantly younger age relative to idiopathic ascending aortic aneurysms.76,78,88,89 In a study of dissecting aortic aneurysms in patients aged <40 years old, 9 (24%) of the 38 cases were associated with BAV.89 From a US cardiovascular registry of dissecting aortic aneurysms, 11 (9%) of the 119 specimens had a BAV, and 5 of those patients were aged <30 years.88 BAV disease carries a 6.14% lifetime risk of aortic dissection, 9-fold higher than the risk in the general population.88 Patients with Marfan syndrome have a much higher lifetime likelihood of aortic dissection (40%) than patients with BAV. However, because BAV disease is ~100 times more common than Marfan syndrome (0.01% of the US population), BAV disease is responsible for an equal or greater number of aortic dissections than Marfan syndrome.84,87

Varying Phenotypes of BAV Disease

Mid ascending aortic dilatation is the most common phenotypic pattern in BAV disease and is correlated with older age, whereas aortic root dilatation is correlated with younger age and male sex.59 A large subset of BAV patients (48% to 63% in 2 studies)70,74 do not have any degree of aortic dilatation. In regard to valve function, in a series of 542 BAV surgical cases, 75% had pure aortic stenosis, whereas 13% had pure aortic regurgitation. Compared with the stenosis group, the regurgitation group had a 10-fold higher male-to-female ratio and a 4-fold higher rate of annular dilatation.91 Anteroposteriorly oriented aortic valves have more severe regurgitation, whereas those with right-left orientation have more severe stenosis.67 Phenotypic heterogeneities in BAV disease are complex and warrant prospective studies to determine their predictive value for patterns of aortic dilatation and aortic dissection or rupture.

Recommendations for Management of Patients With Aortic Dilatation and BAV

Serial Imaging

Valve function as well as diameter of the annulus, sinuses of Valsalva, sinotubular junction, and ascending aorta should be monitored periodically. Transthoracic echocardiography (TTE) is a noninvasive, cost-effective imaging modality. However, adequate TTE views of the mid and distal ascending aorta and arch can be difficult to obtain,92 especially in those with large body habitus. If TTE cannot provide measurements from the aortic root up to the mid ascending aorta, a CT scan or magnetic resonance imaging (MRI) should be performed.93 Furthermore, if the aortic root or ascending aorta is >4.0 cm on TTE, a CT scan or MRI should be performed to evaluate the extent of dilatation as well as screen for coarctation. Thereafter, annual monitoring with echocardiography, MRI, or CT scan should be continued.93

With MRI, ascending aortic dimensions are most accurately measured with the use of ECG-gated black blood pulse

Figure 4. Ascending aortic diameter (cm) as a function of height (cm) among children with BAV (n=101) vs controls with TAV (n=97). The upper slope (circles) represents the BAV group (y=0.0151x+0.2926), and the lower slope (triangles) represents the TAV group (y=0.0117x+0.362). Reprinted from Beroukhim et al,65 with permission from Elsevier. Copyright 2006.
sequences (Figure 5A).94 Another pulse sequence called steady state free precession can assess valve function by detecting flow jets across the aortic valve during systole (Figure 5B) and diastole and can also confirm the number of leaflets in the aortic valve. Contrast-enhanced 3-dimensional magnetic resonance angiography can be used to confirm aortic dimensions as well as increase diagnostic confidence (over MRI alone) regarding intimal tears and coarctation (Figure 5C).94

Multidetector CT scan with 3-dimensional reconstruction offers accurate measurements of the ascending aorta, with reconstruction displays that are as useful as MRI for surgical planning or defining complex aortic anatomy.95 For routine surveillance of aortic diameter, however, standard spiral CT angiography is performed because it emits less radiation than multidetector CT. When multidetector CT is indicated, ECG-gated images can be obtained to minimize radiation exposure as well as reduce motion artifact.95 If there is a contraindication to both CT scan and MRI, transesophageal echocardiography is a reasonable alternative that provides good visualization of the aortic root, ascending aorta, and aortic arch.96

Image Interpretation
Measurements of the aortic root, proximal ascending aorta, and aortic arch by TTE correlate closely with measurements by ECG-gated multidetector CT scan, with an insignificant trend toward underestimation of aortic diameter with the use of TTE.97 Mean TTE and MRI measurements of aortic root diameter were the same in another small study,98 suggesting that TTE is an accurate imaging modality. Nonetheless, 1 study found that interobserver and intraobserver variability of echocardiogram interpretations was 6%.79 Observer variability may give a false impression of aortic size and/or dilatation rate. To overcome this issue, if imaging provides an indication for surgical intervention, then the images should be remeasured by the initial reader as well as a second reader to ensure accuracy before proceeding to surgery. Furthermore, use of multiple measurements, not just the 2 most recent or the oldest and most recent measurements, to calculate dilatation rates will minimize the effect of observer variability and may make apparent the presence or absence of exponential growth.

Pharmacotherapy
Practice guidelines suggest that β-blockers are reasonable for nonoperative candidates with dilated (>4 cm) aortas and BAV (in the absence of significant aortic regurgitation), but this recommendation is based on consensus opinion rather than clinical trials.93 There are many studies regarding medical therapy for prophylaxis and treatment of Marfan syndrome–related aortic pathology.99 β-Blockade has been a mainstay of pharmacotherapy in Marfan syndrome based on a theoretical decrease in aortic wall stress. However, there are conflicting data regarding the effects of β-blockers on aortic elastic properties in Marfan patients.99 A study in 1994 showed a decrease in the rate of aortic dilatation in Marfan patients treated with propranolol,100 but a recent meta-analysis of 6 studies (1 of which was a prospective randomized trial with >800 participants) showed no clinical benefit of β-blockade in Marfan syndrome.101 Whether Marfan data can be extrapolated to BAV aortic disease is debatable.

Medical management of BAV disease should entail aggressive control of hypertension. β-Blockers and either angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers should be considered as first-line agents. Type 2 angiotensin II receptor expression and angiotensin II concentration are increased in Marfan syndrome aortas with medial degeneration, and ACE inhibitors have been shown to decrease cultured VSMC apoptosis.102 In a study comparing enalapril with propranolol or atenolol in Marfan syndrome patients, the ACE inhibitor group had a significantly lower aortic stiffness index and a significantly lower rate of aortic root growth.103 The angiotensin II receptor blocker losartan has also been shown to reduce the rate of aortic dilatation in...
There is no evidence to suggest whether ACE inhibitors and angiotensin II receptor blockers are preferable to β-blockers in BAV disease. These agents may be used individually or as combination therapy of β-blocker plus either an ACE inhibitor or an angiotensin II receptor blocker.

Medical management of BAV disease does not currently include 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins). Statins may potentially limit aortic dilatation by reducing MMP expression and by improving endothelial function via increased endothelial nitric oxide synthase. A recent randomized, placebo-controlled trial involving participants with mild to moderate aortic stenosis showed that statins did not alter aortic valve-related events or progression of aortic valve stenosis. However, only ~5% of the study participants had BAV. Further research focused on the effect of statins on ascending aortic dilatation, dissection, and rupture in patients with BAV disease is warranted.

### Elective Surgical Repair or Replacement of the Aortic Root and Ascending Aorta

The mortality rate for elective surgical repair of ascending aortic aneurysms in large centers is 2.5% to 5%. The risk of perioperative stroke (the major morbidity associated with this operation) is ~1.7% to 2.4%, with repair of the aortic arch incurring a higher risk. Aneurysms with an annual risk of rupture or dissection higher than the combined risks of perioperative morbidity and mortality should be repaired electively. For idiopathic ascending aortic aneurysms, surgical intervention at 5.5 cm has been recommended on the basis of the finding that aortas ≥6.0 cm have a significantly higher risk of dissection or rupture. Those with BAV should have elective surgical repair of the ascending aorta when it reaches >5.0 cm, similar to Marfan syndrome criteria, because ascending aortas associated with BAV have fast growth rates and tend to dissect and rupture at a young age. Those with indications for elective replacement of a dysfunctional aortic valve, for which guidelines are discussed elsewhere, should undergo concomitant repair or replacement of the aortic root or ascending aorta at >4.0 cm.

Although aortic diameter is currently the major criterion for timing of elective surgical repair of ascending aortic aneurysms, it is an imperfect predictor of aortic dissection or rupture. Among 591 ascending aortic dissections in the International Registry of Acute Aortic Dissection, the mean aortic diameter at time of dissection was 5.3 cm. Forty percent of dissections occurred at a diameter <5.0 cm, and nearly 60% of the cases (including 6 of 16 BAV-associated dissections and 11 of 28 Marfan-associated dissections) occurred in aortas <5.5 cm. The current criterion for elective preemptive surgery, aortic diameter ≥5.5 cm, misses 60% of dissections on the basis of these data. Additional methods of risk stratification are needed.

For BAV patients, surgical repair should be considered at an even more conservative limit of >4.5 cm when other clues indicate more severe aortic disease (Table 2). It is important to recognize that the strength of the following recommendations is weak because they are based on either expert opinion or a limited number of trials with varying samples sizes and minimal prospective design. First, a dilatation rate >0.5 cm/y indicates severe disease and should prompt earlier intervention. Second, a history of concomitant aortic coarctation, corrected or uncorrected, indicates more diffuse aortopathy with increased risk for dissection or rupture. Third, a family history of aortic dissection or rupture in a first-degree relative may indicate inheritance of a more severe genotype. Fourth, a long smoking history, especially with chronic obstructive pulmonary disease, should prompt earlier intervention because smoking causes elastin fragmentation, and both smoking and chronic obstructive pulmonary disease correlate with larger aortic size and faster aortic expansion rate. Finally, adults with small body size should undergo earlier intervention because a higher ratio of aortic size to body size is a predictor of increased risk. Calculating the ratio of aortic area in square centimeters to body height in meters, using a ratio of 10 as an indicator of increased risk, has been proposed. The value of 10 was derived from the mean ratio minus 1 SD at time of dissection in BAV patients; it is a conservative threshold that would theoretically precede 95% of dissections. Increasing “aortic size index,” a ratio of aortic diameter in centimeters to body surface area in square meters, was correlated with dissection, rupture, and death in 1 study; an index ≥4.25 cm/m² indicated high risk (20% per year). The aortic size ratios and indexes should be used as rough guidelines until validated by further studies. Measurement of aortic elasticity by echocardiography may aid with risk stratification in the future; prospective studies are needed. Genomewide association studies may identify high-risk genotypes that will aid with risk stratification as well.

**Table 2. Indications for Elective Surgical Repair of Dilated Ascending Aorta Associated With BAV**

<table>
<thead>
<tr>
<th>Aortic diameter (cm)</th>
<th>Indications for Repair</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5.0</td>
<td>Area index (cm²/m²)</td>
</tr>
<tr>
<td>&gt;4.5</td>
<td>Body height (cm)</td>
</tr>
<tr>
<td>&gt;4.0</td>
<td>Body surface area (m²)</td>
</tr>
</tbody>
</table>

Endovascular aneurysm repair (EVAR) is a minimally invasive method for management of aortic aneurysms that has been suggested as an alternative, although controversial, approach for older patients who would be high risk for open surgical repair because of comorbidities. EVAR is not currently a definitive approach to management of ascending aortic dilatation with BAV for several reasons. There is a lack of sufficiently large stent grafts to accommodate the diameter of the ascending aorta. The contour of the ascending aorta is complex, with inadequate landing zones to anchor the stent grafts, especially when dilatation involves the aortic annulus.
and extends into the arch. The region of dilatation frequently involves the coronary artery orifices, eliminating the option of covered stent graft repair. Most of the data regarding EVAR is for descending thoracic aortic aneurysms, with fewer reports for the aortic arch and only selected reports for the ascending aorta. Furthermore, the data on EVAR in patients with connective tissue disease are limited and somewhat concerning. In 1 retrospective study, 8 patients with connective tissue disease were treated with EVAR; over a median 31 months, half of them demonstrated continued aortic expansion, had endoleaks, and required reintervention. Patients with BAV aortic disease typically need intervention at a younger age, and currently EVAR has not been shown to provide a durable long-term solution to aortic dilatation, as does open repair.

**Summary**

Compared with those with a TAV, those with BAV disease have medial defects leading to a higher prevalence and faster rate of ascending aortic dilatation, with increased risk of dissection or rupture at a younger age. BAV disease warrants aggressive control of hypertension. Once the ascending aorta reaches 4.0 cm, annual imaging with echocardiography, MRI, or CT scan is indicated. On the basis of the limited data regarding proper timing of prophylactic intervention, it is suggested that elective surgical repair of BAV-associated aortic dilatation should occur at a diameter of >5.0 cm, with even earlier intervention at >4.5 cm in the subset of BAV patients with factors of higher risk and at >4.0 cm in those with concomitant indication for aortic valve replacement.

**Disclosures**

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Key Words: aneurysm □ aorta □ heart defects, congenital □ valves
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