Nature Versus Nurture in Bicuspid Aortic Valve Aortopathy
More Evidence That Altered Hemodynamics May Play a Role

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There is no disease more conducive to clinical humility than aneurysm of the aorta.1
—William Osler

Bicuspid aortic valve (BAV) is a common congenital cardiac malformation affecting 1 to 2% of the population with a predilection for males.2 Although patients with BAV often develop aortic aneurysms requiring surgical intervention,3,4 the formation of aortic aneurysms is variable and there are currently no good predictors of aneurysm formation. Although studies have shown that patients with BAV have genetically inherited aortic disorders that predispose them to aneurysm development,3,5 there is ongoing controversy concerning the degree to which altered hemodynamics (nurture) and genetics (nature) interact. The study by Mahadevia et al7 in this issue of Circulation provides important additional support for the argument that altered flow patterns attributable to abnormal valve architecture do indeed play a role in BAV aortopathy.

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Phase contrast MRI has been used to measure changes in blood velocity and flow with standard techniques measuring these parameters in 2 dimensions, or through plane. Four-dimensional (4D) MRI allows the speed and direction of aortic flow to be visualized and measured over time in all 3 dimensions, thereby providing not only informative images but an improved tool for the study of flow disturbances. One of the more active areas of research using 4D MRI has been in BAV aortopathy with the hope that understanding flow disturbances will give new insight into BAV-associated aneurysm formation. Prior studies8–10 using 4D MRI have demonstrated altered ascending aortic wall shear stress (WSS) in patients with BAV and have suggested a mechanistic link between the alteration in aortic outflow caused by the fusion of BAV cusps and the development of ascending aortic aneurysms.8–11 However, these studies have focused primarily on BAV patients with right and left coronary cusp fusion, a reflection of the fact this is the most common form of BAV. Using echocardiography and multidetector computed tomography to study 167 subjects with BAV, Kang et al have reported an association between the frequency of different patterns of aortopathy and BAV morphology.14 However, no previous study has attempted to provide a mechanistic link between BAV morphology, alterations in aortic outflow and aortic pathology in the same study cohort.

The study of Mahadevia et al in this issue of Circulation7 expands on earlier studies by using 4D MRI to study the impact of the morphological type of BAV cusp fusion on perturbations in aortic outflow, and the subsequent aortopathy that results. The authors studied aortic flow in 15 healthy volunteers, 30 matched aorta-size controls, and 30 BAV patients all of whom had aortic dilation (>40 mm at ≥1 levels). The authors further divided the BAV group based on morphology of the fused cusps into those with right and left coronary cusp (RL) fusion and right and noncoronary cusp (RN) fusion. Cases with the rarer left and noncoronary cusp fusion variant were not represented in the study. The study’s inclusion of equal numbers (15) of patients with RL and the less common RN fusion is notable because previous 4D MRI hemodynamic studies8–10 have focused predominantly on RL patients. Thus, this is the first study that allows meaningful comparison of the hemodynamics of RL versus RN subjects.

To characterize the hemodynamic effects of BAV, the authors measured WSS, flow angle, and flow asymmetry (measured as normalized flow displacement) at 3 points along the ascending aorta, all using 4D MRI. To provide a framework for assessing the potential impact of hemodynamics on aortic morphology, they categorized aortopathy as type 1 (dilated root), type 2 (enlargement of the tubular portion of the ascending aorta), and type 3 (diffuse involvement of the entire ascending aorta and transverse arch), as has been previously reported.14

The authors confirmed prior studies demonstrating that systolic WSS was significantly higher among patients with BAV compared with the matched aorta-size controls.9 Additionally, they noted different distributions of the locations of maximal WSS in RL versus RN BAV morphologies, although these differences did not reach statistical significance. Although flow angle was not statistically different between BAV and aorta-size controls, flow displacement was greater at the sinotubular junction for both RL and RN BAV patients versus aorta-size controls but in the distal ascending aorta only for RN patients who were more likely to have type 3 aortopathy.

In patients with BAV, aortic outflow may not be directed parallel to the long axis of the vessel as is normal, but may be displaced in a pattern that is dictated by the morphology of the fused aortic cusps. In this study, the authors reported that patients with RL fusion tended to have aortic flow that was predominantly directed toward the right-anterior aortic wall, although those with RN fusion had flow that tended toward...
the right-posterior wall. Aortic flow among the aortic-size controls was more central and parallel to the long axis of the aorta, similar to that of healthy volunteers. The authors argue that BAV morphology dictates displacement of the aortic jet and the portion of the aorta that experiences high WSS, ultimately leading to aneurysm development.

Several previous studies have also used 4D MRI flow in patients with BAV. Barker et al9 studied 60 subjects including 15 patients with BAV (12 of whom had RL fusion), 15 healthy volunteers, 15 age-appropriate volunteers, and 15 age and aorta-sized controls. They found that peak velocities of aortic flow were significantly greater in patients with RL fusion than in all 3 control groups. They also suggested that there was a difference in aortic flow patterns between RL versus RN BAV morphology, but their assertion was limited by the fact that only 3 RN subjects were studied. With a much larger RN cohort, the current study argues this point much more effectively.

In a related study, Hope et al. compared 20 patients with tricuspid aortic valves to 26 patients with BAV (21 with RL fusion) using 4D MRI flow.10 Whereas 19 BAV subjects had eccentric flow, 7 subjects had normal flow, something less commonly encountered in the current study. Inspection of the flow asymmetry maps in the Mahadevia study7 (Figure 4) suggests that some BAV patients had central flow but fewer than in the Hope study. The difference may reflect that fact that in the Hope study, only 9 subjects had aortic dilation, all but 1 of these occurring in the group with eccentric flow. If there is, as suggested, a link between eccentric flow and aortic enlargement, including only BAV patients with enlarged aortas in the Mahadevia study might be expected to favor finding more asymmetrical flow patterns. In addition, Hope et al used more qualitative definitions of asymmetry than the quantitative peak velocity mapping technique used in the current study.

Variation in the degree of flow asymmetry with some patients with BAV having normal central flow raises the question of whether those with normal flow are less likely to develop aortopathy. In a second study, Hope et al provided support for this hypothesis by studying the longitudinal association between 4D MRI acquired flow data and aortic enlargement in BAV patients.12 They studied 12 tricuspid aortic valve controls and 13 BAV patients (all with RL fusion) and performed follow-up MRI studies at 4.3±2.9 years. They found that overall, BAV patients had significantly higher growth in aortic size compared with controls (0.8 versus 0.1 mm/yr, P=0.004), whereas BAV patients with abnormal flow had significantly higher growth rate compared with BAV with normal flow (1.0 versus 0.0 mm/yr, P=0.02). Of the hemodynamic parameters used, Hope et al found that flow displacement correlated better with aortic growth than either maximum velocity or WSS, in keeping with the observation in the Mahadevia study that flow displacement better discriminated between study groups than flow angle. It appears, therefore, that flow displacement, as a quantitative measure of flow asymmetry, is an important parameter to include in future studies of BAV aortopathy.

The association between abnormal flow and aneurysm formation warrants additional study in a larger group of patients that includes those with normal aortas, with an additional question being whether patients with BAV who initially have central flow develop abnormal flow when there is superimposed calcification and/or valve dysfunction (stenosis/regurgitation).

The current study reports that 87% of RL patients had type 2 aortopathy with 53% and 34% of RN subjects having types 1 and 3 aortopathy, respectively. These findings differ from those of Kang who noted that there was no significant difference in the prevalence of type 1 and 2 aortopathy in the BAV phenotypes and that only 32% of the right-left coronary fusion subjects (48% of those with enlarged aortas) had type 2 aortopathy.14 In better agreement with the current study, Kang et al did, however, note that patients with either right-non or left-non fusion (grouped together in their study) were more likely to have type 3 aortopathy than those with right-left fusion. The explanation for these differing findings is uncertain but may reflect the smaller sample size in the Mahadevia study, selection bias or incompletely captured confounding variables such as valve dysfunction. Thus the link between BAV phenotype and the type of aortopathy remains incompletely characterized.

In comparing the Mahadevia study to previous reports and assessing the generalizability of its findings, it would be helpful to have additional information concerning the way in which the study groups were identified as well as study group characteristics. There were no subjects with normally sized aortas, none whose aortic pathology did not fit into the classification scheme used, and none with more than moderate valve dysfunction. It would also be interesting to know about potential confounding variables such as the coexistence of coarctation or other congenital anomalies, hypertension, valve calcification, and medications such as β-blockers or vasodilators. The way in which aorta-size matched subjects were identified is also unclear. Were they matched at both levels measured? Better characterization of valve dysfunction in individual subject groups would also be helpful. Because once can assume that normal subjects had no stenosis or regurgitation, it would be interesting to know whether, for example, all 10 moderate aortic regurgitation subjects fell into 1 BAV phenotypic group, because the study of Barker et al15 reported differences in WSS between groups with flow reversal ratios greater than or less than 0.10. Better characterization of the degree and distribution of aortic stenosis and the methods used for quantitation would likewise be helpful because patients with aortic stenosis tend to have higher velocity aortic flow which may also impact aneurysm formation. Along this line, a follow-up study that includes patients with severe valve dysfunction in large enough numbers to address the impact, if any, of regurgitation or stenosis on flow characteristics and aortopathy would also be interesting.

It would be useful to know whether the radiologists performing the hemodynamic analysis were blinded, to the degree possible, to valve and aortic phenotype. Additionally, in a method that requires manual input at multiple steps, inter- and intraobserver variability data would also be informative particularly because the authors suggest that flow displacement could be an important tool for future studies.

Despite the intuitive appeal of the study findings, the relation of hemodynamics to aortic phenotype must be viewed as preliminary. In Figure 5, the authors recognize this and
appropriately note that the study numbers were too small for meaningful statistical analysis. Similarly WSS measurement displays (Figure 3) appear different for RL versus RN subjects but statistical significance was demonstrated only in the comparison to aorta-size matched subjects. It would be interesting to speculate as to why RN but not (in this series) RL subjects had type 1 aortopathy, because valve flow angles and flow displacement at the sinotubular junction level were comparable in both groups. Although the authors assessed the type of aortopathy according to BAV cusp fusion morphology, perhaps a direct and tighter correlation between the anatomic region of aneurysm formation and the site of maximal WSS or jet impingement would be informative.

As the authors acknowledge, additional studies with larger and more clearly defined study groups and longitudinal follow-up are essential. Given the challenges in recruiting patients with multiple BAV morphologies and the large number of potentially confounding clinical variables, such studies would likely be best accomplished with a multicenter trial and multicenter participation in registries such as that created by the University of Michigan (NCT01756220). The ability to include genetic data and 4D MRI parameters such as those presented in the current study would be highly desirable. Without such data, it is impossible to determine whether 4D MRI flow data have prognostic value or whether they should be used to guide the management of BAV patients. However, it is clear that 4D MRI, using the measures of wall shear stress and flow asymmetry used in the current study, is a valuable tool in studying potential links between BAV morphology, associated flow disturbances and aortopathy. Given the prevalence of BAV and the clinical impact of associated aortopathy, such studies deserve a high priority.

Disclosures

None.

References


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