C'est LAVi
What Left Atrial Dilatation Tells Us About Diastolic Function in Aortic Stenosis

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Calcific degenerative aortic valve stenosis (AS) is the most common acquired form of heart valve disease that afflicts the elderly population and usually comes to attention when an echocardiogram is ordered to evaluate a systolic murmur in an older subject. As is evident to anyone practicing cardiology these days, the advent of transcatheter aortic valve replacement has focused much attention on the evaluation and optimal treatment of patients with AS. AS often has a long latency period in which symptoms are absent, and, importantly, sudden unexpected cardiac death is rare. With symptom onset, survival is markedly reduced without intervention. For symptomatic patients with severe AS and normal flow-high gradient characteristics and normal left ventricular ejection fraction (LVEF) (stage D1), aortic valve replacement (AVR) is a class 1 indication. Similarly, for asymptomatic patients with severe AS and LVEF <50% not because of another cause (stage C2), AVR also is indicated.

Among truly asymptomatic patients with severe AS and normal LVEF, the management can be much more challenging. In this subset of patients, a strategy of watchful waiting or active surveillance is most often used until symptom onset occurs. When close clinical follow-up can be provided along with encouragement of prompt reporting of symptoms by the patient, AVR can be performed with low risk and good long-term results, and we now know that, approximately two thirds of patients will develop symptoms within 5 years. Thus, a balance must be struck between the low risk of sudden death during this watchful waiting period and the morbidity and mortality associated with AVR. In this connection, the cautionary words of Dr Braunwald remain as true today as they were a quarter century ago: “The most common cause of sudden death in asymptomatic aortic stenosis is aortic valve replacement.” However, watchful waiting is not always as easy as it sounds: symptoms are subjective; patients may not recognize or even deny the existence of symptoms or downregulate activity to avoid symptoms. Even within the structured environment of a heart valve clinic program, more than 3 quarters of previously asymptomatic patients delayed reporting of symptoms to their provider until the next scheduled follow-up appointment. Delay in referral is common and recognized to lead to worse outcomes. Importantly, this asymptomatic group with preserved LVEF is not necessarily homogeneous. Patients with very severe AS, defined as peak aortic velocities ≥5.0 m/s or ≥5.5 m/s, are recognized to have worse short-term outcomes, and AVR is a class 2a indication if surgical risk is low. Asymptomatic patients who develop significant exercise-induced symptoms or certain adverse hemodynamic responses to exercise are considered to have a class 1 indication for AVR. In addition to peak velocity, a growing number of morphological and functional indices have been evaluated (Table) to help stratify risk, some being included in guideline recommendations at the level of class 2a or 2b indications for AVR.

In this issue of Circulation: Cardiovascular Imaging, Christensen et al call attention to a relatively novel marker of the hemodynamic consequences of severe AS in asymptomatic patients with preserved LVEF. The authors investigate the functional correlates of increased left atrial volume index (LAVi) among a small group of well-studied patients with asymptomatic severe AS. Left atrial enlargement (LAE), best measured as an increase in LAVi, has justifiably received heightened attention during the past 2 decades and has largely supplanted linear left atrial (LA) size parameters in clinical investigation. LAVi has been shown to be an independent predictor of adverse outcomes. When studied specifically among asymptomatic patients with moderate or severe AS, LAE (variously defined) has been shown to occur commonly, correlate with the severity of AS, and identify patients more likely to develop symptoms and experience adverse cardiovascular outcomes and death. Among patients who have undergone AVR for severe AS, preoperative LAE predicts less left ventricular reverse remodeling and increased morbidity and mortality after successful surgery. Increased LAVi, in the absence of primary atrial pathology or mitral valve disease, in the conventional wisdom, represents the hemoglobin A1c of chronic diastolic dysfunction, that is, reflects the integrated effects of chronically increased left ventricular diastolic pressures. LAE is strongly associated with chronicity and severity of diastolic dysfunction.

Christensen et al add importantly to the LAVi literature. They performed echocardiography for LV volumes and simultaneous right heart catheterization for pulmonary artery and pulmonary capillary wedge pressure (PCWP) measurement.
during supine bicycle exercise. LAE, defined properly as an indexed LA volume (LAVi) ≥35 mL/m², was associated with a higher PCWP and mean pulmonary artery pressure (mPAP) at rest. Furthermore, and most interestingly, the exercise hemodynamic data (mPAP and PCWP) related in a linear fashion to the resting LAVi and the E/e′ ratio–receiver operating characteristic analysis showing relatively high area under the curve for association of PCWP >30 mm Hg and mPAP >50 mm Hg. The hemodynamic burden faced by these patients is impressive: 89% of patients with LAE experienced pronounced diastolic dysfunction during exercise (defined as PCWP >30 mm Hg). Conversely, the group with LAVi <35 mL/m² were less likely to experience such rises in PCWP and mPAP with exercise, especially if their E/e′ ratio was normal at rest. The resting echo data also show that the LAE group had a greater prevalence of abnormal diastolic grade and concentric LV hypertrophy, which is not surprising. Finally, the authors note that at a median follow-up interval of 320 days, composite cardiac event rates were found to be higher among those with more marked alterations of exercise-induced hemodynamics.

To be included in the study, asymptomatic patients with severe AS were identified as having a peak aortic velocity >3.5 m/s and an estimated aortic valve area <1.0 cm². Current guidelines define severe AS as a peak aortic velocity of ≥4.0 m/s. Although a calculated aortic valve area <1.0 cm² is consistent with the presence of severe AS, this calculation is more operator dependent and shows greater variability in clinical practice than the measurement of peak aortic velocity. Thus, it may be possible that some subjects with moderately severe AS were included in the study groups. At first glance, it seems that this population had reasonable cardiac exercise reserve. Despite severe AS, patients were able to double their cardiac output and significantly increase their oxygen consumption on cardiopulmonary testing. However, careful inspection of the exercise data leads to some important conclusions. Although cardiac index overall more than doubled in both groups, end-diastolic volumes and end-systolic volumes were virtually unchanged. This means that all of the augmentation in cardiac output is because of a combination of enhanced contractility and heart rate.

Assuming no significant mitral regurgitation or inflow obstruction, higher diastolic pressures at a similar diastolic volume tells us that these patients developed severe diastolic dysfunction with exercise. These data are reminiscent of those of Kitzman et al, who performed a similar study on patients with diastolic heart failure. In fact, the work of Christensen et al is also perfectly congruous with the previous studies of Clyne et al (AS), Frenneaux et al (hypertrophic cardiomyopathy), and Cuocolo et al (hypertensive heart disease), who have all showed that lack of augmentation in stroke volume with exercise is an important reason for exercise intolerance in hypertrophic remodeling states. The data of Christensen et al emphasize that a second hit of markedly elevated LA pressures that accompanies exercise in AS is an unwelcome manifestation of this worsening diastolic function with exercise. Thus, we have data showing that the hearts of patients with hypertrophic cardiomyopathy, hypertensive heart disease, and heart failure with preserved ejection fraction and now AS must use chronotropy and inotropy to overcome the lack of preload reserve (ie, no change in LV volume) but do so at a severe increase in filling pressure.

As is seen in Figure 2 of the article by Christensen et al, a steep rise in PCWP with progressive exercise occurs in both groups. This ascent occurs in parallel (similar slopes), but the relative change in PCWP with exercise was higher in the group without LA dilatation. The authors speculate that patients with higher resting PCWP may not possess the ability to raise PCWP to the same extent as those with lower resting filling pressures. This is probably correct; the group without LAE likely started at a lower value but reached a similar ceiling of LA pressure. In this connection, it would have been interesting to see whether brain natriuretic peptide values differed between the 2 groups and how they behaved with exercise.

There are some curious findings in this report. Global longitudinal strain values were similar in both groups, and although it is likely that some subjects had reduced values for global longitudinal strain, the mean values for both groups were within the normal range. The global longitudinal strain data are at odds with those reported in a previous investigation of subjects with asymptomatic AS and normal LVEFs. Surprisingly, no difference in left ventricular geometries between the 2 groups existed and no association between concentric hypertrophy and higher PCWPs with exercise was found. Perhaps this observation is because of chance as the number of subjects in each group was small.

How do the results of the present investigation fit in with and add to previous work that has evaluated the effects of LA
size in patients with asymptomatic AS? As noted above, the findings of increased LAVi among asymptomatic AS patients is not novel. In our opinion, the new knowledge created by the work of Christensen et al. is principally the proof of concept. They convincingly demonstrate what we have hypothesized for decades but for which we had scant proof, namely, that increased LAVi tracks with elevated filling pressure; the dramatic increase in LA pressure with exercise experienced by AS patients; and the confirmation that this is because of an underlying profound diastolic dysfunction in these hearts. Much of the hemoglobin A1c of chronic diastolic dysfunction literature has been predicated on older work that showed, in a population of only 70 patients, that there was a strong correlation between LA minimal area (which we seldom measure in the echo laboratory) and PCWP. We now have incontrovertible supportive data to support the hemoglobin A1c notion.

What can we derive from the findings of Christensen et al. that can translate into clinical practice? Unfortunately, this mechanistic study is underpowered to answer the question of whether we can use LAE to risk stratify patients. In the absence of a randomized, controlled trial in asymptomatic AS patients, close clinical follow-up, encouragement of prompt symptom reporting in selected patients, exercise testing, and clinical judgment are paramount. Systemic hypertension should be treated appropriately, especially as this might help improve diastolic dysfunction.

An important aspect of the clinical care of such patients is attempting to recognize which patients may be at higher risk and thus demanding closer clinical follow-up and consideration for referral for earlier operative intervention. Professional guidelines recommend that exercise testing be used to determine whether patients are truly asymptomatic under the controlled conditions of a supervised exercise bout. Exercise echocardiography offers distinct advantages in assessing hemodynamic responses to exercise, which would identify patient as being at higher risk. As suggested by the Heart Valve Clinic International Database Group, further imaging-based risk assessment (Table) may be warranted to identify patients at increased risk who need more frequent follow-up. In this regard, the measurement of LAVi, an easily obtained and routinely recommended parameter on surface echocardiography, provides the clinician with the ability to recognize LAE. Armed with this information, the clinician should be alerted that despite asymptomatic status and preserved LVEF, AS may be imposing an excessive hemodynamic burden on the patient that can be exacerbated markedly with activity. This finding likely should trigger much closer clinical follow-up. However, a cautionary note is that LAE was present in two thirds of patients studied by Christensen et al and may be of limited discriminatory value. Perhaps, future longitudinal studies in the AS population will tell us whether a normal LAVi might identify a subgroup that tolerates the hemodynamic burden better and for longer.

Disclosures

None.

References


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