See Article page 1684.

Commentary: Determining the risk for dissection and rupture in patients with aortic regurgitation—size may not matter

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CENTRAL MESSAGE

Aortic regurgitation results in increased inflammation and medial degeneration of the proximal aorta independent of aortic diameter.

Aortic diameter has traditionally been used to determine the timing for elective surgical repair of ascending aortic aneurysms to avoid the risks of dissection and rupture.¹ The extracellular matrix is crucial to maintaining the integrity and size of the aortic wall. The degradation of the extracellular matrix is controlled by processes involving matrix metalloproteinases and their tissue inhibitors, which are secreted by vascular smooth muscle cells, fibroblasts, and endothelial cells. Wall shear stress (WSS) alters regional and radial wall stress, which can result in abnormal areas of extracellular matrix hemostasis in the ascending aorta. Abnormal valve-mediated flow dynamics, which can occur in patients with aortic stenosis (AS) and aortic regurgitation (AR), result in regional differences in WSS that affect the stress placed on individual endothelial cells in the intimal layer. These altered blood flow patterns predispose to aortic dilatation and aneurysm formation, which ultimately result in dissection and rupture.^{2,3}

Gross and colleagues⁴ describe the differences in flow patterns, gene expression, and histology in the proximal aorta in patients with AS and AR undergoing aortic valve replacement with and without proximal aortic surgery. Patients with connective tissue disorders, endocarditis, and those requiring urgent surgery for dissections or ruptures were excluded. Magnetic resonance imaging was used to assess aortic diameter and turbulent flow patterns. Segments of the ascending aorta associated with altered WSS were

analyzed for inflammatory markers (ie, VCAM1), gene expression of extracellular matrix proteins (ie, COL1A1 and ELN), and evidence for fibrosis, elastin fragmentation, and cystic medial necrosis on histological tissue sections.

Patients with AR exhibited increased expression of inflammation (ie, COL1A1) and histologic expression of medial degeneration compared with patients with AS. When valve morphology was compared in patients with AR, patients with tricuspid valve morphology had increased markers of cystic medial necrosis, but no difference in inflammatory markers. These findings were accentuated in patients with aortic diameters >4 cm. The authors hypothesize that abnormal retrograde flow in AR patients alters the WSS on intimal endothelial cells and predisposes to dilatation and aneurysm formation. In their study, the mean proximal aortic diameter in all patients with AR was significantly higher than in patients with AS (5.2 cm vs 4.3 cm; $P < .001$). These results are similar to those reported by Heng and colleagues,⁵ who found more histological abnormalities in the aortas of patients with tricuspid aortic valves (TAV) versus bicuspid aortic valves (BAV).⁵ Roberts and colleagues⁶ studied elastin fiber loss in aortas >4.5 cm. Only 10% of patients with AS had moderate-to-severe elastin fragmentation compared with 50% of patients with AR.⁶

The inadequacy of aortic diameter alone to predict aortic dissections was demonstrated by Kreibich and colleagues⁷ in a series of patients undergoing surgery for acute type A dissections. Predissection aortas were <5.5 cm in 96% of

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TAV patients and <5 cm in 76% of all BAV patients. Therefore, <5% of all TAV patients and <25% of all BAV patients would meet current guidelines for elective repair of the ascending aorta.¹

If aortic diameter alone is insufficient to predict dissection or rupture, what other parameters can be followed to prevent these devastating complications? Matrix metalloproteinases,⁸ MiR-17 related messenger RNAs,⁸ transforming growth factor beta,⁹ stimulator of interferon genes,¹⁰ and receptors for advanced glycation end products, have all been associated with extracellular matrix degradation and derangements of elastin and collagen fibers in the wall of aortic dissections. WSS cannot be directly measured and must be determined from computational modeling, such as finite element analysis, which has been used to quantify WSS in arteries.¹¹ Further refinements will be needed in magnetic resonance imaging equipment to assess extracellular matrix degradation. This will include 4-dimensional flow imaging for enhanced visualization of transvalvular flow and specific magnetic resonance imaging sequences for more detailed information regarding the degree of fibrosis and inflammatory activity of the aortic wall.

Combining measurements of WSS with biomarkers of inflammation and extracellular matrix degradation may ultimately improve our ability to predict aortic events and determine the timing for prophylactic aorta replacement. However, before these biomarkers and imaging studies can be incorporated into current guidelines, larger, adequately powered, prospective studies from aortic centers of excellence will be needed. Nevertheless, studies such as those by Gross and colleagues⁴ strongly suggest that when

determining the risk for dissection and rupture in patients with AR, size may not matter.

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