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EDITORIAL COMMENT

The Simple Arithmetic of Mixed Aortic Valve Disease

LVH + Volume Load = Trouble*

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Aortic stenosis (AS) is the prototypical pressure overload lesion. The Gunther-Grossman paradigm of the 1970s dictates that as afterload increases, concentric hypertrophy—increases in left ventricular (LV) mass index and relative wall thickness—normalize systolic load and allow for normal ejection fraction despite markedly increased intraventricular systolic pressure (1). In some individuals, this compensatory process appears to be excessive (2) and can be associated with poor outcome even with aortic valve replacement (AVR) (3). Increasingly, attention has been focused on the malefic consequences for diastolic function of such 'compensatory' hypertrophy (4,5).

Aortic regurgitation (AR), by contrast, is predominantly a volume load lesion but systolic stresses (σ) are high by the law of Laplace (σ = pressure × volume/wall thickness). In chronic severe AR, the need for abnormally large stroke volumes leads to eccentric (fiber elongation) hypertrophy, whereas high systolic pressures of AS stimulate concentric hypertrophy (6).

When AS and AR occur simultaneously—mixed aortic valve disease (MAVD)—the combined loads result in an entirely new phenotype of cardiac remodeling (**Figure 1**). The ventricle must not only adapt to the elevated afterload presented by the stenotic valve but must also remodel to accommodate an increased stroke volume. We can make an educated guess as to how the heart will remodel when faced with combined pressure and volume load lesions: a left ventricular end-diastolic diameter less than that seen in pure AR (7), but greater than that seen in pure AS (8). Some studies have suggested decreased ventricular function in MAVD (9), but large-scale natural history studies are lacking in adults.

The American College of Cardiology/American Heart Association Valve Disease Guidelines cite a plethora of large studies about isolated AS, emphasizing the prognostic importance of transaortic peak velocity and onset of symptoms, but only 9 small cohort studies and the "50-55" rule of thumb for asymptomatic severe AR—AVR when the ejection fraction falls below 50% or the LV end-systolic dimension exceeds 55 mm—provide guidance regarding AR. Not surprisingly, data guiding the clinician caring for MAVD patients, arguably a more challenging situation than either lesion alone, are sparse (10).

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Severe degrees of both AS and AR rarely coexist (11), at least not for long. The transcatheter aortic valve experience provides evidence of miserable outcomes when hypertrophied ventricles, conditioned for pressure loads and likely containing at least some fibrosis, are exposed to an acute significant AR volume. During short- and intermediate-term follow-up, moderate or severe and possibly even mild AR portend a worse outcome for the hypertrophied ventricle of severe AS (12). By contrast, moderate AS and moderate AR often do coexist, the subject of the interesting paper by Egbe et al. (13) in this issue of the *Journal*. As noted in the preceding text, very little is known concerning the natural history of MAVD; the cardiac phenotype has not been described, nor has anyone extensively studied

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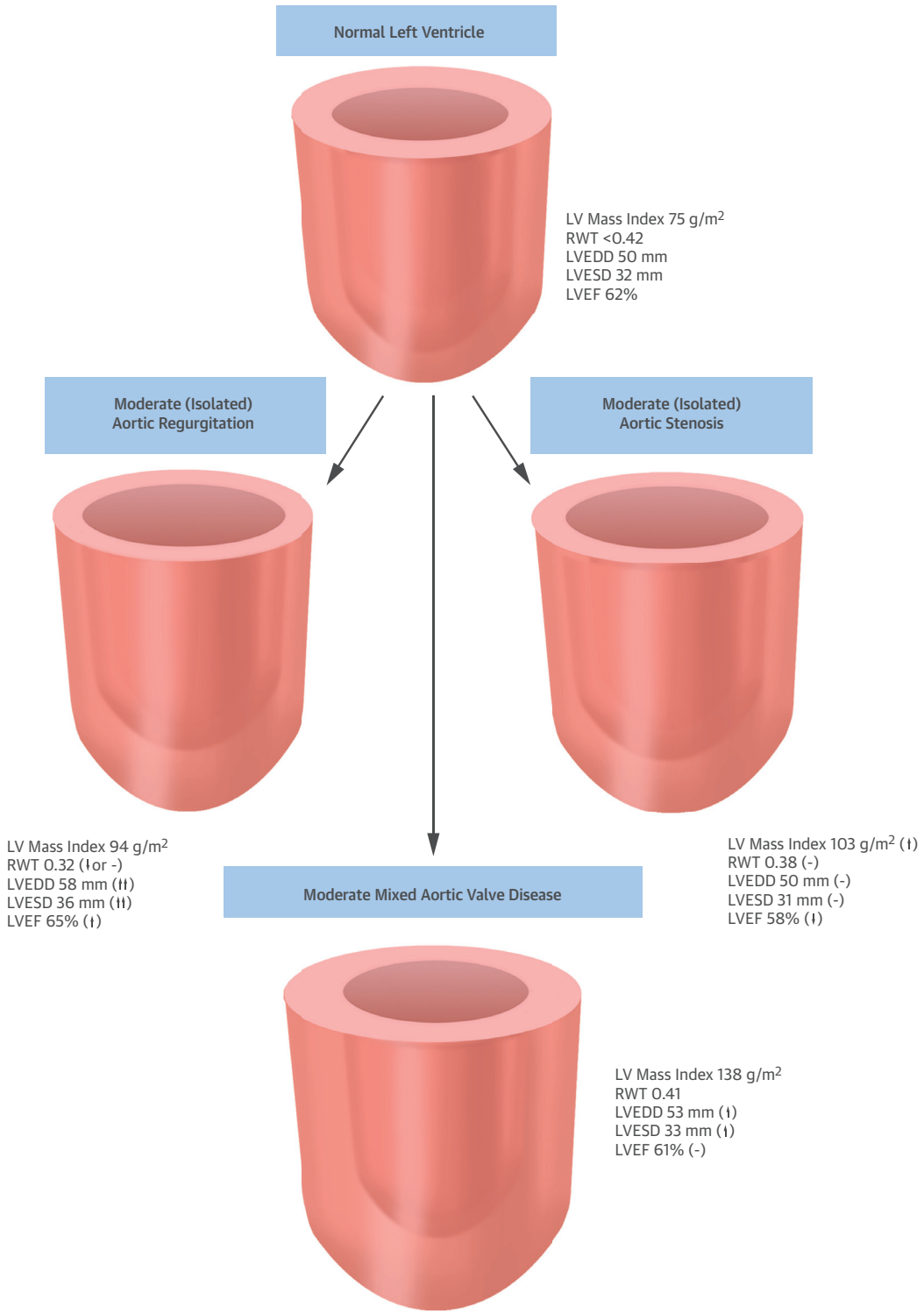
FIGURE 1 LV Phenotypic Responses to Moderate AS, AR, and MAVD



Moderate mixed aortic valve disease (MAVD) leads to increased left ventricular diameters intermediate to that seen in isolated aortic regurgitation (AR) or aortic stenosis (AS) as well as increased relative wall thickness, resulting in larger indexed left ventricular mass than either lesion in isolation. LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; RWT = relative wall thickness.

TABLE 1 5-Year Outcomes of MAVD in Contemporary Cohorts

First Author Year (Ref. #)	Population	Mean Age, yrs	Average LV Mass Index, g/m^2	5-Yr Event-Free Survival
Zilberszac et al. 2013 (17)	71 patients with ≥ moderate AS and ≥ moderate AR	52 ± 17	151*	26%
Rashedi et al. 2014 (11)	190 patients with either moderate AS and ≥ mild AR *or* moderate AR and ≥ mild AS†	65 ± 14	Not reported	40%‡
Egbe et al. 2016 (13)	117 patients with moderate AS and moderate AR	64 ± 8	138	29%

*Calculated from data provided in publication. †Included 130 patients with moderate AS and moderate AR. ‡Extrapolated from figure.
AS = aortic stenosis; AR = aortic regurgitation; LV = left ventricular; MAVD = mixed aortic valve disease.

outcome with or without AVR. Thus there is clearly a need for contemporary data, especially in view of an aging population (more valve disease) and new transcatheter techniques (more valve therapies). For this reason alone, the report by Egbe et al. merits serious consideration.

In a large cohort of moderate MAVD, studied retrospectively clinically and by echocardiography, Egbe et al. (13) describe the natural history of the mixed lesion and compare that to age- and gender-matched patients with isolated moderate AS, moderate AR, or, most provocatively, severe asymptomatic AS (14). At the time of their initial echocardiographic study, MAVD patients demonstrated a ventricular phenotype with an LV end-diastolic diameter intermediate between pure AS and AR. Mean wall thickness was also highest in the MAVD group (11 mm compared with 9 mm in the moderate AR and 10 mm in both the moderate and severe asymptomatic AS patients). The combination of modest LV end-diastolic diameter enlargement and marked LV wall thickening resulted in the MAVD patients having larger indexed LV mass than patients with either lesion in isolation (13) (**Figure 1**).

It is worth remembering that in patients with preserved LV ejection fraction, LV mass has proven to be a key predictor of outcomes across a variety of diseases (3,14,15), so that the very high LV mass indexes encountered in this study suggest the possibility of severe combined volume and pressure overload despite the valve lesions being graded as moderate. Interestingly, the rate of cardiac death reported in trials of advanced hypertensive heart disease, which approaches 5% at 5 years in subjects with the highest indexed LV mass (16), was similar to the 5-year rate of cardiac death in the current study of MAVD.

This suggests to us that the high combined event rates during the follow-up period that severe LV hypertrophy is the fundamental issue underlying poor outcome with MAVD, with progression to either symptoms requiring AVR or cardiac death at rates that parallel severe asymptomatic (isolated) AS over median follow-up of 9.1 years. (Similarly high event rates for this patient population have been reported by others [11,17] as shown in **Table 1**.)

There are some limitations to this study, such as the peculiarly low mean body surface area of this patient population, raising a question about the generalizability of the findings. With a retrospective study, of course, it is hard to know exactly why some patients go on to AVR, whereas others do not, because the clinician's "eyeball" score cannot be quantified. In this study, we are told, the overwhelming majority (89%) of patients who underwent AVR did so because of progression to symptomatic severe AR or severe AS. The remaining minority who underwent AVR did so in the absence of a severe valve lesion and still furnish a valuable lesson: these 19 patients had the largest LV mass in the study (mean relative wall thickness 0.44 and mean indexed LV mass 145 g/m^2) and Doppler echocardiographic parameters consistent with advanced diastolic dysfunction were present in all 14 who had complete Doppler evaluation of diastolic filling, suggesting that perhaps clinicians were either concerned about the degree of hypertrophy or that they felt that the echocardiographic parameters were not adequately capturing the degree of stenosis or regurgitation. To us, a subliminal message from these data was that the development of symptoms was driven by diastolic dysfunction. Protocol-driven serial evaluations of diastolic function were not available, but advanced diastolic dysfunction in patients with increased LV mass is common and could explain the development of symptoms in patients with non-severe valve disease.

The authors conclude that surveillance for the patient with MAVD should be modeled on the patient with severe asymptomatic AS, rather than the common adage to follow such a patient on the basis of the more severe of their two lesions. This provocative conclusion in turn raises additional questions. Which parameter, specifically, is to be followed during surveillance? And which modality should be used to follow it? Markedly increased LV mass appears to differentiate MAVD from predominantly stenotic or regurgitant lesions, but at what threshold of LV mass is AVR most likely to be beneficial? Unfortunately, progression of LV mass in relation to progression of the individual valve lesions or symptoms were not collected serially and may be below the resolution of contemporary echocardiography to reliably detect. Serial analyses of LV geometry and mass in parallel

with hemodynamic measures of AS and AR, either with echocardiography or cardiac magnetic resonance imaging, may lead to better insights than clinically driven interval assessments.

It should be remembered that peak Doppler transaortic systolic velocity integrates both severity of AR and AS and is independently associated with prognosis in pure AS with preserved systolic function (18–20) as well as in MAVD (17). The current report recapitulates the finding by Rashedi et al. (11) that progression in patients with MAVD principally manifests as progression of AS. The authors also report accelerated progression of AS in patients with MAVD when qualitatively comparing with patients with isolated moderate AS. In MAVD, it can be difficult to determine which is progressing, because worsening of both lesions will lead to increasing transaortic valve velocities. This aspect of MAVD is acknowledged by the authors and must also be acknowledged by clinical echocardiographers comparing serial studies, and argues for the calculation of the aortic valve area by the continuity equation when feasible, because this parameter can differentiate between increasing velocity due to increasing stroke volume and increasing velocity due to worsening AS. At the same time, accelerated transvalvular flow may also be responsible for trauma to the aortic valve that leads to fibrosis and calcification (21), which could become a target for medical, rather than surgical, treatments prior to the development of severe, symptomatic disease.

Ultimately, the question of whether patients with MAVD would be better served with a unique indication for AVR can only be answered by a prospective study design. For the present the key clinical message about patients with MAVD should be vigilance. Combined AS and AR is more complex than an isolated lesion, both for ventricle and for the clinician, and precise predictors of symptom onset remain elusive. Careful assessment of LV mass, geometry, diastolic function, as well as parameters of AS and AR, is necessary and may well require multimodality imaging.

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