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EDITORIAL COMMENT

Aortic Stenosis and Diastolic Dysfunction

Partners in Crime*

Allan L. Klein, MD,[a,b] Jay Ramchand, MBBS,[a,b] Sherif F. Nagueh, MD[c]

"The future depends on what you do today."
—Mohandas K. Gandhi (1)

Aortic stenosis (AS) is the leading cause of valvular heart disease in the Western world and is associated with increased morbidity and mortality (2). Progressive valvular narrowing leads to left ventricular (LV) pressure overload, LV hypertrophy, and fibrosis, which can ultimately culminate to LV systolic and/or diastolic dysfunction (DD) (3,4).

Aortic valve replacement (AVR), historically a high-risk endeavor, is a solution to relieve AS and AS-related myocardial dysfunction and can now be carried out with lower operative mortality with either modern surgical or transcatheter techniques (2). Despite the lower risk of adverse outcomes with modern AVR approaches, contemporary management guidelines only recommend AVR after development of overt myocardial systolic dysfunction and/or AS-related symptoms, which if missed, can lead to detrimental consequences (2). There is now increasing appreciation for the need for a more refined approach to AS management with the incorporation of more objective and sensitive markers of myocardial decompensation using biochemical (e.g., N-terminal pro-B-type natriuretic peptide) or imaging-based parameters.

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There is accumulating evidence (**Table 1**) that preoperative DD is a marker of myocardial decompensation and represents an important determinant of outcomes in patients undergoing transcatheter aortic valve replacement (TAVR), although data have been predominantly derived from relatively small studies (5-12). In this issue of the *Journal*, Ong et al. (12) provide important insights to clarify the relationship between baseline and follow-up DD, with adverse outcomes in patients undergoing TAVR from the PARTNER-2 SAPIEN3 registry (13). The registry comprised patients with severe, symptomatic AS who were considered inoperable, high risk, or intermediate risk. Baseline, 30-day, and 1- and 2-year transthoracic echocardiograms (final included n = 1,253) from the PARTNER 2 SAPIEN 3 registry were analyzed by a consortium of core laboratories, and diastolic function was graded using American Society of Echocardiography/European Association of Cardiovascular Imaging criteria (14).

There are 3 key findings (13). First, the presence of grade ≥2 DD was common, with 42% of the cohort affected. As DD increased from grades 1 to 3, there was a significant increase in abnormalities involving indices of myocardial structure and function. Second, incremental grades of DD at baseline were associated with an increase in combined cardiovascular (CV) death/rehospitalization at 1 year. Third, improvement by ≥1 grade in DD or grade 1 DD at 30 days was common (71%), and on multivariable analysis was independently associated with reduced CV death/rehospitalizations at 1 year (hazard ratio [HR]: 0.63; 95% confidence interval [CI]: 0.42 to 0.92) but not at 2 years. Baseline DD3 group was an independent predictor of 1-year CV death/rehospitalization (HR: 2.24;

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From the [a]Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio, USA; [b]Center for the Diagnosis and Treatment of Pericardial Diseases, Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio, USA; and the [c]Methodist DeBakey Heart and Vascular Center, Houston Methodist, Houston, Texas, USA. Deepak L. Bhatt, MD, MPH, served as Guest Editor-in-Chief for this paper.

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TABLE 1 Recent Key Studies Assessing Diastolic Function Post-TAVR and Clinical Outcomes

First Author (Ref. #), Year	Number of Cases	Study Type	Results Summary
Blair et al. (4), 2017*	90	Retrospective, single-center	Baseline diastolic dysfunction grade, but not post-TAVR or changes in diastolic dysfunction grade, was associated with 1-yr death (HR: 1.163; 95% CI: 1.049 to 1.277) and combined death/cardiovascular hospitalization (HR: 1.174; 95% CI: 1.032 to 1.318).
Muratori et al. (5), 2015	358	Prospective, single-center	Survival was better in those with DD grade 3 with improvement in diastolic function grade vs. in those without improvement post TAVR (unadjusted).
Sato et al. (6), 2018*	237	Retrospective, single-center	Over a median follow-up of 1,320 days, neither pre- nor post-TAVR DD grade were associated with prognosis. In patients with grade III DD detected before TAVR and AR ≥2 after TAVR had poorer survival ($p < 0.008$). Patients with grade III DD detected after TAVR and AR ≥2 after TAVR had poorer prognosis ($p = 0.002$).
Thaden et al. (7), 2020*	1,383	Retrospective, single-center	Over a mean follow-up period of 7.3 yrs, increased left ventricular filling pressure (using ASE guidelines) remained an independent predictor of mortality after successful AVR (HR: 1.45; 95% CI 1.16 to 1.81).
Kampaktsis, et al. (8), 2020	359	Retrospective, single-center	Over a mean follow-up of 13 months, DD identified using an E/A ratio cut-off of 1.8 was associated with an increased risk for the outcome measure (HR: 2.02; 95% CI: 1.23 to 3.30). This association was lost in a propensity-matched cohort.
Anantha-Narayan et al. (9), 2020*	222	Prospective, single-center	Over a median follow-up of 385 days, advanced (Grades II–III) and indeterminate DD were associated with increased long-term mortality (25%–28% vs. 5%; $p = 0.02$).
Kampaktsis et al. (10), 2017	195	Retrospective, single-center	At mean follow-up of 14 months, patients with severe baseline DD (E/A >1.5) who developed ≥ mild post-TAVR AI was independently associated with increased mortality compared to all other patients (HR: 3.89; 95% CI: 1.76 to 8.60; $p = 0.001$).
Asami et al. (11), 2018*	777	Prospective, single-center	1-yr all-cause mortality was higher in patients with LVDD grades I (16.3%; HR: 2.32; 95% CI: 1.15 to 4.66), II (17.9%; HR: 2.58; 95% CI: 1.43 to 4.67), and III (27.6%; HR: 4.21; 95% CI: 2.25 to 7.86) than in those with normal diastolic function (6.9%).

*Study assessed diastolic function using 2016 American Society of Echocardiography/European Association of Cardiovascular Imaging criteria guidelines (13).

AR = aortic regurgitation; CI = confidence interval; DD = diastolic dysfunction; HR = hazard ratio; TAVR = transcatheter aortic valve replacement.

95% CI: 1.34 to 3.76) but not at 2 years (HR: 1.48; 95% CI: 0.85 to 2.58).

The authors should be commended for the enormity of data that was compiled. Study strengths include the large sample size, the well-phenotyped patient population, and the availability of follow-up echocardiography at 30 days. The main study limitations include the retrospective nature of the analysis and the lack of external replication. This is essential, as in general, the performance of risk markers is rarely as good in the validation cohort compared with the cohort in which they were initially assessed. Second, it was assumed that all the patients with severe AS had evidence of myocardial pathology and DD; thus, algorithm B from the 2016 American Society of Echocardiography diastology guidelines was used. This assumption may not hold true in all patients with AS, especially post-TAVR, where diastolic function may normalize in a proportion of patients. Further in the study, it appears that peak E-wave velocity was not considered in DD assessment. Thus, study participants with E/A ≤0.8 but with E >50 cm/s would have been classified as having grade I DD (defined in the study as E/A ≤0.8), whereas in the guidelines, the classification may have been either grade II or indeterminate depending on the presence of ancillary criteria. Third, as acknowledged by the authors, the presence of mitral annular calcification was not collected. Calcification is known to influence mitral annular movement used to assess diastology, and as such may have introduced bias in grading a higher E/A ratio and lower tissue Doppler imaging annular velocities. This limitation is in part mitigated by the exclusion of patients with mitral peak velocity >1.5 m/s, though it may have been useful to have incorporated known parameters of DD in this setting such as isovolumic relaxation time (15). Fourth, the presence of antecedent pathologies known to influence diastolic function, such as cardiac amyloidosis, is not reported and may have influenced the occurrence of adverse outcomes (16). Indeed, on multivariable analysis, neither the baseline grade 3 diastolic function nor improvement by ≥1 grade in DD/grade 1 DD at 30 days independently predicted clinical outcomes at 2 years. This suggests that long-term, the prognostic value of DD post-TAVR may not be incremental to pertinent structural parameters and/or comorbidities associated with advanced DD. Finally, nearly 30% of the cohort was excluded because of reasons such as the presence of significant mitral valve disease and/or atrial fibrillation; thus, the findings may not be reflective of a real-world cohort of AS and reflect important challenges of assessing diastolic function in AS.

Other questions remain. It is intriguing why, post-TAVR, DD improves in some but not others. In

those who do not improve, this may potentially reflect irreversible alterations in myocardial architecture that may be better understood through histology studies or cardiac magnetic resonance imaging (3,4). Notwithstanding, the present study supports the concept that once advanced DD develops, there is potential for progression and even irreversibility despite reduction of afterload with AVR. This provides an opportunity to identify patients who would benefit from AVR earlier than using traditional metric of symptoms before the development of irreversible ventricular remodeling and/or advanced DD. Indeed, in patients post-surgical AVR, Krayenbuehl et al. (4) demonstrated that at 18 months post-surgery, myocardial mass decreased primarily due to regression in myocyte hypertrophy, although with relative increase in myocardial fibrosis known to be associated with worsening myocardial stiffness/DD.

The field has evolved and has identified various promising blood and imaging biomarkers previously, but none have ever been fully embraced in current practice guidelines. The findings of Ong et al. (13) describe increasing baseline grades of DD associated with increasing gradations of risk. Timely detection of more advanced stages of DD is therefore important, and could be a marker for poor prognosis that should trigger consideration for closer evaluation in patients who do not meet traditional indications for AVR. For example, stress testing to assess exercise capacity should be considered in those without symptoms but with evidence of significant DD. Furthermore, DD should not be solely attributed to severe AS, as in many circumstances, causes are typically multifactorial. The importance of identifying and managing concurrent pathologies known to coexist with AS that can influence diastolic function, such as hypertension and amyloidosis (16), particularly in elderly patients, cannot be underestimated.

To conclude, the study by Ong et al. (13) supports that the presence of advanced DD has prognostic utility in those with severe AS undergoing TAVR, although it remains to be seen if diastolic function assessment can translate into better clinical outcomes. In the meantime, there is little doubt in our minds that the words by Mr. Mohandas Gandhi are true: "The future depends on what you do today" (1). The same principle applies to the assessment of DD in aortic stenosis. To advance the assessment of diastolic function in the future, we will need to continuously adapt and refine our approaches, for example, through the incorporation of emerging parameters such as LV diastolic strain and left atrial strain (17).

AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. Allan L. Klein, Center for the Diagnosis and Treatment of Pericardial Diseases, Heart and Vascular Institute, Cleveland Clinic, 9500 Euclid Avenue, Desk J1-5, Cleveland, Ohio 44195. E-mail: kleina@ccf.org. Twitter: @AllanLKleinMD1, @DrJRamchand.

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