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EDITORIAL COMMENT

Diastolic Dysfunction Pre-Transcatheter Aortic Valve Replacement

Is it Too Late?*

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And it's too late, baby now, it's too late
Though we really did try to make it.
Somethin' inside has died ….
—Carole King, Tapestry, 1971 (1)

Aortic stenosis (AS) produces chronic left ventricular (LV) pressure overload, typically leading to compensatory concentric LV hypertrophy, impaired early relaxation, decreased compliance, and higher filling pressure. The persistent increase in LV systolic pressure results in supply-demand mismatch and myocardial ischemia, leading to development of myocyte death and progressive extracellular myocardial fibrosis (2,3), exacerbating LV stiffness and diastolic dysfunction (DD), and ultimately leading to pulmonary congestion, heart failure, and death.

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Transcatheter aortic valve replacement (TAVR), which results in immediate relief of LV pressure overload without the requirement for cardiopulmonary bypass, would seem an excellent solution to relieve AS and DD. However, limited data regarding the prognostic value of baseline DD on outcomes following TAVR and the rate of resolution of DD after TAVR have been derived from relatively small studies (n = 90 to 358) with conflicting results (4-6). In this issue of *JACC: Cardiovascular Interventions*, Asami et al. (7) provide important insights into the relationship between severity of baseline DD and survival of patients with AS after TAVR.

In this retrospective analysis of 777 patients enrolled in the Swiss TAVR registry, DD was categorized according to guidelines that considered annular e' velocity, averaged E/e', left atrial volume index, and peak tricuspid regurgitation velocity (8). Clinical follow-up for all-cause mortality at 30 days and 1 year after TAVR was completed in all.

Diastolic function was graded in 632 subjects and was normal in 37%, grade I in 16%, grade II in 31%, and grade III in 16%. Presence of DD was higher than that reported from surgical AVR (SAVR) populations (~50%) (9,10), probably because TAVR patients tend to be older with more comorbidities. One-year mortality was higher in patients with grade I (16.3%), grade II (17.9%), and grade III DD (27.6%) compared with those with normal function (6.9%); this association persisted in a subanalysis of patients with LV ejection fraction ≥50%. Differences in mortality, driven by cardiovascular death, were appreciated as early as 30 days post-TAVR. In multivariate analysis, worsening grade of DD was identified as a predictor of 1-year mortality with an adjusted hazard ratio of 2.36 for grade I DD and 4.41 for grade III DD. Grade III DD was the strongest predictor of mortality, followed by body mass index ≤20 kg/m^2, diabetes, lung disease, and peripheral vascular disease.

Some limitations warrant mention. Included were 107 patients with moderate or severe mitral regurgitation. Mitral regurgitation can induce changes in transmitral Doppler patterns resembling those with advanced DD. Furthermore, baseline mitral regurgitation is known to be a predictor of worse outcome post-TAVR, and may have confounded the relationship (11). Significant mitral annulus calcification, a common finding in elderly patients with AS, was not

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specified, and can lead to reduction in mitral orifice area and restriction of mitral annulus movement, with consequent elevation of E/e'. These patients should have been excluded.

Preoperative DD has also been associated with increased morbidity and mortality after SAVR (3,9,12). LV hypertrophy and myocardial fibrosis may take years to regress post-AVR and may be irreversible (3,9,12). This concept was supported by the elegant work of Krayenbuehl et al. (2) who performed cineangiography, micromanometry, and endomyocardial biopsies in patients with severe AS before, at medium-term (18 months), and late (6 years) after SAVR. At medium-term, myocardial mass decreased, primarily mediated by regression of myocyte hypertrophy; the relative increase in myocardial fibrosis resulted in worsening myocardial stiffness/DD. Late after surgery, both LV mass and fibrous content decreased but never normalized (2). Persistent left atrial enlargement has been associated with increased mortality and morbidity after SAVR (12) and baseline DD has been associated with difficulty weaning from cardiopulmonary bypass (13). Patient-prosthesis mismatch, uncontrolled hypertension, and other causes of DD may also contribute to incomplete or delayed LV remodeling. Persistent influence of preoperative moderate-severe DD after AVR implies irreversible myocardial changes; these negatively affect survival (9).

Asami et al. (7) have also shown that DD grade was not directly related to AS severity. This implies that the cause of DD may be multifactorial. Transthyretin cardiac amyloid, found in 6% of patients with AS >65 years undergoing SAVR, is associated with poor post-operative outcome (14). Similarly, patients with previous mediastinal radiation and severe AS undergoing SAVR had worse longer-term survival versus a matched cohort without radiation (15). Furthermore, presence of preoperative concentric hypertrophy and elevated filling pressure in patients with mixed moderate aortic valve disease identified patients with increased cardiovascular morbidity post-AVR (16). Moreover, low-flow, low-gradient severe AS, increasingly recognized as a distinct presentation of severe AS, seems to be the consequence of a unique remodeling pathway with reduction of LV size and restrictive physiology (17) and worse outcomes after AVR (18). Future studies that investigate the impact of different causes of DD on clinical outcome are needed.

Newer imaging techniques offer promise for detection of subclinical LV dysfunction. Echocardiographic methods include global longitudinal strain (19) and intrinsic wave propagation of myocardial stretch (20), both of which seem predictive of outcome in severe AS. Cardiac magnetic resonance can detect myocardial fibrosis in patients with AS and is associated with outcome (21).

Asami et al. (7) deserve congratulations for delineating the impact of different grades of DD on survival in patients with AS undergoing TAVR. Baseline diastolic function evaluated by echocardiography provided important prognostic information beyond standard risk factors alone. Because even mild DD at baseline can negatively influence outcome 1-year post-TAVR, the challenge remains to identify which parameters in asymptomatic patients with severe AS best identify those who may benefit from early AVR.

Ultimately, potentially life-saving treatments, such as TAVR, must be administered before it is too late. AVR should occur before the development of myocyte death, myocardial fibrosis, and advanced DD, which attenuate the long-term benefit of valve replacement. Echocardiography, a safe, noninvasive, widely available tool, will continue to play a central role in guiding therapeutic decisions; continued refinements to echocardiographic assessment of cardiac function will enhance care of patients with AS.

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