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EDITORIAL COMMENT

Intervention In Severe Aortic Stenosis

It May Be Time When the Left Ventricle Says So*

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There are 2 important unsettled issues with regard to timing of intervention in severe aortic stenosis (AS). One has to do with the reliability of symptoms as the trigger for surgical aortic valve replacement or transcatheter aortic valve replacement (TAVR). And the other related issue has to do with identification of signal(s) for intervention in asymptomatic severe AS. These signals could be related to the biology of the stenotic AV or the effects of the stenotic AV on the structure and function of the left ventricle (LV) or both. Hence, the concept of staging the disease rather than merely classifying AS based on Doppler hemodynamic severity has recently emerged (1). This means that among severe AS, there may be compensated stages (0 and 1), subclinical decompensation stages (1 and 2), and decompensated stages (3 and 4). In this schema, stages 0 and 1 are where one is most likely to encounter individuals with severe AS but who truly do not have symptoms at rest or exercise. These 2 stages are predominantly defined by the state of the structure and function of the LV, other than the hemodynamic severity of the AS (2). Among the structural changes of the LV in severe AS, left ventricular hypertrophy (LVH) and increased mass are the most recognizable morphological changes.

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In this issue of the *Journal*, Chau et al. (3) have reported on the effect of TAVR with a balloon-expandable transcatheter heart valve on regression of LV mass at 1 year post-TAVR, and its impact on clinical outcomes at 5 years post-TAVR. Retrospective analysis of echocardiographic LV mass from 1,434 patients with symptomatic severe AS showed that for every 10% incremental decrease in LV mass at 1 year, there was a 5% to 6% adjusted annual risk reduction of all-cause and cardiovascular deaths and cardiovascular hospitalization during years 1 to 5 post-TAVR. Also, greater reduction in LV mass at 1 year was associated with a better quality of life at 2 years. A noteworthy finding was that despite relief of AS, 25% of patients had no regression of LV mass and about 40% had persistent severe LVH at 1 year post-TAVR. The latter was associated with 71% and 89% increase in risk of mortality and cardiovascular hospitalization between 1 and 6 years after TAVR. In the multivariable analysis, only presence of moderate and severe aortic regurgitation at 30 days post-TAVR was associated with reduced LV mass regression. Notably, change in LV mass was independent of transcatheter heart valve size, AV mean gradient and area post-TAVR, and systolic blood pressure. Despite significant limitations inherent to retrospective registry-based data analysis, this is the largest systematic report of the effect of surgical AVR or TAVR in severe AS on LV mass and LVH, as well as its impact on subsequent clinical outcomes. So, should adverse LV remodeling be among the signals for AVR in severe AS, even in the absence of symptoms?

To meaningfully answer that question, it would serve us well to refresh the basics of the

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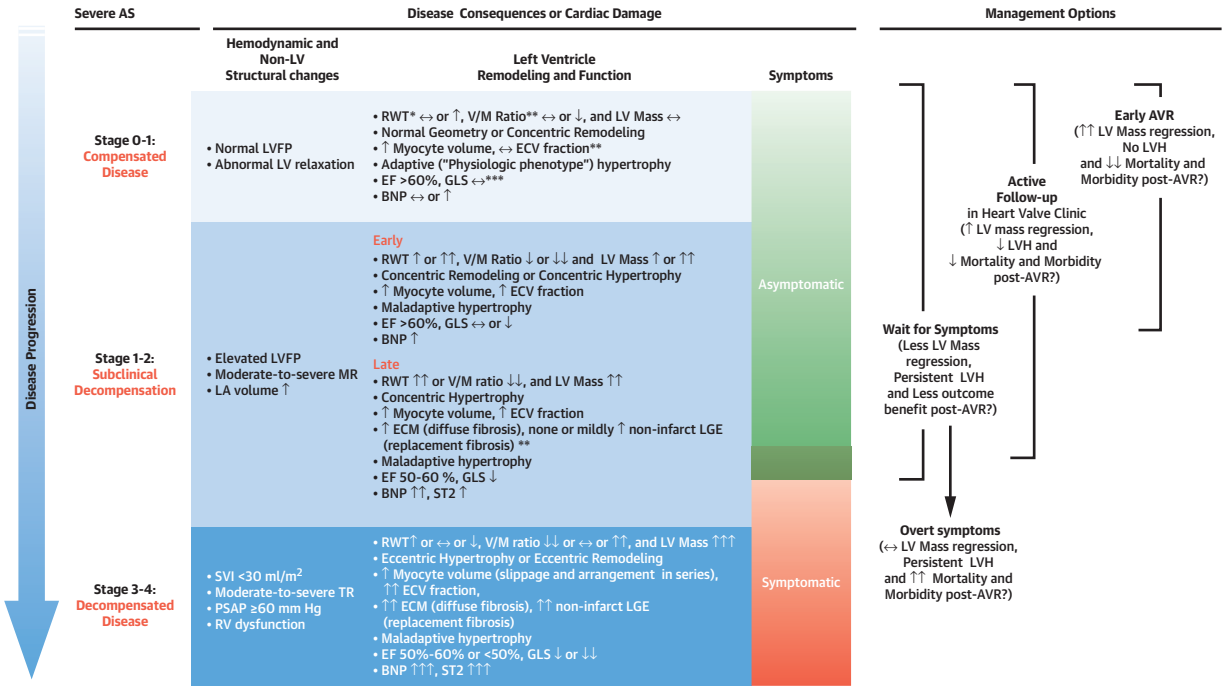
FIGURE 1 Approach to Staging and Management in Severe AS Based on LV Remodeling and Function



This scheme is a proposal to show the management options in the 3 phases of the disease in severe aortic stenosis (AS) and the likely impact of aortic valve replacement (AVR) on left ventricular (LV) mass and clinical outcomes. Absence of symptoms is most likely in the compensated and subclinical phases, and within the latter phase, symptoms are likely in the late period. The decompensated phase is very likely to be symptomatic. The LV and myocardial remodeling features, functional indices, and levels of circulating biomarkers that may characterize the stages are shown. Also shown are the hemodynamic and non-LV damages that may accompany these stages. The features in each category are derived from accumulating rather than proven evidence. Similarly, the management options in an asymptomatic phase and the effect of AVR on adverse changes in the LV and clinical outcomes are a hypothesis based on current knowledge. These need to be confirmed in ongoing prospective randomized trials. ↔ = normal/no change; ↑ to ↑↑↑ = mildly to markedly increased; ↓, ↓↓ = mildly or markedly decreased; * = echocardiography; ** = cardiac magnetic resonance imaging; *** = increased versus normal circumferential and radial strain may potentially distinguish normal geometry from concentric remodeling. Adapted from and modified with permission from Lancellotti and Vannan (2). BNP = B-type natriuretic peptide; ECM = extracellular matrix; ECV = extracellular volume; EF = ejection fraction; GLS = global longitudinal strain; LA = left atrial; LGE = late gadolinium enhancement; LVFP = left ventricular filling pressure; LVH = left ventricular hypertrophy; MR = mitral regurgitation; PSAP = pulmonary-artery systolic pressure; RV = right ventricular, RWT = relative wall thickness; ST2 = soluble tumor factor 2; SVI = stroke volume index; TR = tricuspid regurgitation; V/M = volume to mass.

pathobiology of LV remodeling in AS. The increased afterload of AS triggers the terminally differentiated cardiomyocytes to change size and shape through addition of sarcomeres in parallel throughout the cell so that the cross-sectional area of each myocyte is increased. Thus, the myocytes are short and thicker than normal. This is an adaption to increase the contractile power of cardiomyocytes and thereby the myocardium, normalizing the myocardial systolic wall stress (4). However, for this pathological hypertrophy to be "adaptive," a number of events have to occur concurrently, which ensure optimal cell survival and efficient functioning proportional to the growth of the ventricular wall. These events antagonize pathological signaling, so that the structural changes of adaptive hypertrophy resemble the phenotype of physiologic hypertrophy. At this stage, the myocardial contractile function is preserved and LV wall thickness (WT) may be normal. However, the increased myocytes stress and strain AS, commonly activates an array of pathological signaling pathways also, which result in reappearance of fetal gene expression, impaired calcium handling, mitochondrial dysfunction, altered sarcomere structure, impaired angiogenesis to support cell growth, a slew of cellular metabolic reprogramming, accelerated cell death, myofibroblast activation, expansion of extracellular matrix (ECM), and increased deposition of type I collagen. This is "maladaptive" hypertrophy, which

will eventually lead to contractile dysfunction if AS is not relieved. The progression from normal myocardium to adaptive and maladaptive hypertrophy is not necessarily sequential and is influenced by extensive cross-talk between the various adaptive ("physiological") and maladaptive signaling pathways. Also, age, sex, and other nonvalve factors such as diabetes, obesity, hypertension, and ischemia, which are not uncommon in the AS population, influence the transition from adaptive to maladaptive hypertrophy phenotype (5).

At the gross morphological level, concentric hypertrophy (CH) is the predominant form, upward of 50%, of LV remodeling seen in severe AS with normal ejection fraction (EF). This is followed by concentric remodeling (CR) pattern (about 25%), normal geometry (up to 10%), and eccentric hypertrophy (<10%) (6,7). Because the interplay between myocytes and ECM dictates the contractile and relaxation function of the myocardium, CR potentially represents the adaptive hypertrophic phenotype in which myocardial WT and relative WT are increased, but LV mass is still normal. This seems to be seen more often in women, and T_1 mapping by cardiac magnetic resonance shows expansion of extracellular volume fraction and ECM volume (diffuse fibrosis) together with increased myocyte cell volume (8). Even "normal" LV geometry (normal WT, relative WT, and mass) in severe AS, may be an adaptive phenotype characterized predominantly by thick myocytes and increased myocyte volume without a significant increase in extracellular volume fraction and ECM. Hypothetically, normal global longitudinal strain, LVEF >60%, but increased circumferential and radial strain may distinguish normal geometry from CR, with circumferential and radial strain being within normal limits in the latter. These adaptive phenotypes are most likely to be found in compensated stages 0 and 1 of the disease when circulating biomarkers are normal or only mildly elevated. AVR at these compensated disease stages may yield the maximum benefits of reverse remodeling and long-term survival and decreased morbidity. CH perhaps represents the maladaptive phase of hypertrophic response, characterized by increased LV mass and extensive focal and noninfarct pattern of replacement fibrosis (cardiac magnetic resonance late gadolinium enhancement) in addition to all of the findings seen in CR (9,10). The subclinical decompensated stages 1 and 2 of the disease is likely where the CH phenotype is represented. Within this stage, normal global longitudinal strain, LVEF >60%, and elevated biomarkers may indicate early subclinical decompensation, whereas reduced global longitudinal strain, LVEF of 50% to 60%, and markedly elevated biomarkers may represent late subclinical decompensated stages. In the absence of symptoms, whether AVR done at the compensated versus subclinical decompensation stages yields differential impact on regression of LV mass, reversal of adverse myocardial remodeling, survival benefits and quality of life remains to be seen (11). Also, the incremental beneficial effects of inhibition of the renin-angiotensin-aldosterone system and other newer drug therapies on the reversal of adverse remodeling needs to be explored (12).

In the study by Chau et al. (3), symptoms notwithstanding, relative WT and LV mass were increased at baseline in all the patients with severe AS, so maybe this population exclusively or mostly had CH. It is possible then that the population in quartiles 3 and 4 of LV mass regression post-TAVR were early stage 2 (closer to stage 1), whereas those in quartiles 1 and 2 were late stage 2. This is speculation, but there is evidence that surgical AVR does reverse the CR phenotype of LV and myocardial remodeling, and this is less so in the CH phenotype (13). Eccentric hypertrophy remodeling may be the dominant LV phenotype in the decompensated stages 3 and 4, and AVR may not significantly reverse the adverse remodeling even if there were short-term survival and quality-of-life benefits.

Figure 1 summarizes the concepts outlined herein and provides a potential staging approach in severe AS with regard to timing of intervention based on markers of LV and myocardial remodeling. The ongoing randomized studies using the LV structure and function indices to randomize patients with asymptomatic severe AS to TAVR versus follow-up will provide us with answers (2). The growth of TAVR as a therapeutic option for severe AS has prompted a fresh look at the timing of intervention in severe AS. In the case of severe AS, maybe it is time when the muscle says so.

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