Increased biomechanical stress on cardiomyocytes because of outflow obstruction secondary to aortic stenosis (AS) is thought to induce reexpression of the fetal gene program, which modifies myocyte efficiency, sarcomere composition, and regulation of extracellular matrix, as well as various nuclear signal transduction pathways resulting in autocrine production and secretion of cytokines, neurohormones and growth factors that ultimately promote ventricular hypertrophy.1,2

The traditional view of adaptive concentric left ventricular hypertrophy (LVH) because of parallel replication of new sarcomeres is that wall thickness increases to normalize LV systolic wall stress and preserve systolic performance. This view, accepted for the past 40 years3 and perhaps counterintuitively expected to mitigate the effects of LV pressure overload on cardiovascular morbidity and mortality, has begun to be challenged by new clinical data, suggesting that moderate or severe LVH may be associated with adverse outcomes in AS1,2 and that inappropriately increased LV mass, found in 17% of patients with mild to moderate AS6 and in 67% of patients with asymptomatic severe AS, was associated with a 4.5-fold increased risk of cardiovascular events.7 Conversely, the absence of hypertrophy in one third of the patients with severe AS seems to have no adverse effects on systolic function or survival.8,9 Experimental studies in genetically modified animal models are consistent with clinical observations.10 In addition, no association was found between AS severity and the magnitude or pattern of LVH using cardiac magnetic resonance.11 Thus, it seems that the presence, severity, and the geometric pattern of LVH in AS vary widely, are individual-specific, multifactorial, and may be influenced by comorbidities, and are likely genetically determined.

Because most research on the LV response to pressure overload and associated outcomes has been done in asymptomatic or symptomatic severe AS, less is known about LV phenotypes in milder AS and their prognostic implications.

Analyzing echocardiographic LV mass data from 1656 patients (mean age, 67 years; 60% men; 83% hypertensives) with asymptomatic mild to moderate AS enrolled in the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) study, Gerdts et al.12 in this issue of Circulation: Cardiovascular Imaging, found that LVH prevalence increased by 24%, from 36% to 60%, during a median follow-up period of 4.3 years with similar AS progression rates in both LVH and non-LVH phenotypes. Major cardiovascular events occurred in 34%, with 66 cardiovascular and 129 all-cause deaths. At follow-up, a higher LV mass index was associated with increased cardiovascular morbidity and mortality (+63%) and combined all-cause mortality and hospitalization for heart failure (+44%).

Patients with LVH had worse LV systolic performance, and in models adjusted for variables with prognostic significance in AS, a strong association was found between baseline LV mass index and the prespecified end points regardless of whether LVH was treated as a categorical or continuous variable.

If at least half of these patients had only mild AS,11 what explains increased LV mass at baseline in more than one third of the subjects enrolled in SEAS trial? LVH prevalence in the general population is not insignificant in younger individuals (16% in women and 19% in men in the Framingham study)14 or in the elderly. In a recent report from the Cardiovascular Health Study, which enrolled community-dwelling individuals ≥65 years of age, echocardiographic LVH prevalence was 12.5%, and when associated with elevated biomarker levels, significantly increased the risk of heart failure, especially with reduced ejection fraction.15

In this study, it is conceivable that hypertension, reported in the majority of patients and 8% more common in the LVH group (P<0.01), played a major role in increasing LV mass. Systolic blood pressure was also an independent variable associated with higher LV mass/height7. Although the presence of hypertension increased cardiovascular and all-cause mortality 2-fold, it did not influence the association between LV mass index and the outcome variables. Only limited information was given about the prognostic value of the LV remodeling pattern. At baseline, patients with LVH had eccentric hypertrophy (elevated LV mass with normal relative wall thickness), which evolved toward concentric hypertrophy during follow-up, but progression of LVH was similar in those with and without LVH at intake. In the classic study of LV remodeling in untreated hypertensives, most with abnormal LV geometry also had eccentric hypertrophy (27% versus 21%).16 In contrast, in Aortic Stenosis Progression Observation: Measuring

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See Article by Gerdts et al
Effects of Rosuvastatin (ASTRONOMER) trial, which examined patients with mild to moderate AS and a mean age of 50 years, progression of LVH occurred only in those without LVH at baseline. Efforts to refine evaluation of LV remodeling patterns using cardiac magnetic resonance have included proposals to distinguish asymmetrical septal remodeling and hypertrophy, mixed hypertrophy, physiological hypertrophy, eccentric remodeling, and dilated hypertrophy (concentric and eccentric). Indeterminate hypertrophy, which together with dilated hypertrophy has been proposed as an eccentric hypertrophic pattern, is reportedly associated with the lowest risk for adverse outcomes when compared with other remodeling patterns. Perhaps in this study, the impact of LV mass index on outcome variables was independent of concentricity because of predominance of eccentric hypertrophy of dilated subtype, which in the Dallas Heart Study was associated with an 8-fold increase in incidence of heart failure and cardiovascular death compared with the non-LVH group (16.7% versus 2%, respectively).

In addition to hypertension, the presence of mild to moderate AS contributed to variations in LV geometry in SEAS. Despite similar AS severity by valve area, the LVH group had other echocardiographic variables suggestive of greater stenosis severity compared with the normal LV geometry group: higher transvalvular gradients and lower energy loss index. The latter takes into account the ascending aortic area at the sinotubular junction, and if aortic valve area was similar, the ascending aorta had to be smaller in the LVH than in the non-LVH group. Therefore, the higher prevalence of aortic regurgitation in patients with LVH was probably unrelated to ascending aortic dilatation. Considering the known limitations of echocardiographic aortic valve area calculation, especially measurement of the LV outflow tract area, and the known discrepancies between different echocardiographic indices reflecting AS severity, one cannot completely exclude a higher severity of AS in the LVH group. The association of elevated LV mass index with adverse outcomes in SEAS might be related to the presence of LVH itself, given known correlates including changes in myocardial matrix with increased collagen deposition and extracellular volume, increased coronary vascular resistance and reduced myocardial perfusion reserve, subclinical LV systolic dysfunction expressed as reduced systolic strain, altered diastolic filling, and increased risk of ventricular arrhythmias. Other contributors may include aortic valve calcification, which was shown to be associated with a 50% higher risk of cardiovascular events in the Multi-Ethnic Study of Atherosclerosis (MESA), subclinical coronary artery disease, or adverse systemic vascular hemodynamic characteristics including increased systemic vascular resistance, lower arterial compliance, and increased arterial elastance, described in more severe stenosis.

It would have been of interest to determine whether there were sex and racial differences in LVH prevalence, LV remodeling patterns, and outcomes because sex and racial differences in response to increased LV afterload are known to occur. However, in SEAS, >99% subjects were white. Finally, errors in 2-dimensional echocardiographic LV mass measurements because of basal septal hypertrophy may have lead to overestimation of LV mass in some patients, especially because mean posterior wall thickness was normal (1.02±0.18 and 0.81±0.14 cm; P<0.01) in both groups.

Overall, this study adds novel and important knowledge relevant to the natural history of AS. What might be the clinician’s take-home message? Based on this and prior studies, the Framingham LV mass index, corrected for height, should probably be determined in all patients with AS, regardless of severity and used as a prognostic marker.

**Disclosures**

None.

**References**


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Left Ventricular Hypertrophy in Asymptomatic Nonsevere Aortic Stenosis: Should We Worry?
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