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Commentary: How does the aortic wall interact with the aortic valve?

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The manuscript by Gross and colleagues¹ explores the aortopathy associated with both aortic valve stenosis and regurgitation. They examined aortic tissue harvested during aortic valve-replacement operations from 2 places on the aortic wall (one from the outer curvature of the ascending aortic wall and one from the inner curvature). Analysis of these aortic tissue samples from 64 patients with aortic regurgitation (AR) and from 67 patients with aortic stenosis (AS) having aortic valve replacement allowed comparisons of histomorphology and molecular components of the aortic wall in these 2 forms of aortic valve dysfunction. The authors found that patients with AR had significantly more fibrosis, elastin fragmentation, and inflammation in both aortic wall samples compared with patients with AS. The authors studied fibrotic molecular markers in aortic tissue and found upregulated gene expression of COL1A1 in the AR group and increased CCL2 gene expression on the inner curvature of patients with AR. Their examination of these molecular markers suggested increased inflammation and increased expression of fibrotic markers in patients with AR compared with patients with AS.

The authors highlight the existence of aortic wall disease associated with aortic valve disorders and point out that there is a need for better understanding of the pathophysiology of aortopathy associated with aortic valve disease. There are important clinical implications of the authors' work that relate to arterial wall remodeling as a result of aortic valve pathology. Figure 1 depicts different types of arterial remodeling. There are at least 3 major types of arterial remodeling that can be distinguished: hypotrophic (left column in Figure 1), eutrophic (center column) and hyper-

CENTRAL MESSAGE

Aortic wall changes accompany aortic valve pathology and may be an important component of outcomes of aortic valve procedures.

trophic (right column).^{2,3} In addition, remodeling can be either inward or outward. Hypotrophic remodeling results in a relative thinner wall and a lower wall-to-lumen ratio. Conversely, hypertrophic remodeling is characterized by thickening of the vascular wall due to cellular hyperplasia and/or hypertrophy. There is associated deposition of extracellular matrix material that results in increased wall-to-lumen ratio. When the diameter of the vessel changes but the wall-to-lumen ratio remains the same, it is called eutrophic remodeling. All types of arterial remodeling can occur in cardiovascular disease, depending on the underlying pathophysiology (eg, aneurysm or hypertensive arterial stiffening) and arterial site (eg, central elastic arteries vs peripheral resistance arteries). It seems reasonable to infer that all of these arterial wall remodeling changes occur to varying extents in patients with AS or with AR. Indeed, the authors' results highlight aortopathy changes that differ between patients with AS and with AR.

A surgeon who reads these results will most likely question whether these changes of aortopathy are reversible, especially after valve replacement. The authors suggest, and offer some published reports as support, that these changes in the aortic wall are not reversible and, if possible, should be addressed at the time of aortic valve replacement, especially in patients with AR, even in those without aneurysmal changes. However, the authors do not discuss the impact of aortic wall replacement on remaining native aortic wall remodeling.

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Changes in the Aortic Wall Associated with Aortic Valve Disease

FIGURE 1. Aortic wall changes associated with aortic valve disease.

Do the authors have evidence to suggest that aortic wall changes are irreversible? Are aortopathy changes in the aortic wall reversible or subject to changes from medication or treatment of hypertension? What factors would the authors predict that might be able to modify wall changes of aortopathy?

The authors excluded patients with endocarditis. I wonder whether the patients with endocarditis might be very informative. Examination of the aortic wall in patients with endocarditis might help to explain the timing of aortopathy changes. The authors avoided discussion of aortic wall gene expression in patients with endocarditis. Future studies should address patients with endocarditis and describe the upregulated gene expressions seen in patients with aortic valve infections.

A related question revolves around the natural history of aortic disease in patients with aortic valve pathology. The authors' measurements are static measurements. It is possible that there is a linear relationship between the degree of regurgitation or stenosis and the progression of aortic wall pathology. This raises the question of timing and progression of aortic wall changes that may be paralleling the changes in the aortic valve. It is possible that there is a critical time when aortic wall exposure to AR or AS begins the process of irreversible aortopathy changes. This raises the question of simultaneous disease progression in the aortic wall and in the valve itself. It might be possible to use advanced imaging and even magnetic resonance imaging (MRI) to define the extent of aortopathy and correlate this with the longevity and hemodynamic patterns of valvular pathology. Future studies would do well to correlate the degree of aortic wall disease with progression of valvular disease.

Perhaps more importantly, I wonder if the authors have thought about interventions that might change this natural history of aortic valve-related aortopathy. This question revolves around 2 questions. Are aortic wall changes in gene expression reversible and what factors influence aortic wall stress related to aortic valvular pathology? For example, is it possible that hypertension treatment might impact aortic wall stresses and influence aortopathy? Do patients with aortic valve disease who are treated for hypertension have decreased wall stress and reduced aortopathy? These questions revolve around fixing a problem in the aortic wall, something that has not been traditionally considered in treatment of aortic valve disease. A necessary starting point is to define the simultaneous progression of aortic valve and aortic wall changes. This manuscript addresses a problem that has not been a traditional consideration in patients presenting for aortic valve replacement. These novel findings should provide a basis for future studies about the interaction between valvular pathology and related aortic wall changes.

One thing that will surely surface to the minds of cardiothoracic surgeon readers is the predictive impact of aortopathy. Since the authors show some elegant MRI pictures of aortic wall pathology, readers might ask about the prognostic significance of the abnormal MRI findings in aortic valve and aortic wall images. Several questions might arise. What is the prognostic significance of aortic wall abnormalities in patients with aortic valve disease? Does the finding of MRI aortic wall abnormalities provide evidence that should guide surgeons in the choice and timing of operations for aortic valve pathology? What is the effect of these aortic wall abnormalities seen on MRI on overall prognosis and progression of disease in aortic valve pathology? MRI

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exams are not a typical study done in patients with aortic valve pathology. Is it possible that MRI studies of the aortic wall and aortic valve will be a routine part of assessment of patients who are candidates for aortic valve replacement? To summarize, this manuscript presents some novel and potentially important information that should stimulate surgeons to consider novel factors surrounding patients with aortic valve disease.

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