Advances in Arrhythmia and Electrophysiology

Increased Left Ventricular Mass as a Predictor of Sudden Cardiac Death
Is it Time to Put it to The Test?

Steven M. Stevens, MD; Kyndaron Reinier, PhD; Sumeet S. Chugh, MD

With an annual incidence of 250,000 to 300,000 in the US, sudden cardiac death (SCD) is among the leading causes of death worldwide. The availability of the implantable cardioverter defibrillator (ICD) makes SCD a preventable condition, but the burden lies on investigators and clinicians to identify the highest risk group for ICD implantation efficiently. There is increasing recognition that current risk stratification methodology, largely reliant on measurement of the left ventricular (LV) ejection fraction (EF), is inadequate and requires significant enhancement. It is likely that additional variables can be considered both independently and in combination with the EF to improve the process of clinical SCD risk prediction.

Although currently not used for prediction of SCD risk, LV hypertrophy (LVH) has significant potential for enhancing risk stratification algorithms. The association between LVH on the 12-lead ECG and overall mortality was first reported from the Framingham cohort. Since then, several studies have validated the link between LVH and overall mortality but few have reported an independent association with SCD. Recent findings from the Oregon Sudden Unexpected Death Study (Oregon SUDS) confirmed the LVH–SCD association in the community, also showing that LVH and severe LV systolic dysfunction are independent predictors of SCD that may contribute to risk through distinct mechanistic pathways. This review will discuss studies that have linked LVH and SCD, compare LVH and LVEF as predictors of SCD, discuss the mechanisms of ventricular arrhythmogenesis in LVH, recap how regression of LVH reduces mortality, and discuss the potential role of LVH in risk stratification for SCD. For the purpose of this review, LVH is defined as hypertrophy of the LV distinct from the syndrome of hypertrophic obstructive cardiomyopathy, a condition that is largely familial and known to impart a uniquely increased risk of SCD.

Significant Association of LVH With Overall Mortality and SCD

LVH can be diagnosed on the ECG or by imaging tests, such as the echocardiogram or cardiac magnetic resonance imaging. Sensitivity of the ECG for identification of LVH varies widely depending on the patient population being evaluated and the standard used for evaluation. However, in general, the ECG is less sensitive than the 2-dimensional (D) echocardiogram, when both are compared with necropsy, and ECG-detected LVH has a much lower prevalence (≤5% in patients with hypertension of average severity) than LVH detected by 2-dimensional (2D) echocardiography (which ranges between 20% and 80% in patients with hypertension). In addition, the ECG measures the summation of myocardial voltage and may represent a physiological phenomenon that is distinct from estimation of myocardial mass using echocardiographically determined LV geometry. When compared with 2D echocardiography, magnetic resonance imaging is likely to be a more precise and reliable method for measuring LV mass, although more recent studies argue that real-time 3-dimensional echocardiography could be comparable with magnetic resonance imaging. Since published studies of LVH and SCD have used either ECG or 2D echocardiographic identification of LVH, and these 2 methods could represent different measurements of LVH, we divided these studies based on one or the other specific diagnostic modality.

LVH Measured on the ECG

The association of SCD and LVH diagnosed from the 12-lead ECG was first reported more than 40 years ago. In 1970, a population-based study from Michigan showed an association of LVH by ECG with 98 coronary heart disease deaths (45 SCD events) observed during a 6-year period and predicted an SCD rate of 48 per 1000 for this time period, compared with 2.6 per 1000 with a normal ECG. Subsequently, pooled data from men in the Framingham Heart Study and Albany civil servants study indicated a 5-fold increased risk of SCD with LVH by ECG. There were 14 SCD events per 1000 patients per year for those with LVH, compared with only 2.7 SCD events per 1000 in those without LVH. Among patients with specific comorbidities, LVH becomes an even stronger risk predictor of mortality. The Global Use of Strategies To Open Occluded Coronary Arteries IV (GUSTO IV) Acute Coronary Syndrome Trial demonstrated higher 30-day mortality (5% versus 3%) and 1-year mortality (14% versus 7%) among acute coronary syndrome patients with LVH on ECG, defined by sex-specific Cornell voltage criteria (SV₃+RaVL ≥28...
mm in men and ≥20 mm in women), and the presence of repolarization abnormalities or T-wave inversion. In fact, given the evidence for LVH as a potent marker of mortality, the Losartan Intervention For End point reduction (LIFE) study used regression of LVH by ECG as a surrogate marker for decreased mortality and sudden death, defining LVH as the product of QRS duration and Cornell voltage (RaVL+SV3, with 6 mm added in women) >2440 mm ms or Sokolow–Lyon voltage (SV1+RV56) >38 mm.17

LVH Measured on the Echocardiogram
As a tool for the assessment of LVH, the echocardiogram has been shown to be more sensitive than the ECG when both were compared with necropsy criteria for anatomic LVH.2 Echocardiographically determined LV mass, used as a continuous variable, is also a strong predictor of cardiovascular mortality and SCD.2,3,6,7 The Framingham Heart Study reported that LV mass was strongly associated with cardiovascular morbidity and mortality. For every 50 g incremental increase in LV mass, there was a 1.49-fold increase in risk of cardiovascular disease in men, and 1.57-fold increase in women, adjusting for cardiovascular risk factors and for LVH by ECG. Higher risks (relative risks, 1.73 and 2.12, respectively) were observed for cardiovascular death.20 In a separate cohort of 253 patients with hypertension followed for 10 years, LVH (LV mass index, >125 g/m2) was present in 27% patients. Cardiovascular death occurred in 14% of those with LVH compared with 0.5% in those without LVH.19 Specifically focusing on the relationship between LVH and SCD, Haider et al2 also analyzed data from 3661 Framingham Heart Study participants and demonstrated that LVH, defined as >143 g/m2 in men and >102 g/m2 in women, was present in 21.5% of SCD cases, and for every 50 g increase in LV mass there was a 1.45-fold increased risk of SCD. Overall, there was a 2.16-fold increased risk for LVH with LVH in the Framingham Heart Study.7

Comparisons of LVH and LVEF as Risk Predictors of SCD
On the basis of several SCD prevention trials of the ICD,22,23 severely decreased LV systolic function measured as EF<35% has been established as a predictor of SCD, with resultant inclusion in the primary prevention guidelines as a class I recommendation for ICD implantation. However, more recently, 2 types of studies have demonstrated the overall inadequacy of using LVEF as the sole risk stratifier. Two community-based studies have established that at least two thirds of all SCDs occur in patients with EF<35%.24,25 In a 2-year analysis of the Oregon SUDS, 48% of those experiencing SCD had normal EF, and the EF was severely reduced in only 36%.24 Furthermore, reports from clinical trials and real-world experience indicate that only a minority of patients receiving ICDs actually use this primary prevention modality. An early study compared the predictive ability of LVEF, LVH, and other clinical variables for overall mortality in 2445 consecutive patients who underwent coronary angiography at Cook County Hospital, Chicago.26 It is interesting that LVH, defined in this study as LV mass index >131 g/m2 for men and >100 g/m2 for women, was identified as the most powerful predictor. For every 100 deaths, the attributable risk of LVH was 37 compared with 22 for multivessel CAD, and only 9 for LVEF<45%. However, this study did not specifically evaluate risk of SCD.26

Echocardiographic LV mass was also reported as a stronger predictor of overall mortality and SCD compared with LVEF in the Heart and Soul Study, a cohort of 1016 patients with stable coronary disease followed for 3.5 years. LVH was defined as LV mass index >115 g/m2 in men and >95 g/m2 in women. Total mortality in patients with LVH was 25%, and without LVH only 11%; and mortality from SCD in patients with LVH was 6.7%, but without LVH it was 2.2%. Every 20-U increase in LV mass index increased the adjusted hazard of death by 22% (P=0.001) and adjusted hazard of sudden or arrhythmic death by 40% (P=0.004).21 Both LVH and LV mass also remained predictors of SCD in the subset of patients with normal EF.

The Studies of Left Ventricular Dysfunction (SOLVD) trial, designed to test the use of enalapril in patients with and without systolic dysfunction, reported a strong association between LV mass and mortality. After adjustment for EF, a 1-SD increase in LV mass had a risk ratio of 1.3, P=0.012.18 Although there were no direct comparisons made between LVEF and LV mass, the subset of patients with EF>35% and LV mass >298 g had equivalent risk for SCD compared with those with EF<35% and LV mass <298 g, showing that LVH in patients with preserved systolic function was as powerful a predictor as low EF in patients with normal LV mass.18

A focused comparison of LVEF and LV mass as predictors of SCD was recently reported from the ongoing Oregon SUDS. We evaluated 191 SCD patients with antemortem echocardiograms unrelated to the SCD event and compared these with 203 controls with CAD, defining LVH as LV mass index >134 g/m2 in men and >110 g/m2 in women. After adjusting for other significant risk factors, the odds ratio for EF≤35% was 1.9, compared with 1.8 for LVH. If both conditions were present, the OR increased to 3.5, demonstrating additive effects of LVH and EF≤35% on SCD risk. LVH was significantly more prevalent in SCD patients compared with controls, even in patients with EF>35% (42% in cases versus 21% in controls; P<0.0001). These findings support a potential role for LVH in risk stratification of patients with reduced EF without LVH who are at lower risk for SCD and patients with preserved EF with LVH who are at higher risk of SCD.27 The currently available studies comparing LVH versus LVEF are listed in Table 1. All of these studies reported that LVH was at least equivalent to severely decreased LVEF as a predictor of mortality or SCD.

Mechanisms of Ventricular Arrhythmogenesis in LVH
A large body of literature has accumulated regarding the increased prevalence of ventricular arrhythmias in patients with LVH, and potential mechanisms have been evaluated at the human, animal model, and in vitro levels. Figure 1 compares several mechanisms of ventricular arrhythmogenesis associated with increased LV mass and decreased LVEF. A prospective study of 50 hypertensive patients with LVH, 50 without LVH, and 50 normal controls showed significantly more ventricular ectopy in the LVH group.28 Of those
with LVH, 28% had nonsustained ventricular tachycardia on 48-hour Holter monitoring, compared with 8% in the hypertensive group without LVH, and 2% in the normal group. In fact, every additional millimeter of LV thickness seems to increase the risk of ventricular ectopy by 2- to 3-fold.29 However, SCD requires the occurrence of sustained ventricular arrhythmias, and the possibility exists that risk of SCD with LVH is independent of otherwise asymptomatic nonsustained ventricular arrhythmias.

LVH is accompanied by significant remodeling of the myocardium in both the cellular and interstitial compartments, that promotes ventricular arrhythmogenesis resulting from re-entry and triggered activity. Myocardial electric remodeling manifests as abnormalities of repolarization (prolonged QTc and $T_{\text{peak}}-T_{\text{end}}$ intervals) and depolarization (prolonged QRS interval), both of which facilitate the phenomenon of re-entry.30,31 At a cellular level there is decreased density of sodium and potassium pumps, which leads to decreased intracellular potassium concentrations and prolonged repolarization.32 Along these lines, cellular studies have shown that ATP-sensitive potassium channels are more likely to be open during ischemia in hypertrophied myocytes compared with normal myocytes.33 This can also prolong ventricular repolarization, allowing for after-depolarizations and triggered activity that initiate ventricular arrhythmias. Others have also observed regional variation in the ion channel remodeling that occurs in LVH. Myocytes from Guinea pig hearts with LVH were compared with normal myocytes, and there was increased density of calcium channels in the subepicardium and midmyocardium, but decreased density in the subendocardium.34 Normally there is an endocardio to epicardium gradient in action potential duration, which has been shown to be reversed in hypertrophy, with prolongation of the epicardial action potential duration.35 The link between abnormalities of myocardial electric remodeling and ventricular arrhythmogenesis in LVH has been reported from a variety of in vivo animal models. An early study in a canine model of LVH observed that dogs that were administered calcium agonists had more early after-depolarizations and ventricular arrhythmias than dogs without LVH.36 Rials et al.36 induced LVH with aortic banding in a feline model and observed increased susceptibility to inducible polymorphic ventricular tachycardia. After releasing the constriction, they reported regression of LVH that coincided with normalization of myocardial electrophysiological properties.37 In a rabbit model, LVH created by renal artery ligation displayed increased dispersion of refractoriness, a lower ventricular fibrillation threshold, and action potential prolongation,

### Table 1. Left Ventricular Hypertrophy Versus Left Ventricular Ejection Fraction as Risk Factors for Sudden Death or Mortality

<table>
<thead>
<tr>
<th>Reference</th>
<th>Description of Study</th>
<th>Definition of LVH</th>
<th>Risk of SCD or Mortality</th>
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</thead>
<tbody>
<tr>
<td>Liao et al34</td>
<td>1089 black patients undergoing angiography and M-Mode echocardiography</td>
<td>LV mass index $&gt;$131 g/m and $&gt;$100 g/m in men and women</td>
<td>LVH: RR 2.4 (1.7–3.4) EF$&lt;$45%: RR 2.0 (1.4–2.7)</td>
</tr>
<tr>
<td>Quiñones et al34</td>
<td>1172 patients in SOLVD Registry, patients had baseline EF$&lt;$45%</td>
<td>LVH not dichotomized; LV mass analyzed unadjusted for body size</td>
<td>LV mass index per 1-SD RR, 1.3 (1.06–1.6), adjusted for LVEF and NYHA Class LVEF 1-SD RR, 1.6 (1.22–2.14) unadjusted</td>
</tr>
<tr>
<td>Turakhia et al21</td>
<td>1024 patients with stable coronary disease (Heart and Soul Study)</td>
<td>LV mass index $&gt;$115 g/m$^2$ in men and $&gt;$95 g/m$^2$ in women</td>
<td>LV mass index per 20-U increase: HR 1.4 (1.1–1.7) EF per 5% decrease: HR 1.3 (1.05–2.7)</td>
</tr>
<tr>
<td>Reinier et al8</td>
<td>191 patients with SCD and 203 controls from a community-based study (Oregon SUDS)</td>
<td>LV mass index $&gt;$134 g/m$^2$ for men and $&gt;$110 g/m$^2$ for women</td>
<td>LVH: OR 1.8 (1.1–2.9) EF$&lt;$35%: OR 1.9 (1.1–3.2) LVH and EF$&lt;$35%: OR 3.5 (1.7–7.2)</td>
</tr>
</tbody>
</table>

Summary of 4 studies that looked at both left ventricular mass and left ventricular ejection fraction as risk factors for sudden death or mortality. CI indicates confidence interval; EF, ejection fraction; HR, hazard ratio; LVH, left ventricular hypertrophy; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OR, odds ratio; RR, relative risk; SCD, sudden cardiac death; SOLVD, Studies of Left Ventricular Dysfunction; and SUDS, Sudden Unexpected Death Study.
all proarrhythmic properties. Interestingly, when treated for 3 months with captopril, there was regression of LVH and normalization of the same proarrhythmic electrophysiological properties. \textsuperscript{38} LVH also increases susceptibility to ventricular fibrillation with induced myocardial ischemia compared with normal controls in dog and rat models, \textsuperscript{39–41} analogous to the human studies that have identified LVH as a risk factor for increased mortality and sudden death in patients with coronary disease. \textsuperscript{41} There are additional abnormalities observed in LVH, which affect conduction of the electric impulse. There is reduction in connexin 43 expression that slows cell-to-cell conduction. \textsuperscript{42} Increased myocardial interstitial fibrosis is a consistent finding in LVH with significant effects on electric conduction. \textsuperscript{43} The abundance of collagenuous septae can lead to abnormalities of side-to-side electric coupling between myocardial fibers, resulting in nonuniform anisotropy, increased dispersion of repolarization, and inhomogeneity of intraventricular conduction, all of which facilitate microreentry and arrhythmogenesis. \textsuperscript{44} More recent studies indicate a potentially important role for myofibroblasts that proliferate in conditions of increased myocardial fibrosis, such as LVH. Whereas these cells contribute to enhancement of fibrosis by secreting more collagen and fibronectin, myofibroblasts may promote re-entry by acting as passive and delayed electric conduits for excitatory current flow. \textsuperscript{45} A recent postmortem histological evaluation of LVH and SCD has been reported from the Oregon SUDS, conducted in 12 cases with LVH and SCD, 18 LVH controls and 6 normal controls. \textsuperscript{46} In addition to the expected increase in myocardial mass and overall collagen content, SCD with isolated LVH was associated with relative abundance of Type III collagen, a novel finding that could affect electric propagation and warrants further mechanistic evaluation. These collective alterations in myocardial interstitial remodeling likely result in differential slowing of ventricular conduction, creating the conditions for microreentry and arrhythmogenesis in LVH.\textsuperscript{47} Also, there is greater opportunity for electric dispersion during repolarization that also enables initiation and maintenance of reentrant circuits. In addition, there is evidence for significant abnormalities in autonomic tone with LVH, which contribute further to ventricular arrhythmogenesis. It has long been recognized that increased LV mass in normotensive and hypertensive patients is coupled with increased cardiac sympathetic activity when measured using multiple techniques, including coronary venous plasma concentration of noradrenaline, pressor response to exogenous noradrenaline infusion, 24-hour urinary catecholamine levels, and pressure response to ergometric exercise. \textsuperscript{48,49}

A genetic predisposition to LVH has been identified, which seems to be distinct from genetic transmission of hypertension. \textsuperscript{50,51} A genome-wide association study of LVH determined either by ECG or by echo identified several genetic loci strongly associated with LVH. Interestingly, chromosomes 10, 12, and 17 were associated with ECG LVH, and chromosome 5 was associated with echo LVH\textsuperscript{52} reinforcing the concept that these 2 tests identify LVH by distinctive measures. Another case–control study with hypertensive siblings from the Hypertensive Genetic Network identified 5 candidate genes as highly associated with LVH.\textsuperscript{50} From the same study population, using 101 cases and 101 controls, another genome-wide association study identified 12 single nucleotide polymorphisms associated with LVH. One of these is KCNB1 that encodes a voltage-gated potassium channel and is dephosphorylated by calcineurin, thus identified as a potential candidate gene related to arrhythmogenesis in LVH.\textsuperscript{53} Genomic studies of LVH remain an area of active investigation and have yielded several novel pathways that are likely to advance the mechanistic understanding further of ventricular arrhythmogenesis in LVH.

Regression of LVH

Treatment with angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and β-blockers, but not diuretic therapy, has been shown to reduce LV mass.\textsuperscript{54} Furthermore, this reduction is associated with reduced arrhythmias, mortality, and SCD. In the Framingham study among patients with LVH on ECG, a voltage increase for 10 years was associated with doubling of cardiovascular events, whereas reduction in ECG voltage was associated with 50% reduction in cardiovascular events.\textsuperscript{55} In several animal models, reduction in LV mass improved ventricular fibrillation thresholds and reduced inducible arrhythmias.\textsuperscript{37,38} Human studies have replicated the finding that treatment of hypertension with nondiuretic antihypertensive medication reduces LV mass and ectopy.\textsuperscript{55} The LIFE study showed that for every SD decrease in Cornell product for ECG LVH, there was a 28% reduction in SCD, independent of blood pressure control and use of losartan or atenolol.\textsuperscript{7} Whereas a direct causal association is difficult to ascertain, these findings are strongly suggestive of decrease in SCD risk with regression of LVH.

Potential for LV Mass Measurement to Enhance Risk Stratification for SCD

Current guidelines for SCD primary prevention with ICD implantation are based almost exclusively on measurement of the LVEF.\textsuperscript{22,23,56} This one-size-fits-all approach to ICD implantation is now recognized to be inadequate. Most notably, at least 65% of all SCD cases occur in patients who have EF>35%, and 50% occur with normal EF.\textsuperscript{52,55} Furthermore, only a minority of patients who are implanted with prophylactic ICDs are receiving appropriate therapies from the implanted device.\textsuperscript{23} There is clearly an urgent need to enhance the methodology for selecting the high-risk patient. Some form of risk-stratification index has been discussed that would certainly include measurement of LVEF, but may also include other clinical and genetic predictors.\textsuperscript{2} Our recent findings from the Oregon SUDS suggest that severely decreased LV systolic function and LVH may lead to independent effects on SCD risk.\textsuperscript{8} In fact, when combined for the assessment of SCD risk, these variables had additive effects. Especially, because LVEF and LVH can occur in isolation and in combination across a broad spectrum of cardiac pathogenesis, consideration of LVH may enhance the process of SCD risk stratification (Figure 2). LV mass is easily quantifiable and can be calculated from the routine transthoracic echocardiogram or other imaging test, such as magnetic resonance imaging. The pathophysiology of SCD is complex and multifactorial, but there is clear evidence of increased SCD risk with LVH.
and decreased risk with regression of LVH. It is time to take the next step of prospectively assessing how LVH can improve prediction of the high-risk SCD patient both in the presence, and in the absence of severely decreased LV systolic function.

**Disclaimers**

None.

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