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EDITORIAL COMMENT

Ischemia in Aortic Stenosis

New Insights and Potential Clinical Relevance*

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In aortic stenosis (AS), a longstanding question revolves around mechanisms for ischemia in patients with angina but normal coronary arteries (1). The debate has focused on competing theories of microvascular dysfunction (inability of the myocardium to reduce arteriolar resistance) versus blood flow maldistribution (inability to meet a higher workload due to combined effects of a transmural perfusion flow gradient and reduced diastolic perfusion time). The elegant study by Lumley et al. (2) in this issue of the *Journal* definitively resolves mechanisms of ischemia in severe AS without comorbidities.

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Thirty-eight controls without AS and 22 patients with severe AS without coronary artery disease (CAD) or comorbidities had invasive, simultaneous coronary pressure-flow velocity measurements taken at rest, during supine bicycle exercise, and during adenosine hyperemia. The results were analyzed using wave intensity analysis and augmented by echocardiography done at rest and during exercise. The valve cohort had severe, symptomatic AS with a mean gradient of 57 ± 16 mm Hg, peak velocity of 4.7 ± 0.7 m/s, and an effective orifice area of 0.74 ± 0.16 cm^2.

Importantly, microvascular resistance after adenosine and exercise were similar between severe AS patients and controls, thereby excluding microvascular dysfunction. In support of the maldistribution theory, diastolic time fraction was lower in severe AS compared with controls, reflecting prolonged systole reducing the time of diastolic myocardial perfusion. Myocardial work was higher in severe AS compared with controls, whereas coronary flow reserve (CFR) during adenosine was reduced. Therefore, patients with severe AS failed to increase coronary blood flow in proportion to the increase in cardiac work, thereby making myocardium vulnerable to ischemia during stress.

CORONARY PRESSURE-FLOW VELOCITY WAVE ANALYSIS

For both AS and controls, the magnitude of all 4 waves increased with exercise compared with rest. However, in AS, increased early systolic deceleration was greater than controls (296% vs. 99%; $p = 0.005$). In AS and controls, all waves increased significantly with hyperemia compared with rest, except early systolic deceleration did not change in controls. With hyperemia in AS, percent increase in early systolic deceleration was significantly greater compared with controls (112% vs. 25%; $p = 0.008$) and percent change in systolic acceleration significantly lower (67% vs. 164%; $p = 0.004$).

The authors concluded that efficiency of healthy hearts improved during exercise and hyperemia due to an increase in relative contribution of waves that accelerate flow. However, the reverse was observed in AS due to an increase in contribution of waves that decelerate flow. Therefore, abnormal coronary pressure-flow physiology or "cardiac-coronary coupling" likely caused ischemia in these patients with severe AS, not structural coronary or microvascular disease. These conclusions are consistent with improved coronary flow reserve after valve replacement (3). The only additional evidence needed is quantitative subendocardial and subepicardial

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perfusion at rest and with adenosine hyperemia in severe AS by cardiac magnetic resonance with adequate resolution.

WHAT'S NEW, WHAT'S NEXT?

One new insight was the exaggerated coronary systolic pressure-flow deceleration waves in addition to reduced diastolic perfusion time in severe AS. It also provided insight into conflicting views on mechanisms for low gradient/low cardiac output AS (4,5). As necessary for defining coronary pressure-flow behavior in pure AS alone, the selection of patients for this study (2) excluded significant coronary artery stenosis, diffuse CAD, or other comorbidities, with only 14% having diabetes and only 9% smoked. This low prevalence of comorbidities may explain the observed normal microvascular function in severe pure AS.

However, coronary stenosis, diffuse CAD, or microvascular disease in AS may further compromise reduced coronary flow capacity leading to chronic global low-flow ischemia analogous to adaptive regional hibernating myocardium seen with chronic total occlusion in specific arterial distributions. Combined AS and epicardial CAD or small vessel disease involve global chronic ischemia; therefore, the myocardial adaptive response would be global reduced pump function with low cardiac output. Because ejection fraction is dynamic depending on afterload, sympathetic drive, heart rate, atrial fibrillation, and coronary blood flow, it may remain normal or fall functionally with or without developing fibrosis or structural changes.

A TESTABLE HYPOTHESIS

To identify a potential specific mechanism for low gradient/low output AS based on the current report, what might one expect or hypothesize that coronary pressure-flow wave analysis would show in this syndrome? Aortic transvalvular pressure gradient, cardiac output and stroke volume are reduced in low gradient/low output AS, reflecting reduced force of myocardial contraction. Consequently, coronary pressure-flow wave analysis would likely fail to show exaggerated systolic deceleration waves or shortened diastolic perfusion fraction; instead, all would be normalized to some extent, thereby maintaining myocardial perfusion and potentially reducing the limited coronary flow capacity expected with high-gradient/high-output AS.

Paradoxically, epicardial or small-vessel CAD that reduced coronary flow capacity to or near ischemic levels might therefore reduce decelerating waves and shortened diastolic fraction toward normalized coronary pressure-flow waves, thereby reducing further ischemia as an adaptive response paralleling hibernating myocardium in obstructive CAD without AS. Support for this paradox derives from experimental models of coronary stenosis (without AS) wherein coronary flow during systole increased with progressive stenosis that reduced systolic compression associated with reduced diastolic coronary flow (6).

Although wave analysis addresses mechanisms, it might not provide clinical insights more than noninvasive quantitative myocardial perfusion in AS. **Figure 1A** illustrates normal relative images and adequate CFR in pure AS. In comparison, low-gradient/low-output AS with diffuse CAD (**Figure 1B**) also has relative images with no clinically significant stress defect, but CFR based on absolute perfusion (in cc/min/gm) is severely diffusely reduced to below the low-flow ischemic threshold (7). Both cases had ejection fraction >50% by electrocardiogram-gated positron emission tomography images.

CLINICAL POTENTIAL

Dobutamine stress in low gradient/low output AS increases aortic pressure gradient, cardiac output, stroke volume, and strength of contraction. Correspondingly, coronary pressure-flow wave analysis would likely show the pattern here reported for pure AS. Such results would confirm adaptive mechanisms for low gradient/low cardiac output AS. "Pseudo AS" would have little increase in aortic pressure gradient with increased cardiac output. Failure to increase cardiac output and aortic gradient with dobutamine might reflect adverse structural changes or severe ischemia without exaggerated systolic decelerating waves of pure AS.

Confirmation of such hypothesized mechanisms by wave analysis augmented by noninvasive quantitative perfusion might establish a physiological basis for timing of valve replacement in combined low gradient/low output AS with epicardial or microvascular disease that are now subjects of debate, without mechanistic basis or trial outcomes to guide clinical practice (4,5).

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