# Clinical Diagnosis of Electrical Versus Anatomic Left Ventricular Hypertrophy

## Prognostic and Therapeutic Implications

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Left ventricular hypertrophy (LVH) can develop in association with chronic arterial hypertension and other cardiovascular disorders and is a well-established risk factor for cardiac arrhythmias, cardiovascular events, and mortality.[1] Over 4 decades ago the Framingham Heart Study reported that electrocardiographic evidence of LVH (ECG LVH) was associated with 3- to 4-fold increase in cardiovascular and all-cause mortality, with a disproportionately high risk of sudden cardiac death (SCD).[2,3] Subsequently, multiple studies in different population samples have confirmed these associations.[4,5]

In early studies, the 12-lead ECG was the only available method to diagnose LVH in living subjects. In subsequent years, anatomic LVH diagnosed by echocardiography (echo LVH) became the gold standard.[6,7] Despite the development of fairly detailed diagnostic ECG criteria for LVH,[8] echocardiographic measurements have virtually replaced the ECG diagnosis of LVH. This shift in clinical practice was driven by the low reported sensitivity (usually <25%), albeit high specificity (up to 95%) of ECG criteria for diagnosis of LVH with echocardiography, magnetic resonance imaging (MRI), or during autopsy.[9,10]

More recently, however, we are learning that ECG LVH and echo LVH may be clinically distinct entities. In fact, there are now data to suggest that although these 2 entities can often overlap, each may provide distinct prognostic and potentially, mechanistic information, especially in the context of cardiac arrhythmias. This review will attempt to put these findings into perspective for the clinical electrophysiologist, by discussing the significance of electrical versus anatomic LVH for occurrence of atrial fibrillation (AF) and SCD.

## Electrical (ECG) Versus Anatomic (Echo/MRI) LVH: Evidence in Support of 2 Distinct Entities

To diagnose increased left ventricular (LV) mass from the 12-lead ECG, over 30 different ECG criteria have been developed. Most of the commonly used LVH criteria, such as Sokolow and Lyon, and Cornell voltage, rely solely on measuring QRS voltage. However, some also take QRS duration into account (eg, Cornell voltage–duration product) as well as other ECG abnormalities (Romhilt-Estes point score). There is also significant variation in the echocardiographic definition of LVH. Although most studies have used standardized formulae based on M-mode measurements to determine LV mass with adjustment for body surface area, this was not a uniform practice. Taking the available data into account, the correlation between these LVH ECG criteria and echo LVH is, at best, a moderate one.[8] Therefore, the ECG was considered to be an insensitive method for diagnosing anatomic LVH, and the increased risk associated with ECG LVH was thought to be directly related to increased LV mass. At the outset, we would like to recognize that some of the discordance between ECG and echo LVH could result from extracardiac factors, such as age, sex, race, or body habitus or even temporal separation of when the 2 tests were performed. However, we remain open to the possibility of an alternative explanation for this apparent low sensitivity of the ECG. At least in a subgroup of patients, could ECG LVH and echo LVH be distinct entities, one reflecting electrical and the other anatomic remodeling?

It has long been recognized by clinicians that abnormal ECG changes can precede pathological echocardiographic findings in patients with underlying cardiac pathology, such as hypertrophic cardiomyopathy, and that electrical alterations add additional clinical information to the imaging of cardiac structure and function in these patients.[11,12] The first evidence that this may also be relevant for common forms of LVH came from a Swedish study, which demonstrated that ECG LVH and echo LVH carry somewhat different prognostic information (Figure 1A).[13] In their cohort of 475 men of white European descent investigated at the age of 70 years with a 5-year follow-up, both ECG LVH and echo LVH expectedly predicted total and cardiovascular mortality, but, intriguingly, ECG LVH (defined as Cornell product >244 μVs) was associated with 2.89-fold increase in mortality even after adjustments for echo LVH and several other cardiovascular risk factors. However, given the subjects included in this study, these results could not be generalized to females or other racial/ethnic groups.

A more recent analysis from the Oregon Sudden Unexpected Death Study (Oregon SUDS) has demonstrated that ECG LVH also provides unique prognostic information for increased risk of SCD, even when adjusted for echo LVH.[14] Among patients who suffered SCD, there was a relatively low level of agreement between ECG and echocardiography for diagnosis of LVH; 57% of patients with ECG LVH did not have evidence of echo LVH, and conversely, 84% of patients

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with echo LVH did not have ECG LVH (Figure 1B). In multivariate analyses, ECG LVH by Sokolow–Lyon criteria was associated with >2-fold increase in the risk of SCD (odds ratio, 2.5; 95% confidence interval, 1.1–6.0), and this risk was not markedly attenuated when adjusted for LV mass (odds ratio, 2.4; confidence interval, 1.0–6.0). Similar risk of SCD was also associated with echo LVH (odds ratio, 2.7; confidence interval, 1.5–4.9), but the study lacked power to evaluate the risk of SCD in the subgroup with both ECG and echo LVH. The authors concluded that in some patients, ECG LVH may occur in the absence of echo LVH, and that in these patients ECG LVH is potentially a distinct entity with an independent contribution to risk of ventricular arrhythmogenesis and SCD.

Another recent study comparing LVH diagnosed by ECG with cardiac MRI in the Multi-Ethnic Study of Atherosclerosis (MESA) population also showed a discrepancy between diagnoses of LVH by ECG and cardiac MRI (MRI LVH)[15]; 2.4% of the participants demonstrated LVH by both ECG and MRI, and 8.2% had only MRI LVH and 4.4% presented with isolated ECG LVH only. Also, the presence of ECG LVH by Cornell voltage or Sokolow–Lyon criteria was independently predictive of cardiovascular morbidity and mortality to a similar extent as MRI LVH. When LVH was diagnosed on both ECG and MRI, the risk of cardiovascular events was almost 3-fold compared with subjects without LVH.

It turns out that these observations regarding ECG versus anatomic LVH have also been made in patients with AF. LVH is often associated with development of atrial arrhythmias, such as AF, a risk that seems to correlate alongside with the severity of ECG LVH.[16,17] In the MESA study, LVH detected by cardiac MRI or ECG were associated with an increased risk of incident AF, but the increased risk associated with ECG LVH using Sokolow–Lyon voltage product persisted even after adjusting for MRI LVH (Figure 1C), suggesting that ECG LVH may provide some independent value in AF prediction.[18] Taken together, these 4 studies do suggest that, in a subgroup of patients, ECG LVH can occur in the absence of LVH observed by echo or MRI and confers independently increased risk of overall mortality, SCD, as well as AF. These findings are summarized in Figure 1.

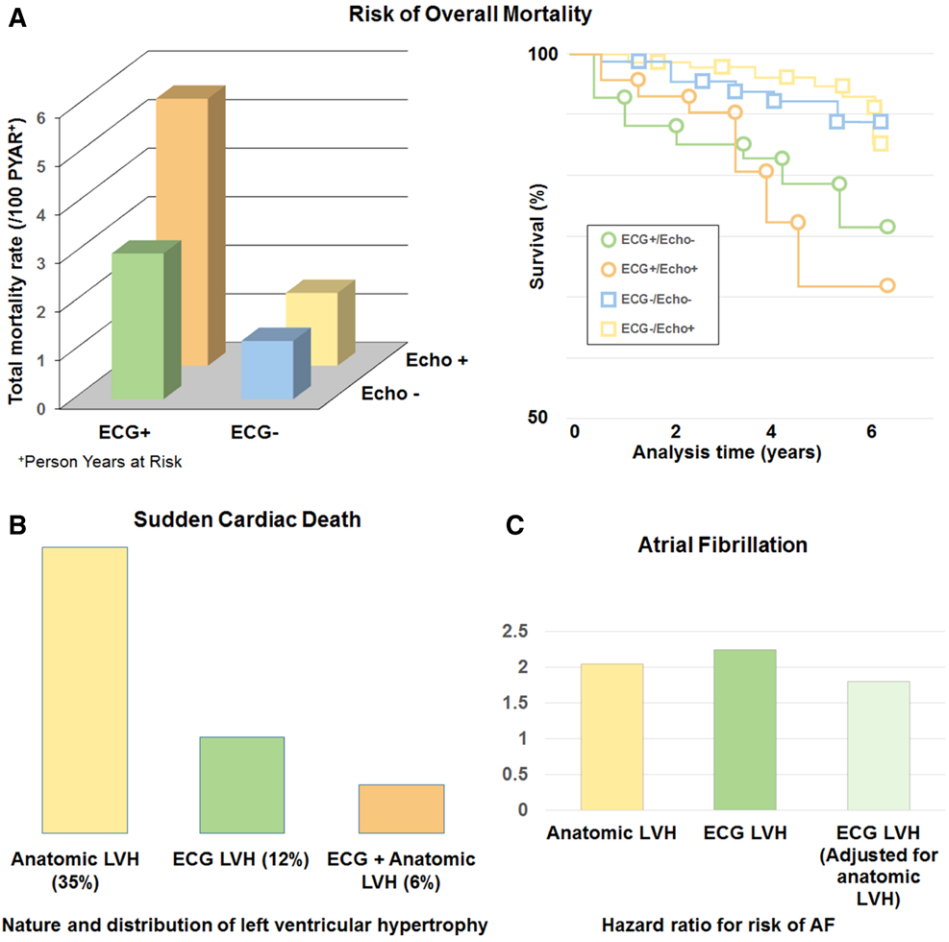


**Figure 1.** Evidence suggesting that anatomic vs electrical left ventricular hypertrophy (LVH) is distinct entities that not only can overlap but also have independent effects on outcomes. **A**, Risk of mortality associated with and without ECG LVH (Cornell product criteria, ECG+/ECG–) and echocardiographic LVH (echo+/echo–). Adapted from Sundström et al[13] with permission of the publisher. Copyright © 2001, American Heart Association, Inc. **B**, The relatively small overlap between echo and ECG LVH among cases that suffered sudden cardiac death. Adapted from Narayanan et al[14] with permission of the publisher. Copyright © 2014, Elsevier. **C**, The independent effects of ECG LVH on increased risk of atrial fibrillation (AF) even when adjusted for anatomic LVH. Adapted from Chrispin et al[18] with permission of the publisher. Copyright © 2014, Elsevier. Authorization for these adaptations have been obtained both from the owners of the copyright in the original work and from the owners of copyright in the translation or adaptation.

## Mechanisms of Arrhythmogenesis in Electrical Versus Anatomic LVH

To understand the unique aspects of ECG LVH versus echo LVH, it may be useful to examine the potential mechanisms of arrhythmogenesis that are operative in either entity, along with the fundamental causes of ECG LVH versus echo LVH. In the big picture, a diagnosis of LVH is independently associated with an increased risk of ventricular arrhythmias.[19,20] In the presence of LVH, ventricular arrhythmias are associated with increased mortality.[21] The increased risk of SCD associated with LVH seems to be over and above the risk predicted by clinical factors or LV systolic function.[7,22,23] The frequency and complexity of these arrhythmias seem to rise with increased LV mass, with 2- to 3-fold increase in the arrhythmias for every 1 mm increase in the thickness of LV wall.[24] However, from a structural perspective, ECG LVH seems to be distinct from echo LVH (Figure 2). For example, if there is no significant increase in LV mass, it seems unlikely that isolated ECG LVH involves myocyte hypertrophy of the extent that is observed in echo LVH. Yet, ECG LVH is associated with an increased risk of ventricular and atrial arrhythmias. In patients with hypertension, ECG LVH is associated with increased prevalence of ventricular arrhythmias.[25,26] Findings from the MESA study indicate that ECG LVH has also a role in predicting risk of AF independent of MRI LVH.[18] It is, thus likely, that there is some mechanistic overlap between the 2 entities, but some of the mechanisms may be unique to each form of LVH.

## Myocardial Cellular, Electrical, and Interstitial Remodeling

Myocardial hypertrophy involves extensive alterations at the systemic as well as cardiac levels. There are adverse effects on intravascular hemodynamics and neuroendocrine activation that correlate with myocyte hypertrophy, cell death, myocardial fibrosis, and altered electrophysiological properties of the myocardium, such as increased action potential duration and decreased conduction velocity (Figure 2).[27–29] Slowed impulse conduction, a dominant electrophysiological feature of hypertrophied myocardium, can result from increased size of ventricular myocytes, increase in extracellular matrix, reduced cell-to-cell coupling, as well as reduced membrane excitability because of changes in properties of the ion channels.[27,30] LVH is associated with prolongation of ventricular action potentials and increased dispersion of repolarization.[27] In animal models, alterations in calcium and Na–Ca exchange currents as well as reductions in potassium currents have been demonstrated in hypertrophied myocardium.[31–33] This remodeling of the ion channels is ultimately responsible for prolongation of the action potential, which can be observed as prolonged QT-interval on the surface ECG.[34] Prolongation of the action potential duration may predispose to arrhythmias based on early or delayed afterdepolarizations and triggered activity,[35,36] and local differences in the action potential duration may lead to increased dispersion of the repolarization and refractoriness, enabling initiation and maintenance of reentrant electrical circuits.[37,38] Increased interstitial fibrosis and collagen deposition in LVH are other prominent features especially in advanced hypertrophy[27] and can create anatomic uncoupling of adjacent myocytes leading to discontinuous and slowed conduction, which may manifest as abnormalities in QRS morphology and duration. This increase in myocardial fibrosis and altered ratios of collagen subtypes has been especially observed in individuals with LVH and SCD.[39] Gap junctions are other important determinants of myocardial conduction, and when LVH is present, expression of the predominant ventricular gap junction protein, connexin43 (Cx43), is significantly reduced,[40] which has been associated with slowing of impulse propagation and increased susceptibility to ventricular arrhythmias.[41] Furthermore, delayed conduction resulting from interstitial remodeling and increased interstitial myocardial fibrosis can result in nonuniform anisotropic cellular coupling, which may be responsible for increased inhomogeneity of myocardial

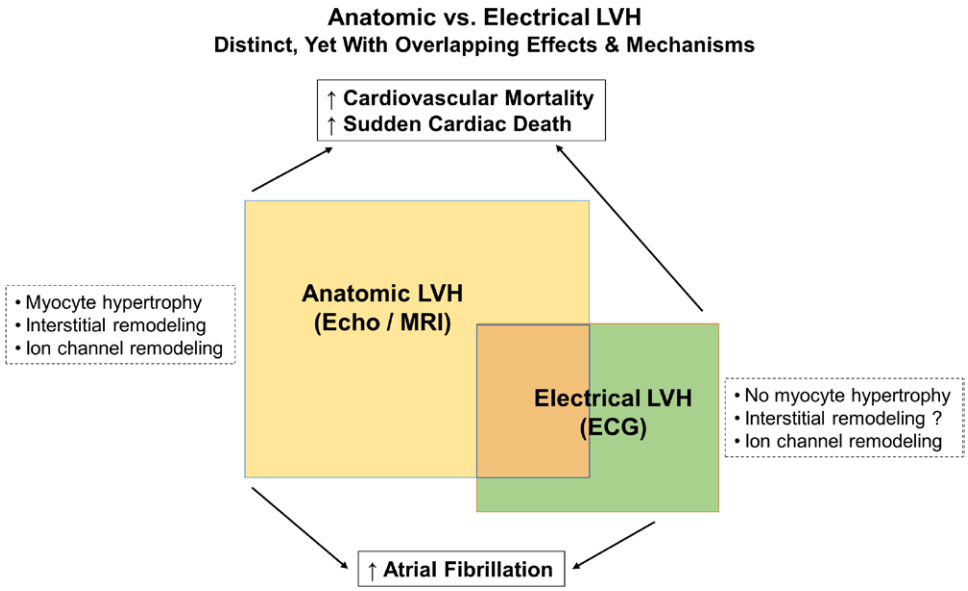


**Figure 2.** Consequences and mechanisms of anatomic vs electrical LVH. MRI indicates magnetic resonance imaging; and LVH, left ventricular hypertrophy.

conduction and dispersion of repolarization, creating conditions for microreentry and arrhythmogenesis.[42]

It is logical that myocyte hypertrophy and extensive interstitial remodeling, commonly found in echo LVH, are unlikely to be the dominant mechanisms of arrhythmogenesis in ECG LVH. Although the exact mechanisms responsible for increased propensity of ventricular and atrial arrhythmias in ECG LVH still need to be elucidated, it is reasonable to hypothesize ion channel remodeling involving both cell membrane and the gap junctions as the dominant mechanism. The exact nature of true electrical remodeling in LVH has been the subject of active investigation[43] and is likely to largely explain the observed differences between electrical and anatomic LVH. These altered electrophysiological properties of the myocardium seem to be somewhat independent from the morphological transformations in LVH[29] and may serve as a substrate for triggering and maintaining ventricular arrhythmias.[44] In some experimental models, reduced Cx43 expression has been associated with diminished QRS amplitudes,[41,45] a phenomenon that along with extracardiac factors may partly explain the common "false-negative" results of ECG in diagnosing anatomic LVH. However, these factors would not explain the existence of ECG LVH in the absence of anatomic LVH.

## Causes of Electrical Versus Anatomic LVH

It follows that a clinical history of hypertension, the major and most common factor associated with LVH, may not be a key player in the process of developing ECG LVH. Could there be a special genetic contribution to development of ECG LVH? The greater heritability of ECG LVH compared with anatomic LVH[46] would lend support to this idea. In a genome-wide scan of families with hypertension, a stronger genetic contribution was observed for ECG LVH than echo LVH, and genetic determinants of each of these seemed to be distinct.[47] However, these genome-wide association analyses have limitations that will likely be overcome with next-generation sequencing technologies,[48] and more work is needed. Finally, in the subset of patients who suffer SCD, we should remain open to the possibility that while they manifested with ECG LVH, they may have died before developing echo LVH.

## Prognostic and Therapeutic Implications

Because both electrical and anatomic LVH are associated with increased risk of arrhythmias and overall mortality,[5,14] prevention and treatment of either form of LVH is likely to make a significant impact on the burden of cardiovascular disease. However, based on the findings discussed in this review, it is likely that separate consideration of these 2 entities instead of lumping them together is likely to provide more useful prognostic information, for risk of overall cardiovascular mortality, SCD, as well as AF. Once the specific form of LVH is established, there are potential downstream therapeutic implications. Published reports suggest that antihypertensive therapy can cause regression of anatomic LVH,[49,50] with reduction of cardiovascular morbidity and mortality, over and above that predicted by lowering blood pressure.[51] In animal models, LVH regression has resulted in normalization of electrophysiological cellular abnormalities, such as action potential prolongation and altered repolarization, as well as reduced vulnerability to ventricular fibrillation.[52,53] Reduction of ECG LVH was first associated with lowered cardiovascular risk in the Framingham Heart Study population over 2 decades ago.[54] Since then, studies on pharmacological treatments, such as ramipril in the Heart Outcomes Prevention Evaluation (HOPE) trial[55] and losartan in the Losartan Intervention For End point Reduction in Hypertension (LIFE) study,[56] have shown that reduction of ECG LVH predicts lower risk of cardiovascular mortality, independent of the degree of blood pressure reduction or other clinical factors. Reduction of ECG LVH is associated with reduced risk of SCD, as reported by Wachtell et al[57] from a substudy of the LIFE trial that included patients with hypertension and ECG LVH. Again, because evaluation of LVH was performed only by ECG, we do not have the corresponding echo findings that would enable us to understand the role of treating the 2 different forms of LVH.

Although ECG LVH and echo LVH seem to be distinct entities that do not overlap in a subgroup of patients, there is much that we need to learn about the subgroup that only manifests with ECG LVH. It would be important to put these patients under a microscope to understand how the pathogenesis and natural history of this condition are different from echo LVH. If there is a larger genetic contribution, are these patients younger and do they have a history of hypertension? Is the increased voltage on the ECG a transient phenomenon triggered by specific factors or is it a permanent phenomenon? A large proportion of patients with echo LVH have diastolic dysfunction. Is this true of subjects with lone ECG LVH? In the LIFE study, wall motion abnormalities were observed in one eighth of the patients with ECG LVH, and these abnormalities were associated with higher values of Cornell voltage–duration product and higher prevalence of ST strain pattern.[58] However, these patients were not stratified according to the LV mass, so we are not able to ascribe the findings to those with lone ECG LVH. There is limited evidence that ECG LVH is associated with diastolic dysfunction independent of LV mass,[59] but further investigation is needed.

## Conclusions

Based on the evidence, we hope to have made the case that the clinical manifestation of LVH takes 2 forms: electrical LVH observed on the 12-lead ECG and anatomic LVH seen on the echocardiogram. Furthermore, although a large proportion will have both electrical and anatomic LVH, there exist subgroups that will have isolated electrical LVH or isolated anatomic LVH. Although absence of LVH by voltage could be attributed to low sensitivity of the 12-lead ECG or other factors, absence of anatomic LVH in a patient with ECG LVH denotes a special subgroup of LVH patients. Although there clearly exists overlap between these 2 conditions, patients with lone ECG LVH or lone echo LVH should be separated from a clinical standpoint. This will enable improved risk stratification of ventricular and atrial arrhythmias, while providing a much-needed opportunity to carefully investigate the potentially divergent causes/mechanisms as well as therapeutic implications of these 2 distinct entities.

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## Disclosures

None.

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KEY WORDS: death, sudden, cardiac ■ electrocardiography ■ echocardiography ■ hypertrophy, left ventricular ■ mortality

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