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EDITORIAL COMMENT

Fate Versus Flow

Wall Shear Stress in the Aortopathy Associated With Bicuspid Aortic Valves*

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Highly prevalent and commonly associated with complications, bicuspid aortic valve (BAV) disease presents a more significant burden than any other congenital heart disease (1). Although the individual course is variable, many patients eventually require surgical intervention to address valve dysfunction or aortic aneurysm (2,3).

The aortic involvement in BAV has been attributed to an intrinsic, genetic abnormality and may be encountered with or without functional impairment of the valve. The presence, severity, and location of aortic involvement is variable, which begs an important question: Beyond the genetic predisposition to dilation, how and to what extent do long-term hemodynamic conditions in the aorta contribute to the incidence, progression, and outcomes of aortic remodeling in BAV patients? Intrinsic or acquired abnormalities of the vascular wall at multiple sites are known to be exacerbated by hemodynamic conditions, including systemic hypertension and hyperdynamic systolic ejection. In this issue of the *Journal*, Guzzardi et al. (4) examine abnormal local hemodynamics and their relation to potential mechanisms contributing to aortic root dilation in BAV patients.

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ABNORMAL AORTIC WALL STRUCTURE WITH BAV: FORM FOLLOWS FUNCTION

The aortic wall's normal structure is highly organized with a very rigid architecture of elastic fibers and surrounding matrix. Recent studies have identified an induction/imbalance of proteolytic pathways in patients with ascending aortic aneurysms (5–7). In resected aortic samples from patients with BAV and ascending aneurysms, overall matrix metalloproteinase (MMP) activity has been reported to be increased more than 3-fold from referent normal aortic specimens (6). The MMPs constitute a large family of proteolytic enzymes with a diversity of substrates, but the relative levels of some more common MMP types, such as MMP-2 and MMP-9, are altered in BAV/aneurysm specimens (5,6). MMP induction and activity are regulated in part by endogenous tissue inhibitors of the MMPs (TIMPs). The 4 known TIMPs are differentially regulated in pathophysiological conditions and have dissimilar effects on cell viability, growth, and matrix remodeling (8). In the context of BAV and aortic aneurysms, a dysregulation of these TIMPs appears to occur, concomitant with a shift in MMP expression and activity (5–7). Thus, a shift in the MMP/TIMP balance within the aorta of BAV patients most certainly contributes to changes in aortic wall matrix structure and composition, and the aortic aneurysm development and progression. What remains unclear, however, is what are the biological/biophysical stimuli driving the imbalance in the MMP/TIMP portfolio in BAV patients? Although the stimuli are likely to be multifactorial, the study by Guzzardi et al. (4), provides new insight on a biophysical stimulus that may propel changes in local matrix homeostasis and, in turn, ascending aortic structure: wall shear stress (WSS). They found that in regions of high WSS, elastin content and structure were severely disrupted compared with distal regions

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of lower WSS. Moreover, these regional differences in WSS patterns and elastin content and structure were associated with a shift in the expression of specific MMPs and TIMPs. These findings provide additional insight into how alterations in local flow dynamics in BAV patients may be transduced into proteolytic events, which in turn drive adverse aortic remodeling.

Although the study by Guzzardi et al. (4) is associative and derived from a set of measurements at 1 point in time, there are other studies that support the postulate that regional changes in mechanical stress caused by a BAV can induce matrix proteolysis within the ascending aorta (6,9). In an ex vivo porcine aortic valve preparation, the WSS caused by BAV morphology induced changes in MMP/TIMP expression levels (9). In resected aortic samples from BAV patients with ascending aneurysms, different MMP/TIMP expression profiles were observed in patients with different patterns of aortic valve fusions (6), providing indirect evidence that differences in local flow patterns and WSS likely contributed to these changes in matrix proteolytic potential.

However, it is unlikely that changes in local WSS are the only driving force for changes in aortic structure in patients with BAV. First, this is a congenital malformation and thus changes in gene expression and development patterns likely exist. Second, a number of polymorphisms in both MMP and TIMP sequences have been identified, which may predispose patients to an acceleration of aortic aneurysms (10). Third, the expression of certain MMP types in patients with thoracic aortic aneurysms with normal aortic valves, as well as with BAVs, are associated with cytokine receptor-mediated pathways (5–7), suggesting local inflammatory cascades may be operative. What is clear is that changes in MMP/TIMP profiles and subsequent degradation of the aortic matrix is a likely common pathway for thoracic aortic aneurysm development and progression. The new study by Guzzardi et al. provides evidence that, in BAV patients, an additional stimulus that may drive a feed-forward effect on matrix proteolysis within the ascending aorta is changes in WSS.

AORTIC FLOW AND ESTIMATION OF WSS

Recent work using 4-dimensional flow visualization with cardiac magnetic resonance imaging (4D CMR) has confirmed that aortic flow is distorted in the setting of BAV and/or aortic dilation. Altered blood flow direction and velocity, with changes in flow asymmetry, helicity, and reversal, are findings associated with BAV and other aortic aneurysm (11). The spatiotemporal characteristics of distorted flow in the setting of aortic valve dysfunction and abnormal aortic geometry can be expected to result in altered WSS, which is an estimate derived from the velocity data from 4D CMR. One of the lessons of recent work on aortic 4D flow is that regions of elevated WSS are not readily predicted by jet direction alone. As wall shear is the force parallel to the wall, the location and degree of turning of flow in the ascending aorta and root will influence where high velocities occur along the wall, thereby increasing the WSS in regions not directly impacted by a jet from a stenotic valve.

Among the approaches to studying the regional hemodynamic forces on the proximal aorta, shear forces are appealing as they have well-recognized impacts on vascular function and disease (12,13). Shear can be studied during a systolic interval, as in Guzzardi's study (4) where high shear was assumed to be the most relevant; low shear, shear gradients, and oscillation in shear have also been associated with vascular dysfunction and atherogenesis. Diastolic wall shear is also abnormally high in the proximal aorta in BAV patients and will reflect peripheral vascular properties as well (14). Whether systolic WSS alone would be the best target to define the hemodynamic exacerbators of BAV aortopathy has not been proven. WSS estimated at the clinical stage where surgery is indicated selects a patient group with significant longstanding hemodynamic abnormalities; the degree to which wall vulnerability and abnormal forces have combined to create aortic dilation is difficult to parse at this single time point. By this late stage, the shape, the flow, and the load are all likely abnormal, and it is not surprising that this is reflected in the WSS.

The 4D CMR methods to estimate WSS used in this study and other studies share well-recognized limitations. Limited spatial resolution, partial volume effects, and numerical derivation of the velocity field are sources of inaccuracy when measuring event at the flow-wall interface, and are likely to introduce underestimations in WSS (15). The degree of underestimation is more marked with increased WSS (16). The approach of comparing regions within the same patient to minimize the influence of changeable load or frequency avoids some, but not all, of the important provisos about using these estimates of WSS.

INTEGRATION OF LOCAL SHEAR STRESS MEASUREMENTS IN PRE- AND POST-OPERATIVE BAV

Can a better understanding of 4D aortic flow in BAV inform patient assessment at other time points? Surveillance and prediction of progression are important in the care of these patients, and the opportunity exists to include flow analysis with the surveillance