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CLINICIAN UPDATE

Clinical and Pathophysiological Implications of a Bicuspid Aortic Valve

Paul W.M. Fedak, MD; Subodh Verma, MD, PhD; Tirone E. David, MD; Richard L. Leask, PhD; Richard D. Weisel, MD; Jagdish Butany, MD

You are contacted by a concerned 34-year-old airline pilot with a leaky bicuspid aortic valve recently diagnosed by an echocardiogram that had been requested by his new employer as part of a routine medical assessment. He claims that he is perfectly healthy but is at risk of losing his job over his condition. He is concerned that his disease is hereditary and that his children may also be at risk. The patient, his attorney, and his insurance company have requested a statement from you as to the cause, possible complications, and treatment options associated with a congenital malformation of the aortic valve.

The bicuspid aortic valve (BAV) is the most common congenital cardiac malformation, occurring in 1% to 2% of the population. The majority of BAV patients develop complications requiring treatment. Physicians are often challenged when asked to provide evidence-based advice about BAV disease because the pathogenesis and pathophysiology of this disease are not well understood.

What Causes Bicuspid Aortic Valves?

BAVs are the result of abnormal aortic cusp formation during valvulogenesis. Adjacent cusps fuse to form a single aberrant cusp, larger than its counterpart yet smaller than 2 normal cusps combined. BAVs are likely the result of a complex developmental process, not simply the fusion of 2 normal cusps. In fact, congenital aortic valve malformations may reflect a phenotypic continuum of unicuspid valves (severe form), bicuspid valves (moderate form), tricuspid valves (normal), and the rare quadricuspid forms[1] (Figure 1).

The pathogenesis of congenital aortic valve malformations is unknown. Proponents of environmental causes believe that abnormal blood flow through the aortic valve during valvulogenesis results in a failure of cusp separation. However, there is no convincing evidence to support this claim. A genetic cause of BAV disease is perhaps a more substantiated explanation, although it is not conclusive. In support of a genetic cause, BAV is highly associated with congenital abnormalities of the aorta (coarctation of the aorta and patent ductus arteriosis) and the proximal coronary vasculature. After development, BAV is associated with aortic dilation, aneurysms, and dissection (Figure 2). In light of this, the BAVs should be considered a disease of the entire aortic root.

The extracellular matrix (ECM) plays an important role in providing both structural support as well the environmental cues necessary for normal tissue development and homeostasis. In fact, ECM proteins help to direct cell differentiation and cusp formation during valvulogenesis. Microfibrillar proteins act as scaffolding for embryonic cells and regulate tissue formation in the developing aortic valves. In fact, the differentiation of cushion mesenchymal cells into mature valve cells correlates with the expression of the microfibrillar proteins fibrillin and fibulin.[2] Microfibrillar proteins within the aortic matrix may be deficient in patients with BAV. Inadequate production of fibrillin-1 during valvulogenesis may disrupt the formation of the aortic cusps, resulting in a bicuspid valve and a weakened aortic root. Our preliminary data support the hypothesis that microfibrillar proteins are deficient in adults with BAV disease, disrupting the structural support of the aortic root.

Defects in the genes that encode matrix elements have not yet been identified in patients with BAVs. Although the gene for fibrillin-1 may be structurally normal, transcriptional elements that control protein production may be defective.

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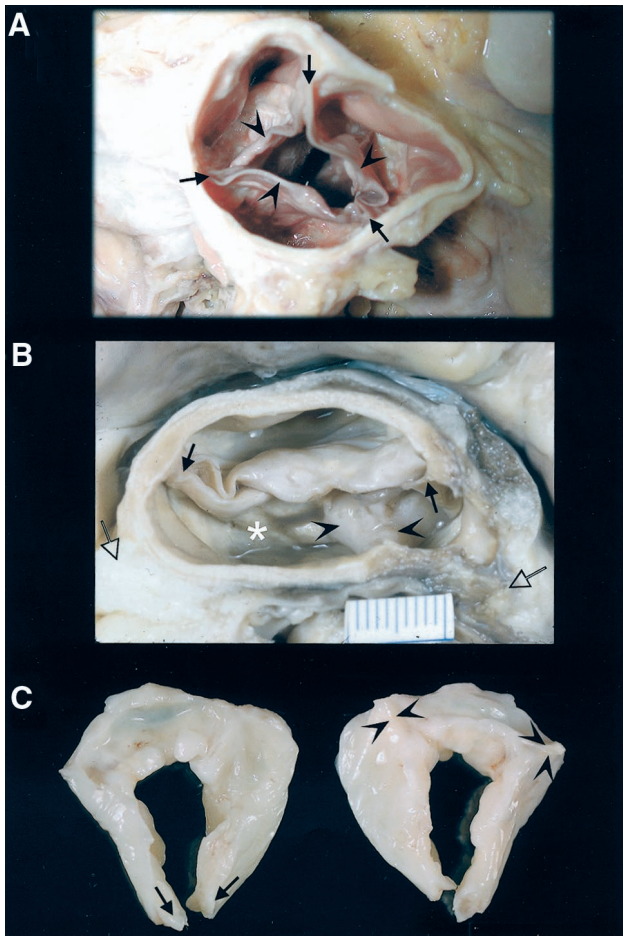
Figure 1. A, Normal tricuspid aortic valve. The cusps (arrowheads) and the 3 commissures (arrows) are clearly seen. Three sinuses of Valsalva are also seen. The cusps coapt normally to give a functionally normal valve. B, Congenitally bicuspid aortic valve, with one cusp larger (asterisk) than the other. The cusps show thickening due to fibrosis. Two commissures (arrows) are seen. One raphe (arrowhead) is seen. The raphe shows marked fibrosis and calcification. Both coronary arteries (open arrows) arose from the sinus of the cusp with the raphe. C, An aortic valve surgically excised from a 33-year-old male who had clinical evidence of aortic stenosis and insufficiency. The valve and proximal ascending aorta were excised and replaced with a composite graft (St Jude Medical 27-mm valve). The excised valve has the features of a congenitally unicommissural aortic valve with only 1 (cut) commissure (arrows). Flow surface appears on the left and nonflow surface on the right. The cusp tissue shows diffuse fibrosis, thickening, and multifocal nodular calcification. The nonflow surface shows 2 raphes (arrowheads). The resected aorta was dilated and showed significant medial change.

Transcriptional elements are emerging as important mediators of many other congenital cardiac defects.[3] Abnormalities of the gene encoding endothelial nitric oxide synthase (eNOS) is also an important candidate, because mice with eNOS deficiency have a high incidence of congenital BAV.[4] Although a single "BAV gene" has yet to be identified, there is likely a heterogeneous mechanism of causation resulting in diverse clinical phenotypes. Advances in molecular biology will most certainly uncover the molecular and cellular mediators involved in this common disorder.
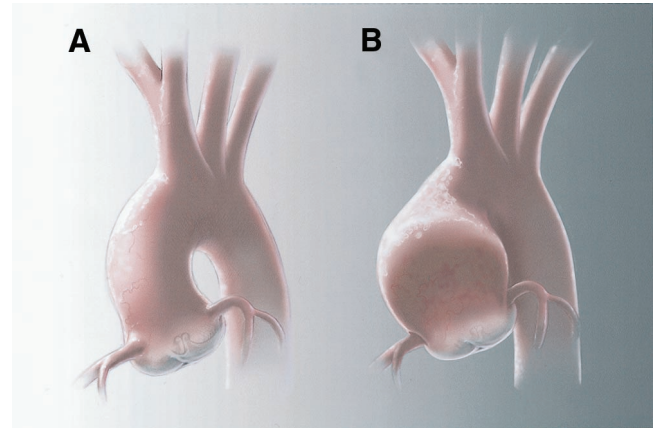
Figure 2. Normal aortic root (A) and dilated aortic root (B) characteristic of patients with BAV.

Are BAVs Hereditary?

It is not clear that BAVs are inheritable. Chan and associates[5] determined the rate of familial occurrence of BAV with the use of echocardiography to screen family members of affected individuals. Of the 30 families screened, 11 families (36.7%) had >1 first-degree relative with BAV. The high incidence of familial clustering is compatible with autosomal dominant inheritance with reduced penetrance.[5,6] Interestingly, males are affected 4:1. Echocardiographic screening of first-degree relatives is therefore warranted.

What Are the Risks of BAV?

BAV occurs in 1% to 2% of the population, compared with 0.8% for all other forms of congenital cardiac disease combined. Given that serious complications will develop in ≥33% of patients with BAV, the bicuspid valve may be responsible for more deaths and morbidity than the combined effects of all the other congenital heart defects.[7] Although patients with BAV may go undetected or without clinical consequences for a lifetime, the vast majority will require some intervention, most often surgery. The important clinical consequences of BAV disease are valvular stenosis, regurgitation, infective endocarditis, and aortic complications such as dilation and dissection, as shown in the Table.

Valvular Complications

Aortic stenosis is the most frequent complication of BAV, in many cases requiring aortic valve replacement. Bicuspid valves are present in the majority of patients aged 15 to 65 years with significant aortic stenosis, reflecting the propensity for premature fibrosis, stiffening, and calcium deposition in these abnormally functioning valves (Figure 3). In fact, aortic stenosis associated with congenital aortic valve malformations is age dependent: The fewer the number of cusps, the greater is the chance that the valve is stenotic from birth. The anatomy of the bicuspid valve may also influence the propensity for obstruction: Stenosis is more rapid if the aortic cusps are asymmetrical or in the anteroposterior position.[7] In addition, patients with poor lipid profiles and those who smoke are also at an elevated risk of developing hemody-

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AI indicates aortic incompetence; AS, aortic stenosis.

namically significant bicuspid aortic stenosis.[8] These are potentially modifiable risk factors amenable to treatment.

Aortic regurgitation occurs in the presence of a BAV usually from cusp prolapse, fibrotic retraction, or dilation of the sinotubular junction. Isolated regurgitation usually occurs in younger patients,[9] as in the case presented above, and may reflect a subset of patients more prone to aortic complications. Endocarditis is a potentially devastating complication that occurs in ≈30% of patients with BAV, particularly with regurgitant valves and in younger patients.

Vascular Complications

The vascular complications of BAV disease are less understood and cause significant morbidity and mortality. The presence of a BAV is an independent risk factor for progressive aortic dilation, aneurysm formation, and dissection. Despite considerable controversy, it is believed that the vascular complications of BAV disease are not secondary to valvular dysfunction[10,11] and can manifest in young adults without significant aortic stenosis or regurgitation and in patients in whom the native BAV was replaced by a prosthesis. In fact, ≥50% of young patients with normally functioning BAVs have echocardiographic evidence of aortic dilation.[11] Aortic dilation is believed to be a precursor to aortic rupture and dissection, both potentially fatal events.

BAV is associated with accelerated degeneration of the aortic media, indicating that BAV disease is an ongoing pathological process, not a discrete developmental event. We and others[12–16] have identified focal abnormalities within the aortic media of patients with BAV, such as matrix disruption and smooth muscle cell loss, suggesting a degenerative process that may result in structural weakness of the aortic wall. These lesions are similar in
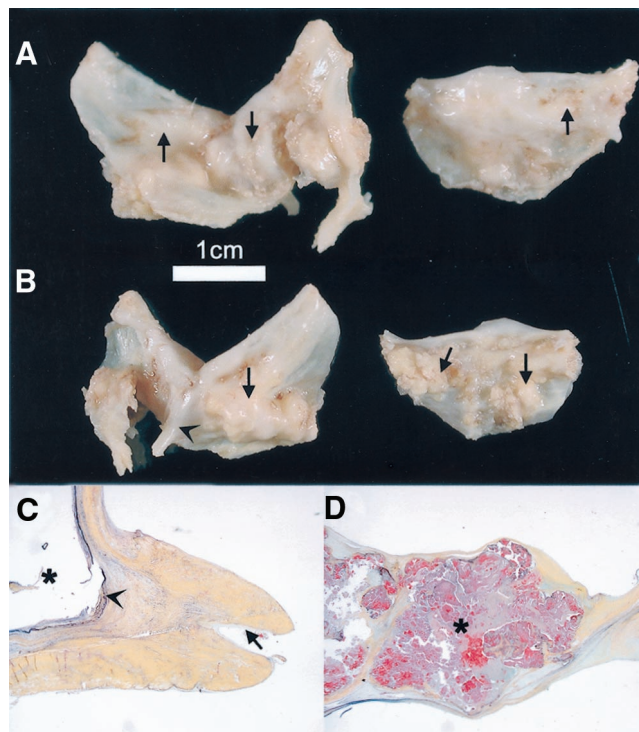
Figure 3. A through D, This aortic valve was excised surgically from a 71-year-old male, for aortic stenosis. He underwent a Bentall repair for the aortic stenosis. The aortic valve was received in 2 pieces with one piece (one cusp) larger than the other. The larger piece has a central indentation and raphe (arrowheads) and the configuration of a "bird's wings in flight." Extensive (virtually diffuse) fibrosis and nodular calcification of the cusps is seen, consistent with clinically significant aortic stenosis. The smooth but nodular flow surface (A) and the more nodular nonflow surface or sinus surface (B) are shown. The raphe and adjacent tissue show extensive thickening and calcification. A transverse section through the region of the raphe shows marked fibrosis (C). The outer or sinus end of the raphe also shows mild cellular proliferation (arrow), likely related to hemodynamic changes. The elastic lamina (arrowhead) runs from one end to the other. A histological section of a cusp shows marked calcification (asterisk) with destruction of cusp layers and a marked thickening of the cusp (D). The latter would correspond to cusp stiffening.

fibrillin-1–deficient aorta[17,18] and patients with Marfan Syndrome,[16] who also suffer from abnormal fibrillin-1 content. A loss of fibrillin-1 microfibrils may dissociate smooth muscle cells from medial matrix components, resulting in accelerated cell death and matrix disruption (Figure 4). Matrix metalloproteinases (MMPs), endogenous enzymes that degrade matrix components, have been implicated in atherosclerotic aortic aneurysm formation.[19] MMPs become activated in fibrillin-1–deficient tissues,[17,18,20] degrading the structural support of the aorta and resulting in dilation, aneurysms, and dissection. Our preliminary data suggest that MMP activity may be elevated in the aorta of patients with BAV. Understanding the pathophysiology of the aortic complications associated with BAV may facilitate the discovery of underlying gene defects and possible therapeutic targets and strategies to prevent these life-threatening complications.
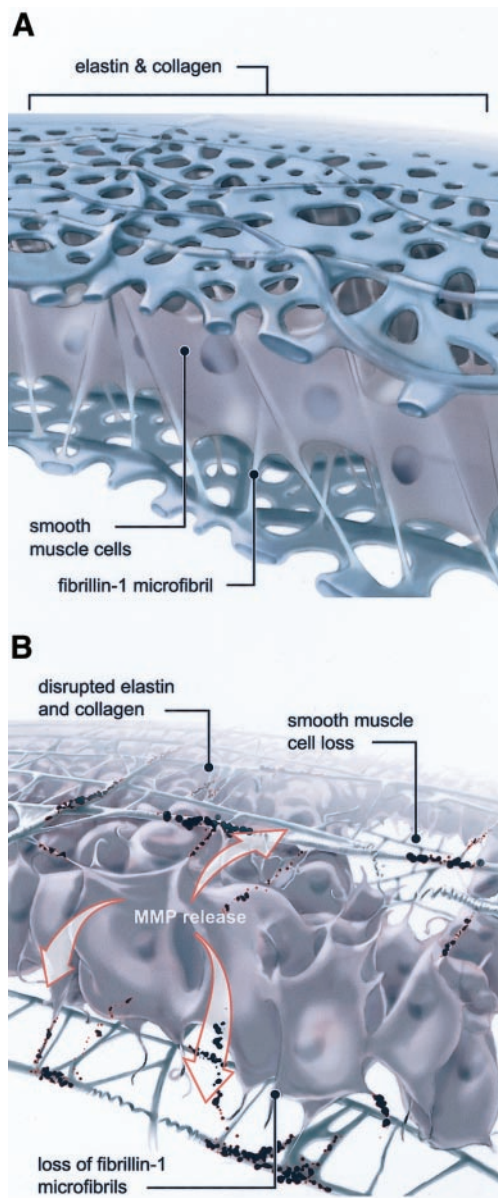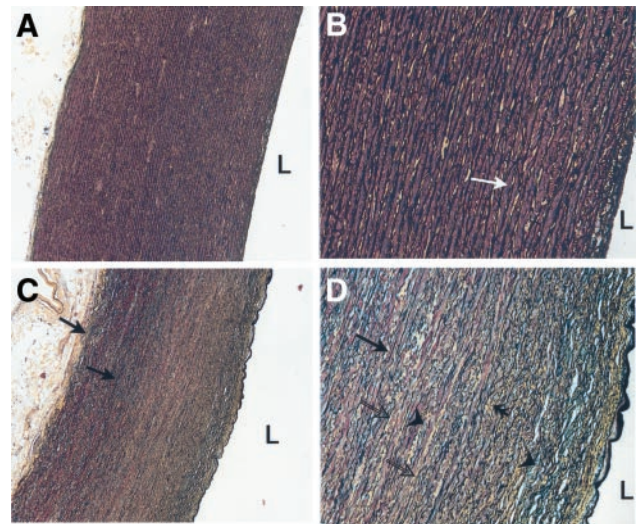
Figure 4. The elastic laminae of the aortic media provides structural support and elasticity to the aorta. In normal tricuspid valve patients (A), fibrillin-1 microfibrils tether smooth muscle cells to adjacent elastin and collagen matrix components. In patients with BAV (B), deficient microfibrillar elements result in smooth muscle cell detachment, MMP release, matrix disruption, cell death, and a loss of structural support and elasticity.

Figure 5. The healthy aorta of a patient with a tricuspid aortic valve (A and B) has a highly organized media of smooth muscle cells (stained red, white arrow), elastic plates (stained black), and collagen (stained yellow). In patients with BAV malformations (C and D), the aorta shows significant changes. Loss of smooth muscle and fibrosis (open arrows) causes collapse of the elastic plates (arrows). Mucopolysaccharides (stained greenish blue) and disarray of the elastic plates (double arrow) are evident in the media. L indicates lumen. Stain: Movat pentachrome. Original magnification: A and C, ×5; B and D, ×10.

How Should BAV Disease Be Treated?

Serial assessment of the aortic valve by echocardiography is a valuable tool to evaluate the functional state of the valve as well as to measure the aortic diameter, chamber dimensions, and ventricular function.[21] However, echocardiographic identification of a BAV can be obscured in severe stenosis and after cuspal fusion secondary to inflammation. A definitive diagnosis of congenital BAV can only be made by histological examination after valve excision.

In general, patients with mild-to-moderate valvular dysfunction and normal left ventricular (LV) dimensions and function should be monitored by echocardiography at regular intervals. Aortic valve replacement is indicated for severe valvular dysfunction, symptomatic patients, and/or those patients with evidence of abnormal LV dimensions and function (Table). Because many of these patients will require cardiac surgery during their lifetime, early referral to a surgeon with experience in aortic valve surgery is recommended. Patients with isolated aortic regurgitation may be candidates for aortic valve repair, an intervention that obviates the need for long-term anticoagulation.[22] Early referral before significant deterioration of the cusps may increase the chance for a successful valve repair. Use of the pulmonary autograft (Ross procedure) for aortic valve replacement has been advocated as an important alternative to prosthetic valve implantation, particularly in younger patients. Underlying medial abnormalities in patients with BAV may predispose to postoperative autograft dilatation[23] because the pulmonary artery has the same embryological origin as the aorta and undergoes similar degenerative changes[13] (Figure 5).

Aortic dilation should be carefully monitored by echocardiography[21] and aortic root replacement recommended more aggressively for patients with BAV[24] with aortic dilation (ie, 4 to 5 cm) than for those of patients with tricuspid valve (ie, 5 to 6 cm). Combined aortic valve repair with a valve-sparing root replacement can be performed successfully in young patients with aortic regurgitation and aortic dilation. The benefit of β-blockers to prevent aortic dilation in BAV disease is not clear; however, hypertension should be carefully monitored and controlled. The role of MMP inhibitors and gene or protein therapy to augment deficient extracellular matrix components in the bicuspid aorta is an exciting prospect that warrants further investigation.

Conclusions

You explain to the concerned pilot that: (1) The BAV is the most common congenital cardiac abnormality and may result from defects in genes that encode matrix elements; (2) BAV malformations are inherited, particularly in males, and echocardiographic screening of his children is appropriate; (3) the BAV is a disease of the entire aortic root and has a propensity for both valvular and aortic complications, often requiring surgery; (4) endocarditis is a devastating complication that can be prevented by antibiotic prophylaxis; (5) early referral to a cardiac surgeon can facilitate a plan for surgery that may prevent life-threatening complications. After reviewing his echocardiogram in detail, you note that his aortic regurgitation is mild, LV dimensions and functions are normal, and aortic root diameter is within normal limits. You reassure him that surgery is not yet required, but regular follow-up and antibiotic prophylaxis are recommended. The patient agrees to consult a cardiac surgeon for more information about the future need for surgery and the possibility of valve repair.

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