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EDITORIAL COMMENTARY

Real estate of the bicuspid aorta: Location, location, location!

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Central Message

Remodeling of ECM in the aortas of patients with BAVs is distinct from patients with TAVs.

See Article page 1718.

As the most common congenital heart defect, bicuspid aortic valve (BAV) disease is a significant health care burden.¹ With an understanding that patients with BAVs may have a predisposition to aortic complications secondary to an underlying aortopathy, surgeons often are challenged with decisions to prophylactically resect a moderately dilated aorta in those with BAVs. Surgeons' perspectives on the cause and mechanisms of bicuspid aortopathy may influence the timing and extent of their surgical approach.^{2,3} Bicuspid aortopathy is characterized by extracellular matrix (ECM) remodeling resulting in degeneration of elastic and collagen fibers within the aortic wall.⁴ Does the remodeling process of bicuspid

aortopathy reflect a distinct disease entity compared with patients with tricuspid aortic valves (TAVs)? Should these patients be resected more aggressively? Some recent data challenge this long-held belief and suggest that histologic changes are not more severe in the BAV compared with the TAV.⁵ Studies that help define the molecular, cellular, and structural alterations within the aorta of patients with

BAVs compared with patients with TAVs can provide meaningful insights for surgeons that could influence resection strategies.⁶

In this issue of the *Journal*, Tsamis and colleagues⁷ show that the orientation of elastic and collagen fibers is distinctly different in BAVs compared with TAVs. The authors use an innovative and quantitative multi-photon microscopy technique to evaluate and compare the ECM of explanted aortic tissues, and in so doing provide novel insights into structural ECM remodeling that exceeds the clear limits of conventional histology with semiquantitative grading of disease severity. The study examines 3 regions above the sinotubular junction coinciding with the left, right, and noncoronary aortic sinuses. Compared with TAVs, elastic fibers in the medial layer of BAVs exhibit fewer undulations adjacent to the right and noncoronary sinuses, suggestive of elastin fiber recruitment from excessive mechanical load bearing. This observation is consistent with asymmetric dilatation of the greater curvature commonly found in patients with BAVs, associated with fusion of the right and left coronary cusps.¹ In contrast, increased undulations and a decreased orientation of collagen fibers in the BAV wall were found adjacent to the left coronary sinus, corresponding to the lesser curvature. These data collectively suggest that location is important in the BAV. It remains unclear if these regional alterations in ECM architecture will predispose a patient to a higher risk of aortic rupture or progressive enlargement that would warrant prophylactic surgical resection.

Valve-mediated hemodynamics in the ascending aorta may help explain the regional tissue remodeling observed in this study.⁸ By using 4-dimensional flow magnetic resonance imaging, we observed regional ECM remodeling in patients with BAVs corresponding to altered valve-mediated wall shear stresses, which also correlated with patterns of cusp fusion and aortopathy.^{9,10} Valve-mediated hemodynamics and wall shear stress can be different between BAV and TAV cases, even when comparing valves without stenosis or regurgitation.¹⁰ The implication of these data for surgeons is that the BAV may not be identical to the TAV. If indeed altered valve-mediated hemodynamics drives maladaptive ECM remodeling in the ascending aorta of patients with BAVs, then location may be an important consideration in resection strategies. Resection strategies may need to evolve beyond size criteria alone and become more individualized and targeted to locations most at risk.

The Pittsburgh team has made important past contributions to our understanding of a distinct process of ECM remodeling in the ascending aorta of patients with BAVs.¹¹⁻¹³ Their current study has some limitations to consider. The impact of changes in elastic fiber undulations (quantified as the amplitude of angular undulation) on the biomechanics of aortic tissue, although suggestive of

tissue dysfunction, requires further validation with correlation to tissue biomechanics and meaningful clinical end points. It remains unclear what magnitude of change in elastic fiber alignment (eg, 10.5° vs 15.5°) will translate into regional tissue dysfunction. As acknowledged by the authors, this study had a limited sample size with only 6 patients per group. Coupled with their comparison of 18 locations between these 2 groups of patients, we must consider the risk of statistical errors. On the other hand, the differences observed are even more striking given the limited sample size.

Tsamis and colleagues⁷ further contribute to our understanding that BAV remodeling occurs regionally and perhaps in a pattern that is distinct compared with patients with TAVs. This study, although not conclusive, provides further support that specific locations within the BAV may be at greater risk of biomechanical complications. Studies to further evaluate the direct functional consequences of these altered indices of elastic fiber architecture will be useful and likely are forthcoming.

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