Ascending aortopathy with bicuspid aortic valve: More, but not enough, evidence for the hemodynamic theory

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Disclosures: Author has nothing to disclose with regard to commercial support.

Received for publication Oct 2, 2016; accepted for publication Oct 3, 2016.

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J Thorac Cardiovasc Surg 2017;153:6-7

0022-5223/\$36.00

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<http://dx.doi.org/10.1016/j.jtcvs.2016.10.033>

Bicuspid aortic valve (BAV) is the most common congenital cardiac defect and it is frequently associated with progressive dilation of the ascending aorta. Two theories exist to explain the association between BAV and ascending aortopathy—the genetic theory and the hemodynamic theory.¹

Even without stenosis or regurgitation, blood passing through a BAV is abnormally directed toward the greater curvature of the ascending aorta, often with slight flow acceleration. Studies using either 4-dimensional cardiac magnetic resonance imaging (CMR), or conventional magnetic resonance angiography (MRA) with computational fluid dynamics (CFD) have shown that flow asymmetry and helicity are increased in BAV, and that aortic wall shear stress (WSS) is greatly increased in the greater curvature of the aorta, compared with normal patients.^{2,3} Studies have demonstrated that these fluid dynamic stresses can promote local medial degeneration via matrix metalloproteinase-dependent pathways.^{4,5}

Youssefi and colleagues⁶ add to the body of clinical evidence that aortic hemodynamic parameters are abnormal in BAV. They performed MRA with CFD studies on 5 groups of patients (N = 45) with different valve pathologies. Patients with BAV with right-noncoronary leaflet fusion and aortic stenosis had the largest ascending aortas, greatest flow asymmetry, greatest mean WSS, and lowest oscillatory shear stress. Although the calculated values were generally in line with prior studies, the patient groups were not matched for age, body surface area, gender, or ventricular function; cardiac output was not adjusted for; and WSS was not indexed to aortic diameter. These omissions make comparison of the groups somewhat difficult to interpret. Inclusion of BAV groups without aortic stenosis and aortic regurgitation could have added significant insight to the analysis.

In a comparable work but using 4-dimensional CMR, Bissel and colleagues⁷ studied 142 subjects (95 with BAV and 47 normal controls) using groups with comparable distributions in age, peak velocity, regurgitant fraction, and left ventricular function. All hemodynamic variables in BAV

with right-handed helical flow were abnormal compared with normal controls. Most variables were more abnormal in the right-noncoronary leaflet fusion group compared with the right-left fusion group. The presence of valve stenosis significantly accentuated most of the hemodynamic abnormalities.

The hemodynamic theory is supported by the fact that aortic valve replacement (AVR) seems to slow the progression of aortic dilation. In 93 patients undergoing AVR, Regeer and colleagues⁸ found that the preoperative rate of dilation was 0.42 mm/year (BAV) and 0.15 mm/year (trileaflet) ($P = .02$). Postoperatively, these values were 0.28 mm/year (regression coefficient [growth rate] with 95% confidence interval, 0.15-0.42 mm/year) and 0.35 mm/year (regression coefficient [growth rate] with 95% confidence interval, 0.24-0.46 mm/year), respectively ($P = .5$). Kinoshita and colleagues⁹ studied 47 BAV patients undergoing AVR and found that the only variable associated with rapid postoperative dilation was greater-than-moderate preoperative regurgitation.

We still have inadequate evidence to show which theory dominates, and the heterogeneity of this disorder suggests that both mechanistic pathways can coexist. This compels us to move to the next levels of investigation. CFD should incorporate formal fluid-structure interaction modeling. Four-dimensional CMR, augmented perhaps with intravascular ultrasound, must look with greater precision at aortic

Research approach to bicuspid aortic valve. Reprinted with permission.¹¹

Central Message

Evidence is increasing for the hemodynamic role of aortic dilation in patients with a bicuspid aortic valve. It is time to move to the next level of investigation of this morbid disorder.

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FIGURE 1. The research approach to BAVaortopathy: past and future. Up to a few years ago, research on BAVaortopathy interpreted clinical aspects (eg, rate of progression, relation with severity of valve dysfunction, risk of dissection) with the aim of drawing inferences on the pathogenesis, that is, alternatively supporting the hemodynamic or the genetic theory. Inconclusive results and increasing awareness of the phenotypic heterogeneity have led to an inversely oriented approach: the contribution of either pathogenetic factor is investigated to identify the respective potential prognostic value in the clinical setting. AVR, Aortic valve replacement; BAV, bicuspid aortic valve. Reprinted with permission.¹¹

wall structure and mechanics. To distinguish between the competing theories, longitudinal studies using multivariable risk-hazard models are needed that account for standardized and state-of-the-art (eg, 4-dimensional CMR or MRA with CFD) hemodynamic as well as genetic (including familial) variables. Millions of people in the US population have BAV, but based on a search of [ClinicalTrials.gov](https://clinicaltrials.gov), only 1 registry-based clinical trial is in progress—and that study has a targeted enrollment of 500.¹⁰ A multi-institutional registry that targets a substantially larger enrollment with intention to follow for life may be necessary to power the proposed risk-hazard models. The International BAV Consortium is working on this and other means to address the current knowledge gaps (Figure 1).¹¹ With this leap in progress we may effectively determine optimal therapeutic algorithms for BAV in a patient-specific manner.

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