Paravalvular Regurgitation After Transcatheter Aortic Valve Replacement
Striving to Perfect its Prognostic Evaluation With Hemodynamic Data

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To improve is to change, so to be perfect is to have changed often.
—Sir Winston Churchill (1)

Paravalvular aortic regurgitation (PVR) is among the most important predictors of mortality after transcatheter aortic valve replacement (TAVR) (2,3). Undoubtedly, PVR is best avoided through judicious case selection and the application of cross-sectional measures of TAVR sizing (4–6). Moreover, the advent of new TAVR devices such as the SAPIEN 3 (Edwards Lifesciences, Irvine, California) appears to have substantially reduced the frequency of moderate PVR (7), but even with these advances, there remains a substantial percentage of patients with mild PVR, which could still be prognostically significant, particularly with the treatment of younger, lower surgical risk TAVR candidates (7).

PVR is extremely difficult to quantify, particularly in the intermediate (mild to moderate) range of severity, and despite several attempts to do so reliably using many different imaging modalities, including transthoracic echocardiography, transesophageal echocardiography, and angiography, the reproducibility and reliability of findings remain limited, even when evaluated at experienced core laboratories. Magnetic resonance imaging is an accurate modality in the outpatient setting but is for the most part not feasible periprocedurally to guide management.

It was for these reasons that Sinning et al. (8) devised in 2012 the aortic regurgitation index (ARI) with the use of transcatheter hemodynamic monitoring to guide the need for immediate therapeutic maneuvers to ameliorate PVR. They subsequently validated these data in an additional multicenter study (9) and other investigators further showed its clinical merit, with the addition of heart rate adjustment to the algorithm in some series (10,11).

In this issue of JACC: Cardiovascular Interventions, Sinning et al. (12) report a study in which they sought to further improve the discriminatory value of the ARI by adjustment for pre-procedural hemodynamic status with the ARI ratio (the quotient of post- over pre-procedural ARI). They found this adjustment to increase the specificity of the ARI for the prediction of 1-year mortality from 75.0% to 93.3%. Importantly, of post-TAVR patients with ARI values <25, only those with ARI ratios <0.6 had significantly elevated mortality at 1 year, indicating that an ARI ratio ≥0.6 in this setting is relatively reassuring and raises the threshold for additional maneuvers to reduce PVR, including post-dilation and transcatheter valve-in-transcatheter valve therapy, which carry potential risk.

Indeed, the Latin maxim primum non nocere carries some weight here, as therapies to reduce PVR post-TAVR have been associated with an increase in peri-procedural complications. Post-dilation, although often effective in reducing the severity of PVR, has been linked not only to higher rates of stroke (13) but also to the rare but often fatal complication of aortic root injury (14). In the PARTNER (Placement of Aortic Transcatheter Valve) trial, transcatheter valve-in-transcatheter valve therapy (15) was associated with a greater need for hemodynamic support, a higher
volume of contrast used, longer procedure times, more bradycardia, and new pacemakers and was also an independent predictor of late cardiovascular mortality. That said, it is crucial that patients not be left with hemodynamically significant PVR, as data have shown that they will often succumb to this and experience prognostically important heart failure, if not immediately then in the ensuing months post-procedure.

The ARI ratio is an important step forward in evaluating not only the hemodynamic severity of PVR seen after TAVR but also a patient’s ability to tolerate PVR, adjusting for important confounders and placing the data in the context of the pre-TAVR hemodynamic state; as the investigators (12) state, the ARI ratio facilitates the correction for conditions such as severe diastolic dysfunction and increased aortic stiffness that often coexist with severe aortic stenosis. It may also facilitate objective quantitative comparisons of hemodynamic performance among devices.

However, one should examine the evidence objectively and not stick rigidly to the ARI paradigm. The investigators (12) discuss specificity, but the head-to-head comparison of a prognostic parameter is most reliably compared by the receiver-operating characteristic method of DeLong et al. (16), and there is no mention in this article of receiver-operating characteristic curves. Our own systematic assessment of prognostic hemodynamic data found systolic blood pressure, the denominator of the ARI, to be redundant prognostically and, in fact, to weaken the predictive model, given that evidently, lower systolic blood pressure is not a good result post-TAVR and yet, being the denominator, it increases the ARI (11).

The other crucial omission from the ARI and the ARI ratio is the influence of heart rate. The simple fact remains that lower heart rates reduce the difference in left ventricular and aortic diastolic pressures (diastolic delta) with the prolongation of diastole, while higher heart rates shorten diastole and increase the diastolic delta. The investigators (12) do acknowledge the important influence of heart rate and suggest that the ARI parameter should be measured at a heart rate of 60 to 80 beats/min, pacing if lower heart rates are encountered, but it is not unusual to encounter a heart rate post-TAVR of 80 beats/min or higher, and more important, a change from 60 to 80 beats/min or vice versa will dramatically alter the ARI.

Although the investigators (12) state that the discriminatory value of the ARI ratio could not be increased by heart rate adjustment, in the absence of receiver-operating characteristic curve analysis, this is not well substantiated. Moreover, it would be of interest to see what removing their denominator of systolic blood pressure from the ARI does objectively to its prognostic value. There is clearly room for some improvement, as the survival of the “reduced ARI but favorable” group (ARI <25 with ARI ratio ≥0.6) is far from superimposed on the Kaplan-Meier curve, with almost twice the 1-year mortality compared with those with ARI values ≥25 (Figure 3). There is some discussion of other parameters accounting for the influence of heart rate, including the diastolic/systolic pressure-time integral (10), the composite heart rate-adjusted hemodynamic-echocardiographic aortic insufficiency score (11), and the time-integrated aortic regurgitation index (17), but it is stated that these “increased accuracy at the price of losing simplicity and straightforwardness, since they cannot be calculated without a computer in the acute implantation setting” (12).

In the catheterization laboratory, we do not calculate mean transvalvular gradients or transcoronary fractional flow reserve by mental arithmetic. So why should we do so for such an important prognostic parameter after TAVR, particularly one we could potentially ameliorate immediately? Indeed, even with its relative simplicity, there is marked underuse of the ARI in catheterization laboratories, except for the most fervent proponents of transcatheter hemodynamic evaluation, such as Dr. Sinning’s laboratory in Bonn, Germany, or the Cedars-Sinai catheterization laboratory, where hemodynamic monitoring using the pulmonary artery catheter was introduced by our eminent forefathers in Los Angeles, Drs. H.J.C. Swan and William Ganz. There is a fundamental need to integrate the ARI ratio or, better, the most refined related parameter regardless of additional arithmetic, into catheterization laboratory monitoring algorithms so that they may be appropriately used and demonstrated immediately on a screen, just as transcatheter gradients are. Perhaps then we will strive to change the subtleties of TAVR hemodynamic evaluation often to facilitate perfection.

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REFERENCES