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Commentary: How form and function of the aortic valve influence the proximal aorta

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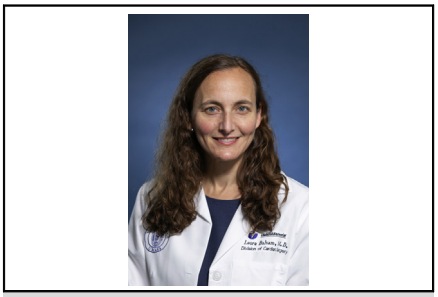

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CENTRAL MESSAGE

The mechanisms that underlie the aortopathy associated with unicuspid aortic valve disease are poorly understood. A new study lends insight into the molecular basis of this process.

In this issue of the *Journal*, Balint and colleagues[1] re-evaluate the relationship between nitric oxide signaling, hemodynamic forces, and aortopathy in patients with tricuspid aortic valve and unicuspid aortic valve (UAV) disease. Over the recent past, the overarching focus of this research group has been to better understand the processes that lead to proximal aortic dilatation in patients with aortic valve disease. To do this, they have examined aortic specimens from patients with tricuspid aortic valve disease, bicuspid aortic valve (BAV) disease, and even UAV disease.[1-4] Two hypotheses are commonly discussed in the literature for the development of aortopathy in patients with aortic valve disease. The first is that the aortopathy is secondary to sheer stress from turbulent blood flow through the diseased aortic valve. The second is that aortopathy is genetically mediated. In the case of BAV and UAV disease, the cumulative findings from Balint and colleagues lend greater support to the genetic hypothesis.

Endothelial nitric oxide synthase (eNOS), an enzyme responsible for the generation of nitric oxide in the vascular endothelium, is important for maintaining aortic integrity, and its dysregulation may lead to aortopathy. Balint and colleagues[1] evaluate eNOS mRNA and protein expression in both the concave and convex portions of the aorta. These areas may experience different sheer stress due to flow through an asymmetric valve. In the case of BAV with the more common morphology of fusion of the right and left cusps, for example, greater sheer stress exists on the convex portion of the ascending aorta. This group has previously shown that dysregulation of eNOS occurs in BAV aortopathy; however, they did not identify regional differences in eNOS expression in areas of higher and lower sheer stress on the ascending aorta. In the current study, they report similar findings in aortic specimens from patients with UAV. These findings are taken as support for the hypothesis that genetic, rather than hemodynamic forces, underlie eNOS dysregulation in BAV and UAV.

The literature is sparse when it comes to understanding the mechanistic basis of UAV-associated aortopathy as well as its natural history. This is not surprising, as UAV is an exceedingly rare congenital anomaly that has been described in only 0.02% of the echocardiography referral population.[5] Balint and colleagues have amassed an unusually large experience, with 22 adult patients with UAV in this series. That said, with a sample this size, there is lack of uniformity in patient characteristics, which may affect some of their results, including variable degrees of aortic valvular disease (stenosis, insufficiency, or both). There are also inherent limitations in using pathologic specimens to try to understand the mechanism of disease. Abnormalities may be identified; however, it is not possible to know whether they are causative or secondary to the underlying

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disease process. The practicing clinician may wonder how these experimental findings can be leveraged into therapies in the future, but the reality is that they require further validation.

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