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Electrocardiographic Versus Echocardiographic Left Ventricular Hypertrophy and Sudden Cardiac Arrest in the Community

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Abstract

Background—Left ventricular hypertrophy (LVH) is associated with increased risk of sudden cardiac arrest (SCA); whether LVH diagnosed by 12-lead ECG versus echocardiogram conveys identical or distinct risk information has not been previously evaluated.

Objective—To compare the association between ECG versus echocardiographic LVH and SCA in the community.

Methods—In a large, prospective population-based study (Oregon SUDS; population approximately one million), cases of SCA were compared to controls recruited from the same geographical area. The association between LVH and SCA was evaluated, specifically comparing LVH diagnosed by ECG versus echocardiogram.

Results—Cases (n=132; 66.9 ± 13.5 years; 58.3% male), compared to controls (n= 211; 66.2 ± 12 years; 59.2% male) were more likely to have both ECG LVH (12.1% vs. 5.7%; p=0.03) and echocardiographic LVH (35.0% vs. 15.5%; p<0.001). However, there was poor agreement between the tests (kappa statistic = 0.128). A large subgroup of patients with ECG LVH (57.1%) did not have echocardiographic LVH; conversely 83.6% of patients with echocardiographic LVH did not have ECG LVH. In multivariate analysis, ECG LVH was significantly associated with SCA (OR 2.5; 95% CI 1.1–6.0; p=0.04). When echocardiographic LVH was added to the model, this association was only mildly attenuated (OR 2.4; 95% CI 1.0–6.0; p=0.05) and echocardiographic LVH was also independently associated with SCA (OR 2.7; 95% CI 1.5–4.9; p=0.001).

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Conclusions—ECG and echocardiographic LVH may convey distinct risk information in patients with SCA, reflecting electrical vs. anatomic remodeling. These findings have potential implications for SCA mechanisms and risk stratification.

Keywords

sudden cardiac arrest; arrhythmia; electrophysiology

Introduction

Sudden Cardiac Arrest (SCA) is a major cause of cardiovascular mortality with an estimated 300,000–350,000 cases annually in the United States¹. While coronary artery disease is likely to be responsible for the majority of SCA cases in the general population², in over half, SCA may be the first manifestation of heart disease³. The unexpected nature of the event and poor survival rates (nationally less than 5%) cause a devastating societal impact. Prediction of risk for SCA has therefore been an important area of research, made even more relevant with the advent of the implantable cardioverter defibrillator (ICD). The left ventricular (LV) ejection fraction (EF) currently occupies center-stage in risk stratification and continues to be the basis for decision-making with regard to ICD implantation⁴. However, population based studies have highlighted that only a minority of SCA victims have severe LV dysfunction^{3, 5}. Further, among patients who get an ICD based on current guidelines, only a small fraction will have appropriate therapies⁶, suggesting that the use of EF as an overarching marker of risk is inadequate. Therefore, there is a pressing need to identify novel, clinically useful markers to identify those at high risk for SCA.

Left Ventricular hypertrophy (LVH) has been recognized as a risk factor for both cardiovascular mortality as well as SCA^{7, 8}. From the Oregon Sudden Unexpected Death Study (Oregon SUDS) we have previously reported that increased left ventricular mass measured by echocardiogram is an important risk predictor for SCA independent of the EF⁹. Similarly, LVH diagnosed by the 12 lead ECG has been shown to increase SCA risk¹⁰ and regression of LVH by medical therapy to reduce this risk¹¹. Whether assessment of LVH by ECG adds any benefit over an echocardiogram for SCA risk assessment remains to be evaluated, since the ECG is generally considered to be a less sensitive technique for identification of LVH¹². We considered the hypothesis that LVH detected by ECG vs. echocardiogram may be reflecting distinct forms of LV remodeling (electrical vs. anatomic), with implications for risk prediction in sudden arrest.

Methods

We performed a comprehensive evaluation of LVH by ECG and echocardiogram in the ongoing Oregon SUDS. Detailed descriptions and methods for this study have been published earlier^{5, 13, 14}. Briefly, cases of SCA are prospectively ascertained in the Portland, Oregon metropolitan area (population approximately 1 million). SCA cases are identified through multiple sources including first responders, local hospitals and the medical examiner's office. Cases with known terminal illnesses and non-cardiac causes of sudden death (such as drug overdose) are excluded. SCA is defined as an unexpected sudden,

pulseless condition of cardiac etiology, occurring within 1 hour of symptom onset in witnessed cases and within 24 hours if unwitnessed. SCA is diagnosed based on an in-house adjudication process involving three physicians. Survivors of sudden cardiac arrest are also included. Controls are recruited from the same population and consist of patients with diagnosed CAD or healthy controls recruited from the general population. The controls with CAD were recruited from subjects undergoing angiography or visiting a cardiology outpatient clinic at one of the region's major participating health systems, those who were transported by the emergency medical system (EMS) for symptoms of acute coronary ischemia, and patients with documented CAD from a regional health maintenance organization. CAD was defined as $\geq 50\%$ stenosis in a major coronary artery. For the purpose of this analysis, the majority ($>90\%$) had established significant CAD but no prior history of ventricular arrhythmias with a minority of population-based controls ($<10\%$) without evidence of known CAD. Subjects with CAD were chosen as controls in order to be able to identify risk factors specific to SCA, as previous studies have shown that the majority of SCA cases in the general population are found to have associated significant CAD^{2, 15}. Cases and controls over a 10 year period (2002–2012) with both an ECG and echocardiogram available from clinical records, prior and unrelated to arrest for cases were included in the present analysis. Subjects with severe aortic stenosis or hypertrophic cardiomyopathy (HCM) were excluded from this study. Detailed demographic and clinical information was collected for cases and controls from available medical records.

Diagnosis of LVH

All ECGs were read by a cardiologist blinded to all details of subjects. The Sokolow-Lyon criteria ($S V_1 + R V_5$ or $V_6 \geq 35$ mm) were used to diagnose LVH by ECG¹⁶. LV Mass was calculated using the American Society of Echocardiography recommended formula using LV linear dimensions, $0.8 \times (1.04 [(LVDD + PWT + IVST)^3 - (LVDD)^3]) + 0.6$ g (LVDD- Left ventricular internal diameter in diastole, PWT- posterior wall thickness in diastole, IVST-interventricular septal thickness in diastole). LV mass index was calculated as the LV mass divided by the body surface area in m^2 . Echocardiographic LVH was defined as LV mass index greater than 134 g/ m^2 for men and 110 g/ m^2 for women¹⁷. LV EF measurements were also obtained from the same echocardiograms. In addition, we assessed the association of ECG versus echocardiographic LVH with SCA by using alternative ECG criteria including the gender-specific Cornell voltage criteria (S in $V_3 + R$ in $aVL > 28$ mm in men and 20 mm in women) as well as QRS duration. Patients with intraventricular conduction delay and bundle branch blocks (where the diagnosis of ECG LVH may not be straightforward) were not included in the present analysis.

Statistical Analysis

Univariate case-control comparisons were performed using the t-test for continuous variables and the chi-square test for categorical variables. Agreement between the diagnosis of LVH by ECG versus echocardiogram was assessed using the Kappa statistic. Multivariable logistic regression was performed to arrive at the odds ratio (OR) for association of ECG LVH with SCA, adjusting for age and other covariates significant in univariate comparisons. Echocardiographic LVH was then added to this model to evaluate the extent to which ECG LVH was associated with SCA even after adjusting for

echocardiographic LVH. All analyses were conducted using SPSS version 21.0 (SPSS Inc. IBM Corporation, New York.).

Results

Demographic and Clinical Characteristics

A total of 343 subjects (132 cases, 211 controls) were analyzed. Table 1 shows the demographic and clinical characteristics of the subjects. The population consisted predominantly of White Non-Hispanic subjects (78.8% of cases and 84.8% of controls). Cases and controls were similar with respect to age (66.9 ± 13.5 vs. 66.2 ± 12.0 ; $p=0.61$), proportion of males (58.3% vs. 59.2%; $p=0.87$), prevalence of hypertension (78.0% vs. 75.4%; $p=0.57$), cholesterol level (179.1 ± 50.5 vs. 177.2 ± 52.5 ; $p=0.77$) and smoking status ($p=0.14$). A definite diagnosis of coronary artery disease was established in 91.5% of the controls and 90.1% of the cases who had adequate information. Cases had a significantly higher prevalence of diabetes (44.7% vs. 31.3%; $p=0.01$), chronic renal disease (31.1% vs. 14.2%; $p<0.01$) and severe LV dysfunction (EF $\leq 35\%$) (19.5% vs. 9.6%; $p=0.01$). Use of anti-hypertensive agents was similar between cases and controls except for greater use of angiotensin receptor blockers (ARB) among controls (5.4% vs. 14.1%; $p=0.01$).

LV Mass and LV Hypertrophy by ECG and Echocardiogram

The distribution of LV mass by echocardiogram as well as presence of LVH as diagnosed by ECG or echocardiogram in cases and controls is shown in Table 2. The mean adjusted LV mass was significantly greater in cases (113.3 ± 38.1 g/m² vs. 96.9 ± 31.4 g/m²; $p<0.001$). A diagnosis of LVH by ECG was significantly more frequent overall, among cases, compared to controls (12.1% vs. 5.7%; $p=0.03$). Similarly, echocardiographic LVH was also more likely to be observed among cases compared to controls (35.0% vs. 15.5%; $p<0.001$). The proportion of cases with LVH diagnosed by either ECG or echocardiogram or both, was significantly greater than controls (Figure 1).

Agreement between ECG LVH and Echocardiographic LVH

As evident from Table 2, the overall prevalence of ECG LVH was lower than echocardiographic LVH in both cases and controls. Additionally, the degree of overlap between ECG and echocardiographic LVH was low. Table 3 shows the extent to which there was agreement between LVH diagnosed by either ECG or echocardiogram in all subjects. The Kappa statistic for agreement was low (0.128) indicating very little overlap between LVH diagnosed by the two modalities. Also, the overlap was smaller among cases than in controls (Kappa values of 0.06 and 0.16 respectively; data not shown). Overall, 57.1% of those who had ECG LVH did not have LVH on echocardiogram. Conversely, 83.6% of all subjects with echocardiographic LVH did not demonstrate ECG LVH (Table 3). The extent of overlap between ECG and echocardiographic LVH for cases and controls is graphically illustrated in Figure 2.

Odds of SCA by ECG and Echocardiographic LVH

In a multivariable logistic model adjusted for age, diabetes, renal disease, ARB use, and severe LV dysfunction, ECG LVH more than doubled the odds for SCA (OR 2.5; 95% CI

1.1–6.0; $p=0.04$). When echocardiographic LVH was added to the full model, only a mild attenuation of the OR associated with ECG LVH was observed (OR 2.4; 95% CI 1.0–6.0; $p=0.05$; Table 4); and echocardiographic LVH was also an independent predictor of SCA (OR 2.7; 95% CI 1.5–4.9; $p=0.001$).

We examined possible interaction between echo and ECG-determined LVH using dummy coding; patients with neither ECG nor echo LVH were the reference category. There was no evidence that having both conditions increased risk beyond the effect of either condition alone ($p=0.13$), though small numbers of subjects may have limited the power to detect such an interaction since the number of subjects with both ECG and echo LVH were low.

Assessment by Other ECG Criteria

Using gender-specific Cornell voltage criteria, ECG-LVH was observed in 13.6% of cases and 8.5% of controls (versus 12.1% and 5.7% respectively by Sokolow-Lyon voltage). While this difference was not statistically significant ($p=0.13$), the trend was very similar to that observed using the Sokolow-Lyon index. Among subjects with ECG-LVH by Cornell criteria, 52.9% did not have echocardiographic LVH; conversely 78.1% of subjects with echocardiographic LVH did not have ECG-LVH by Cornell voltage. The Kappa statistic for agreement was low at 0.182. Thus, the results were very similar to that seen with the use of Sokolow-Lyon criteria.

With regard to QRS duration in the present study, the mean QRS duration in patients with echocardiographic LVH was not significantly different from patients without echocardiographic LVH (89.2 ± 8.9 ms vs 87.6 ± 9.0 ms, $p=0.18$) with a weak correlation between the adjusted LV mass and QRS duration (Pearson's correlation coefficient: 0.23).

Discussion

These findings from a population-based analysis of SCA indicate that LVH diagnosed by ECG vs. echocardiogram has distinct associations with SCA indicating that one may reflect electrical remodeling of the LV and the other, anatomic remodeling. A diagnosis of LVH by ECG increased the risk of SCA twofold and this risk was not attenuated when adjusted for echocardiographic LVH. This is an unexpected and novel finding that, together with the low level of agreement between ECG & echocardiographic LVH, suggests that the two tests may be measuring different aspects of cardiac pathology among SCA cases.

These findings are especially interesting when considered in the context of existing perceptions about ECG merely being a less sensitive tool to detect LVH. If that were so, one would expect no additional predictive value for ECG LVH when considered with echocardiographic LVH, since echocardiographic LVH would account for the observed risk. Furthermore, the finding that a proportion of cases and controls had ECG LVH in the absence of echocardiographic LVH supports the concept that high QRS voltage on the ECG may not always indicate the presence of increased LV myocardial mass. We used a single ECG criterion viz the Sokolow Lyon voltage which is simple, standardized, as well as the most commonly used in clinical practice. However, the results were similar when assessed using alternative indices such as the Cornell voltage criteria and QRS duration.

Causes for more frequent LVH in the case group are likely to be multifactorial. While the prevalence of hypertension was similar between cases and controls, several other factors including duration & severity of hypertension, medication regimen, compliance etc. may influence LV mass. Further, presence of other metabolic risk factors^{18, 19} as well as genetic variations²⁰ has been shown to influence presence and severity of LVH.

To the best of our knowledge, this is the first study to examine the similarities and differences of LVH diagnosed by ECG versus echocardiogram in the context of SCA in the community. The findings have potential implications for enhancement of risk stratification for SCA in the general population through a better understanding of the mechanisms underlying SCA.

The interplay between anatomic hypertrophy and increased QRS voltage is likely to be complex. The “false negative ECG” or absence of ECG changes in LVH by echocardiogram has been well recognized. Extracardiac factors such as chest wall adipose tissue or chronic obstructive pulmonary disease can serve to diminish the voltage recorded on the surface ECG, thus potentially “missing” LVH. Further, it has been postulated that alterations in electrical properties of the pathologic hypertrophied myocardium may create a relative “voltage deficit” and the QRS amplitude is not increased as anticipated. The term specific potential of the myocardium (SP) has been used to refer to the ratio of the QRS voltage to the LV mass. Studies have shown that the SP may be lower in subjects with hypertensive LVH compared to normal subjects²¹.

Another possible factor may be the existence of a temporal discordance between ECG and echocardiographic LVH. In subjects with HCM, it has been observed that Q waves and repolarization abnormalities may detect mutation carriers even prior to development of echocardiographic LVH²². However, similar observations are lacking in the context of LVH in the absence of HCM. It has also been suggested that regressions of anatomic LVH and ECG voltage with anti-hypertensive therapy may not occur in a similar fashion, again creating a potential mismatch between the two parameters²¹. However, further evidence that ECG and echocardiographic LVH may be separate pathophysiologic entities comes from genetic studies. Mayosi et al, using genome-wide linkage analysis showed that genetic determinants of ECG LVH were distinct from those of echocardiogram assessed LV mass.²³

While the mechanisms governing the relationship between ECG and echocardiographic LVH continue to be debated, the more important finding of the current study is that high QRS voltage carries an adverse risk for sudden death, irrespective of anatomic LV hypertrophy. This suggests that ECG LVH may represent a form of electrical remodeling which is arrhythmogenic and may increase risk of SCA without abnormalities identified on the echocardiogram. This could be of particular significance for subjects in whom electrical remodeling is a “harbinger” of future anatomic remodeling. Animal models have demonstrated that changes in calcium and sodium currents accompany structural changes of LVH^{24, 25}. Whether QRS changes on the surface ECG reflect such remodeling of ion channels is yet to be established. Studies have also shown that arrhythmic risk in LVH is potentially mediated by alterations in action potential duration²⁶, impulse propagation²⁷, and increased susceptibility to early after-depolarizations²⁸. Considering the fact that SCA is

primarily a manifestation of electrical disturbances, ECG LVH may reflect this risk in a manner that is distinct from echocardiographic LVH²⁹. Interestingly, use of angiotensin receptor blockers (ARB) was less likely to be associated with SCA in this study. There is some evidence to suggest that regression of LVH with ARB therapy may be associated with reduction in SCA risk¹¹. In this study we did not find any significant association between ARB use and diagnosis of LVH by either ECG or echocardiogram, which may be partly due to the low numbers of subjects overall with ARB use.

If ECG and echocardiographic LVH carry separate prognostic information, it would also be of interest to see if a combination of both conditions carries additive risk. An analysis of hypertensive subjects from the LIFE study showed that people with both forms of LVH tended to have greater evidence of cardiac disease and were more likely to be hospitalized for heart failure³⁰. We did not find evidence of additive risk in the present study; however this needs to be explored further in larger studies with greater number of subjects..

Important strengths of this study include the prospective ascertainment and adjudication of SCA cases, and the use of a community-based approach. In addition, our analysis compared cases of SCA to controls with CAD, and thus any identified differences are likely to be specific for SCA. However, due to the population-based nature of this study, some inherent limitations need to be acknowledged. Unlike cohort studies, subjects ascertained in the community do not have tests conducted in a uniform manner. This is particularly true for SCA cases since 50% of patients will present with cardiac arrest as the first and only manifestation of heart disease. Therefore the majority of these subjects may not have seen a health care provider for a cardiac evaluation. However given the relatively low annual incidence of SCA in the overall population (60/100,000)¹⁴ cohort studies do not provide the ability to study a suitable number of patients on analyses such as the present one. Given the specific nature of SCA, the community-based case-control design offers an efficient alternative to large cohort studies. Therefore, while only the subset of SCA cases that had an echocardiogram or ECG available from a time period prior and unrelated to the SCA event were included in this analysis, we were able to obtain sufficient numbers for analysis. As with any case-control analysis, results may be influenced by the nature of controls selected and though we strove to achieve control subjects who would be optimal to identify SCA-specific risks, some residual bias cannot be ruled out. We assessed LV mass using information from the echocardiogram which is the usual test employed clinically for this purpose. However, the concept that there is a subgroup of patients who have ECG LVH in the absence of anatomic hypertrophy will require further studies with more rigorous assessment of LV mass using a gold standard such as magnetic resonance imaging (MRI). Echocardiographic image acquisition was not standardized. This is an inherent limitation of any population based study. Furthermore, these data are likely to represent the “real world” scenario for utilization of the echocardiogram for assessment of LV mass Further prospective investigation specifically assessing the predictive value of identifying LVH by ECG or echocardiogram in terms of SCA risk prediction are needed prior to application in the clinical arena. Finally, these results will need to be confirmed elsewhere before generalizing to other populations.

Conclusions

LVH diagnosed by ECG vs. echocardiogram potentially conveys distinct risk information for SCA in the community, with a subset of cases having increased myocardial voltage in ECG without anatomic hypertrophy on echocardiogram. Contrary to traditional thinking, ECG changes of LVH may have unique prognostic importance as a marker of adverse electrical remodeling rather than being solely a poor reflection of increased LV mass. Further research is needed to more clearly delineate the mechanisms underlying ECG changes in LVH and their contribution to ventricular arrhythmogenesis.

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List of Abbreviations

SCA	Sudden Cardiac Arrest
LV	Left ventricular
EF	Ejection fraction
CAD	Coronary artery disease
ICD	Implantable cardioverter defibrillator
LVH	Left ventricular hypertrophy
LVD	Left ventricular dysfunction

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Figure 1.
Proportion of Cases and Controls with LVH by either ECG or Echocardiogram or Both
(LVH-Left Ventricular Hypertrophy)

Figure 2.

Venn diagram showing extent of overlap between ECG and echocardiographic LVH among cases and controls. The percentages in each circle represent the overall percentage among cases or controls. The darker shaded regions represent the proportion of cases or controls with LVH by both tests. (LVH- Left Ventricular Hypertrophy)

Table 1

Demographics and Clinical characteristics

	Cases (n = 132)	Controls (n = 211)	P value
Age	66.9 ± 13.5	66.2 ± 12.0	0.61
Male	77 (58.3)	129 (59.2)	0.87
White Non-Hispanic	104 (78.8)	179 (84.8)	0.15
BMI*	29.4 ± 10.1	29.7 ± 6.7	0.73
Diabetes	59 (44.7)	66 (31.3)	0.01
Systemic Hypertension	103 (78.0)	159 (75.4)	0.57
Cholesterol (mg/dL)	179.1 ± 50.5	177.2 ± 52.5	0.77
Smoking status [†]			
Current smoker	34 (25.8)	43 (20.4)	0.14
Former smoker	36 (27.3)	64 (30.3)	
Non-smoker	37 (28.0)	45 (21.3)	
Diagnosed Definite CAD [‡]	82 (90.1)	193 (91.5)	0.70
Chronic Renal Disease	41 (31.1)	30 (14.2)	<0.01
Use of ACE Inhibitors [‡]	60 (46.2)	89 (44.7)	0.79
Use of ARBs [‡]	7 (5.4)	28 (14.1)	0.01
Use of beta-blockers [‡]	79 (60.8)	125 (62.8)	0.71
Severe LVD (EF 35%) [§]	25 (19.5)	20 (9.6)	0.01

Data are presented as mean ± SD or n (%). BMI- Body Mass Index; CAD-Coronary artery disease; ACE- Angiotensin Converting Enzyme; ARB- Angiotensin Receptor Blocker; LVD- Left Ventricular dysfunction; EF- Ejection fraction;

* BMI available for 117 cases and 206 controls

[†] Smoking status available for 107 cases and 152 controls

[‡] CAD status was definitively known for 91 cases

[‡] ACE/ARB information available for 130 cases and 199 controls

[§] EF information available for 128 cases and 208 controls

Table 2

LV Mass Index and Proportion of LVH by Echocardiogram or ECG in cases and controls.

	Cases (n=132)	Controls (n=211)	P value
LV Mass Index *	113.3 ± 38.1	96.9 ± 31.4	<0.001
LVH by Echocardiogram [†]	41 (35.0)	32 (15.5)	<0.001
LVH by ECG [‡]	16 (12.1)	12 (5.7)	0.03

LVH-Left Ventricular Hypertrophy

* Data available for 117 cases and 206 controls

[†] Defined as LV Mass Index greater than 134 g/m² for men and 110 g/m² for women

[‡] By Sokolow-Lyon Index

Table 3

Measure of agreement (Kappa statistic) between ECG and Echocardiographic LVH

			LVH by ECG		Total	Kappa Statistic	
			Yes	No			
LVH by Echocardiogram	Yes	Count	12	61	73		0.128
		Percentage within echo LVH [*]	16.4	83.6	100		
		Percentage within ECG LVH [†]	42.9	20.7	22.6		
No		Count	16	234	250		
		Percentage within echo LVH [*]	6.4	93.6	100		
		Percentage within ECG LVH [†]	57.1	73.9	77.4		
Total		Count	28	295	323		
		Percentage within echo LVH [*]	8.7	91.3	100		
		Percentage within ECG LVH [†]	100	100	100		

^{*} Row percentage[†] Column percentage

LVH- Left ventricular hypertrophy

Table 4

Multivariate Adjusted Odds Ratios for SCA

Parameter	Odds Ratio (95% CI); p value	
	Adjusted Model with only ECG LVH	Adjusted Model with ECG and Echocardiographic LVH
Age	1.01 (0.98–1.02); 0.46	1.00 (0.98–1.02); 0.80
Diabetes	1.5 (0.9–2.5); 0.14	1.4 (0.8–2.5); 0.21
Chronic Renal Disease	2.3 (1.3–4.2); 0.01	1.8 (1.0–3.5); 0.06
ARB Use	0.3 (0.1–0.7); 0.01	0.2 (0.1–0.7); 0.01
Severe LV dysfunction	2.2 (1.1–4.3); 0.02	2.0 (1.0–4.0); 0.05
ECG LVH	2.5 (1.1–6.0); 0.04	2.4 (1.0–6.0); 0.05
Echocardiographic LVH	--	2.7 (1.5–4.9); 0.001

Abbreviations as before