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EDITORIAL COMMENT

The Interface Between Coronary Physiology and Severe Aortic Stenosis

Relax and Go With the Flow*

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Although transcatheter aortic valve replacement (TAVR) was initially approved for inoperable or high-risk symptomatic patients with severe aortic stenosis (AS), expansion into intermediate- and low-risk patients will continue to increase the adoption of TAVR into clinical practice (1). Significant coronary artery disease (CAD) is reported to coexist in more than 60% of patients with severe AS (2). Concomitant coronary revascularization at the time of surgical aortic valve replacement is associated with improved long-term outcomes without adversely affecting perioperative risks (3). It is not surprising, therefore, that current guidelines recommend revascularization for obstructive CAD of >70% diameter stenosis in major epicardial vessels and >50% in the left main coronary artery for patients undergoing surgical aortic valve replacement (4). A recent meta-analysis of patients undergoing TAVR demonstrated an increased 1-year mortality rate among those with residual significant CAD (5). Although small studies have failed to demonstrate the benefit of routine revascularization before TAVR (2), current recommendations are to perform percutaneous coronary intervention prior to or at the time of TAVR (6).

There is, however, a lack of consensus for the definition of "significant CAD" in patients with severe AS. In addition to the known limitations of angiography for predicting hemodynamically significant stenosis, all pivotal TAVR trials excluded patients with angiographically significant CAD. Another nuance in the assessment of lesion severity in patients with AS is the potentially heterogeneous etiology of concomitant left ventricular (LV) dysfunction. Indeed, LV dysfunction could be related to LV outflow obstruction, to prior myocardial infarction, or to repetitive stunning or hibernating myocardium related to severe epicardial lesions. Given this complex pathophysiology, there remains a need for objective tests to assess the functional significance of epicardial lesion severity in patients with severe AS destined for TAVR. Whether fractional flow reserve (FFR) or instantaneous wave-free ratio (iFR) can reliably detect myocardial ischemia in patients with severe AS is currently not known.

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In this issue of *JACC: Cardiovascular Interventions*, 2 simultaneous studies provide thought-provoking insights into the utility of coronary physiological indexes to assess epicardial lesion severity in patients with CAD and severe AS. In the first study, Yamanaka et al. (7) investigated the diagnostic performance of FFR and iFR against a gold standard of adenosine 99mTc single-photon emission computed tomographic (SPECT) myocardial perfusion imaging (MPI) in patients with severe AS and intermediate CAD. Invasive physiological assessment was performed in 95 patients and adenosine SPECT MPI in 78 patients. iFR demonstrated strong reproducibility ($r = 0.997$) and a robust correlation with FFR ($r = 0.854$), similar to that observed among patients without AS. The etiology of microvascular dysfunction in this study may have been multifactorial, given that 25% had

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diabetes mellitus and 25% had chronic renal failure. Interestingly, the optimal iFR threshold for detecting ischemia on SPECT MPI was 0.82 (area under the curve = 0.84), while the optimal cutoff for FFR was 0.83 (with a higher area under the curve of 0.93). These observed thresholds are different from the established FFR and iFR cutoffs derived from large outcome-based clinical trials in patients without AS (iFR <0.89 and FFR <0.80) (8-10). One may be able to attribute a higher FFR cutoff value for detecting myocardial ischemia on SPECT MPI to the microvascular dysfunction caused by AS, diabetes, or renal failure. However, heterogenous microvascular dysfunction related to these varied etiologies may also affect the accuracy of SPECT MPI for detecting epicardial lesion severity. Likewise, it should be pointed out that SPECT MPI has not been specifically validated among patients with severe AS.

How can one explain a lower iFR threshold for ischemia? One possibility is that it takes a more severe epicardial obstruction in the presence of the blunted autoregulatory reserve associated with severe AS to generate sufficient flow heterogeneity to induce reversibility of SPECT MPI. In other words, because there is diffuse microvascular dysfunction in severe AS, only a severe stenosis with very low iFR can induce reversible ischemia seen with SPECT MPI. Perhaps a more comprehensive study design of performing FFR, iFR, and SPECT imaging, then TAVR, and repeating FFR, iFR, and SPECT imaging would have shed additional light on the impact of severe AS on both invasive indexes and SPECT MPI.

The second study, by Ahmad et al. (11), although quite modest in size (n = 28), provides further insights into coronary hemodynamic parameters in this patient population by conducting intracoronary pressure and flow velocity measurements before and after TAVR. The investigators found that although resting systolic flow increased significantly (by 33%) after TAVR, resting diastolic flow did not change (only a 5% increase; p = NS). In addition, they observed a significant increase in systolic (24%) and whole-cycle (21%) but not diastolic hyperemic flow after TAVR. They then assessed the impact of these observations on changes in Pd/Pa, iFR, and FFR before and after TAVR. They report that although there were no significant changes in the resting indexes (Pd/Pa and iFR), a significant reduction in FFR (from 0.87 ± 0.08 to 0.85 ± 0.09; p = 0.0008) was observed from before to after TAVR. The authors argue that FFR, which is a whole-cycle hyperemic index, may underestimate lesion severity in patients with severe AS, while iFR, calculated during the resting diastolic wave-free period, is neither vulnerable to the impact of blunted systolic coronary flow nor to the dampened hyperemic response in patients with severe AS. From a pathophysiological standpoint, patients with severe AS have systolic LV outflow obstruction, elevated LV end-diastolic pressures, and significant LV hypertrophy, all of which will preferentially reduce systolic over diastolic coronary blood flow. It is therefore not surprising that these investigators observed a significant increase in resting systolic flow but no significant change in diastolic flow from pre- to post-TAVR. In addition, the aforementioned pathophysiological features of AS will reduce the hyperemic reserve of the coronary bed and thus result in a higher FFR than when the AS is relieved, as observed in this study. However, as evident by the 5% increase in diastolic flow (albeit nonsignificant with this sample size), even the diastolic phase of the cardiac cycle may not be completely immune to the structural and microvascular changes induced by severe AS. Larger studies will be helpful to confirm the observation that iFR is truly not affected by the pressure and flow changes induced by severe AS. Moreover, the influence of changes in evolving mean pressure gradient across the aortic valve after TAVR, paravalvular leaks and reverse remodeling of the left ventricle on FFR and iFR needs further investigation. Future studies should also investigate the reproducibility of these physiological indexes at different time points after the procedure, when not only the acute but the chronic LV changes have reversed.

While the first study (7) revealed a good correlation between FFR and iFR, and robust diagnostic accuracy for these indexes compared with SPECT MPI, the second study (11) demonstrated that iFR of lesions does not change before compared with after TAVR, whereas FFR does slightly reduce after TAVR. It is important to remember that both studies are small in size and that neither investigated clinical outcomes related to an iFR- or FFR-guided approach to revascularization of CAD in patients with severe AS undergoing TAVR. Indeed, while we wait for clinical outcomes trials to investigate the utility of physiology-guided percutaneous coronary intervention among patients undergoing TAVR, it would be reasonable to use either FFR or iFR as an adjunct to angiography according to the local expertise and comfort level. For now, using the established thresholds (<0.80 for FFR, <0.89 for iFR) and a heart-team approach is highly recommended. For iFR, one can assume it will remain relatively unaffected by severe AS. Similarly, FFR <0.80 should

remain clinically useful in patients with AS. Only if FFR is in a higher gray zone (e.g., 0.80 to 0.84), one could repeat the measurement after TAVR, expecting that the FFR may decrease to <0.80 in some cases. Ultimately, although these 2 studies have provided further insight into the complexity of coronary physiology in patients with severe AS, large prospective clinical trials comparing physiology-guided percutaneous coronary intervention compared with medical therapy are warranted in patients with CAD and severe AS undergoing TAVR. Until then, when encountering lesion assessment in patients with AS, it would be reasonable to "relax and go with the flow."

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