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Editorial

The Elephant in the Room: Bicuspid Aortic Valvulopathy

THE BICUSPID AORTIC VALVE (BAV) is the most frequently encountered congenital heart disease, present in approximately 2% of the general population.[1] The presence of a BAV substantially increases the risk of the subsequent development of aortic stenosis (AS), aortic regurgitation (AR), or mixed aortic valve disease (MAVD: both AS and AR), with approximately half of these patients requiring surgical aortic valve intervention (SAVI) during their lifetime. In patients with a normal tricuspid aortic valve, controversy persists regarding the influence of left ventricular ejection fraction (LVEF) and deciding when to surgically intervene for AS, AR, or MAVD. American[2] and European[3] guidelines differ a bit regarding the "important" LVEF below, in which surgical intervention is more strongly indicated for all 3 pathologies, yet hovers between an LVEF of 50%-to-60%. Because little is known regarding patients with BAV disease, Hecht et al. set out to determine the prognostic impact of LVEF in these patients, and their results have been published recently in the *Journal of the American College of Cardiology*.[4]

Hecht et al. had 2 stated objectives as follows: (1) determine the prognostic impact (SAVI and/or all-cause mortality) of LVEF in patients with a BAV, and (2) determine a "cutoff value" of LVEF below which risk of adverse outcomes (SAVI and/or all-cause mortality) becomes significant in patients with a BAV and AS, AR, or MAVD. To do this, they retrospectively reviewed 2,672 patients listed in an international BAV registry, finding 1,493 patients with significant BAV disease to assess (after the application of the exclusion criteria). Initially, they divided these 1,493 patients into 5 categories, depending on LVEF (>70%: 269 patients; 60%-70%: 679 patients; 50%-59%: 316 patients; 30%-49%: 182 patients; <30%: 47 patients). To investigate the impact of LVEF on clinical outcome, they then divided the 1,493 patients into 4 groups (whole cohort: 1,493 patients; isolated AS: 749 patients; isolated AR: 554 patients; MAVD: 190 patients). "Follow-up" started on the first date of confirmed BAV via echocardiography, and was reasonable (around 90% of patients, mean 3-5 years). The primary endpoint was all-cause mortality occurring before or after SAVI. The secondary endpoint was the composite of SAVI and all-cause mortality.

The main findings of their analyses included the following. Overall, patients with reduced LVEF (<50%) were older, more frequently men, and had worse cardiovascular profiles. Of the 1,493 patients, the primary endpoint was reached in 117 patients (8.8%), and the secondary endpoint was reached in 675 patients (51%); 602 patients underwent SAVI, with 73 dying. Using Kaplan-Meier analysis, the LVEF stratum <50% was associated significantly with higher rates of all-cause mortality, and an LVEF <60% was found to be associated with increased risk of mortality. Additional statistical analyses of the specific subgroups (isolated AS, isolated AR, MAVD) were presented as well. After intense statistical analyses, the authors summarized their 2 main findings as follows: (1) there is a stepwise increase in the risk of all-cause mortality with decreasing strata of LVEF in patients with BAV disease, and (2) this increased risk of adverse outcome appears to become significant with an LVEF <60%.

There are numerous issues here that substantially prohibit the generation of clinically useful conclusions. We are all aware of the problems associated with any (even finely conducted) retrospective analysis. One wonders at the accuracy and/or reliability of echocardiographic assessment (eg, LVEF, aortic valve morphology, grading severity [mild-moderate-severe] of AS and AR, etc) when many different researchers (26 total authors) and institutions (14 different centers and/or multiple countries) are involved in data collection. The diagnosis of BAV and LVEF was determined solely by an initial echocardiogram (not ultimately confirmed via additional imaging and/or echocardiographic assessment or surgical inspection). Lastly, although guidelines exist, we anticipate each institution applied them in different ways when initiating (or not) SAVI, which was not uniform (eg, biologic valve, mechanical valve, homograft/autograft, valvulotomy, transcatheter aortic valve replacement, aortic valve repair).

Again, their conclusions—"This study shows that there is a progressive increase in the risk of mortality with decreasing LVEF in patients with BAV disease. A significant increase in the risk of mortality was observed at an LVEF threshold of <60% in AS and AR and <55% in MVAD." If true, does this represent substantially new, clinically useful information? On

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the surface, ejection fraction is an important marker of heart disease; however, the timing of intervention has always been complex and multifactorial. Symptoms, anatomy, severity, and sequelae of valvular disease (eg, pulmonary hypertension, new-onset atrial fibrillation, worsening ventricular function, etc) comprise the moving parts of disease classification, and ultimately inform clinical management. Furthermore, all of these variables are dynamic, differing in severity, and are not always in tandem throughout the course of disease progression. Clinical symptoms, exercise tolerance, frailty, and other variables that impact outcomes and mortality are not presented in the study by Hecht et al., and the authors stated that “the criteria for valvular intervention may have varied across each center.” The European Society of Cardiology and the European Association for Cardio-thoracic Surgery revised their 2017 guidelines to a new version in 2021 due to contemporary evidence in evaluation for the timing of intervention in asymptomatic patients with AS, particularly those deemed to have a high fragility index.[3,5] A lack of uniformity and clinical context make the interpretation of the results presented by Hecht et al. inscrutable. In a way, this is akin to the famed parable of the blind men who have never encountered an elephant and are asked to describe the animal by touching one part of it. Each describes the elephant as the part touched rather than the sum of its parts. Of course, the elephant is not just a tree trunk (legs) or a rope (tail) but a complex creature, and the decision for intervention in the BAV patient is not just dependent on the LVEF but rather a complex array of multifaceted factors.

Albeit routine, Hecht et al. using a common modality for left ventricular (LV) function assessment as the sole method of LVEF evaluation in a clinical trial is controversial. Echocardiographic quantitative assessment of LVEF has broad diagnostic and prognostic applications; however, it is amenable to subjective bias. The biplane Simpson method of discs using a 2-dimensional linear method is limited by inherent technical limitations and interobserver variability.[6] Accurate LVEF measurement via this method is dependent on several assumptions. First, quality images are required for accurate manual or automated border tracing; second, the LV geometry is assumed to be ellipsoid shape; third, optimal loading conditions are present such that over- or underestimation do not occur; and fourth, the patient is neither bradycardic (overestimation of LVEF) nor tachycardic (underestimation) and in sinus rhythm.[7] Recognizing these substantial limitations, additional quantification methods have been proposed, including myocardial strain imaging.[8-10] Strain is the assessment of myocardium deformation in the longitudinal, circumferential, and radial planes. Longitudinal and circumferential shortening during systole yield a negative value, whereas radial thickening is a positive value, overall yielding a dimensionless index. Global longitudinal strain is the most common clinical application that measures LV strain in the long axis. There are numerous studies on strain as it pertains to global LV function in various clinical situations. Strain assessment has been reported to be a superior predictor of mortality to LVEF, and it can predict prolonged hospitalization and long-term outcomes in severe asymptomatic AS.[11-14] Determining LVEF via the Simpson's method of discs as the sole measure of ejection fraction is likely imprecise, and may be a source of significant error in the study by Hecht et al.

The LVEF assessment in concentric remodeling (commonly observed in patients with stenotic BAVs) can be misleading. Pathologic remodeling leads to LV hypertrophy, according to Laplace's law, to offset an increase in pressure exerted by valvular stenosis. Increased myocardial thickness and subsequent small intraventricular cavity size frequently can lead to overestimation of LVEF even when the systolic function is reduced.[15] In these patients, there is an uncoupling of LVEF and systolic function, and one cannot be used as a surrogate for the other. Ejection fraction can be normal even in the presence of substantial systolic dysfunction in this subset of patients.[16] This is observed in various cardiac disorders, including hypertrophic cardiomyopathy. Strain imaging has been reported to detect early abnormal sub-clinical LV dysfunction prior to changes in LVEF.[13] Findings by Hecht et al. alluded to this phenomenon, as patients with AS with normal LVEF still experienced a clinically meaningful increase in the risk of mortality, likely suggesting covert ventricular dysfunction.

Another questionable aspect of the methodology in the study presented by Hecht et al. was patient stratification. The method of stratification of LVEF into categories (>70%, 60%-70%, 50%-59%) potentially may cause overlap along important borders of distinction. The European Society of Cardiology and the European Association for Cardio-thoracic Surgery guidelines consider LVEF <55% as a Class IIa indication for aortic valve replacement in patients with severe AS.[3] However, Hecht et al. did not specifically separate patients along this threshold, and the group was clumped together (LVEF 50%-59%) in the analysis. If this important distinction had been made, would it have changed the findings? Would results have indicated that the meaningful cutoff value of LVEF was 55% or another value at which adverse outcomes became significant within the studied cohort? Clearly, further investigation is warranted to determine the optimal threshold for intervention in this patient population.

Although there were several limitations, as discussed, with the study conducted by Hecht et al., it is important to recognize the sheer difficulty in conducting large multicenter studies in the field of echocardiography. Differences in echocardiographic equipment, expertise, observer variability, and nonuniformity in patient selection and/or criteria for intervention are just some of the challenges posed in conducting research. The authors should be congratulated for their outcomes-based study that contributes to understanding this disease and likely will bring about new investigative clinical trials in this field.

Conflict of Interest

None.

Richa Dhawan, MD, MPH*[,1]
Mark A. Chaney, MD*
*Department of Anesthesia and Critical Care, University of Chicago, Chicago, IL

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