

ORIGINAL ARTICLE

Electrocardiographic Predictors of Sudden Cardiac Death in Patients with Left Ventricular Hypertrophy

Ragesh Panikkath, M.D., D.M.,* Kyndaron Reinier, Ph.D.,*
Audrey Uy-Evanado, M.D.,* Carmen Teodorescu, M.D., Ph.D.,*
Karen Gunson, M.D.,† Jonathan Jui, M.D., M.P.H.,‡ and Sumeet S. Chugh, M.D.*

From the *Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA; †Department of Pathology, Oregon Health and Science University, Portland, OR; and ‡Department of Emergency Medicine, Oregon Health and Science University, Portland, OR

Background: Left ventricular hypertrophy (LVH) has been associated with increased risk of sudden cardiac death (SCD), and improvements in risk stratification methodology are warranted.

Methods: We evaluated electrocardiographic intervals as potential markers of SCD risk in LVH. Corrected QT, QRS, and JT intervals were evaluated in consecutive cases with SCD and LVH from the ongoing Oregon Sudden Unexpected Death study who underwent a 12-lead electrocardiogram (EKG) and echocardiogram prior to and unrelated to the SCD event. Comparisons of age, gender, body mass index, LV ejection fraction, and EKG intervals together with clinical conditions (hypertension and diabetes) were conducted with geographically matched controls that had coronary artery disease but no history of ventricular arrhythmias or cardiac arrest. LVH was determined using the modified American Society of Echocardiography equation for LV mass. Independent samples *t*-test, Pearson's chi-square test, and multiple logistic regression were used for statistical comparisons.

Results: Of the 109 cases and 49 controls who met study criteria, age, gender, and comorbidities were similar among cases and controls. The mean LV mass index was not significantly different in cases compared to controls. However mean QTc (470.6 ± 53.6 ms vs 440.7 ± 38.7 ms; $P < 0.0001$) and QRS duration (113.6 ± 30.0 ms vs 104.9 ± 18.7 ms; $P = 0.03$) were significantly higher in cases than controls. In logistic regression analysis, prolonged QTc was the only EKG interval significantly associated with SCD (OR 1.72 [1.23–2.40]).

Conclusion: Prolonged QTc was independently associated with SCD among subjects with LVH and merits further evaluation as a predictor of SCD in LVH.

Ann Noninvasive Electrocardiol 2013;18(3):225–229

sudden cardiac death; left ventricular hypertrophy; QT interval; risk prediction

Sudden cardiac death (SCD) continues to be a major public health problem accounting for 250,000–300,000 deaths in the United States on a yearly basis^{1,2} and constituting 50% of overall cardiovascular mortality.³ Even with advanced first responder systems, the survival rate after a sudden cardiac arrest is less than 5%.⁴ While the use of the implantable defibrillator has contributed to SCD prevention, current risk stratification methods

are likely to be inadequate.^{5,6} Improvements in methodology of risk stratification will be critical for effective prevention of SCD.

Left ventricular hypertrophy (LVH) has been associated with SCD.^{7,8} Since it is a relatively common condition with 9–15% prevalence in the overall community⁹ only a small proportion of overall subjects with LVH will suffer SCD. Mechanisms of ventricular arrhythmogenesis in patients

Address for correspondence: Sumeet S. Chugh M.D., The Heart Institute, S48 Saperstein Tower, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, California 90048. Fax: 310-423-3522; E-mail: sumeet.chugh@cshs.org

This study is funded by National Heart, Lung, and Blood Institute Grant R01HL088416 to Dr. Chugh. Dr. Chugh is the Pauline and Harold Price Professor of Cardiac Electrophysiology at the Cedars-Sinai Medical Center, Los Angeles, California.

Disclosures: The authors have no conflicts to disclose.

with LVH are likely to be multifactorial¹⁰ but there is clear evidence of cardiac electrical abnormalities. In experimental models of LVH, ventricular repolarization is abnormal, manifesting as prolonged action potential duration; and myocardial conduction abnormalities have also been described.^{11–14} In subjects with LVH diagnosed by electrocardiogram (EKG), the QT and QRS intervals have been found to be prolonged.^{15,16} Given the importance of SCD risk stratification and the wide availability of the 12-lead EKG, we evaluated EKG markers of abnormal ventricular repolarization and depolarization as potential predictors of SCD in LVH.

METHODS

Oregon SUDS is an ongoing study that prospectively identifies all the SCDs that occur among the one million residents of Portland, Oregon metropolitan area, from the emergency medical response system, the medical examiner's office, and local hospitals.¹⁷ SCD was defined as a sudden unexpected pulse-less condition of likely cardiac origin. Survivors of sudden cardiac arrest were also included. Detailed analysis of available medical records, circumstances of cardiac arrest, and autopsy data (when available) were performed prior to in-house adjudication of SCD cases. Deaths due to terminal illness such as cancer and known noncardiac causes like pulmonary embolism, cerebrovascular accidents, and drug overdoses were excluded. Since up to 80% of cases of SCD will have associated significant coronary artery disease (CAD),¹⁸ controls with CAD were ascertained from the same geographical location. CAD was defined as a $\geq 50\%$ stenosis of a major coronary artery or history of myocardial infarction (MI), coronary artery bypass grafting, or percutaneous coronary intervention. The analysis was restricted to subjects ≥ 18 years of age. Echocardiographic criteria were used to identify cases of LVH. Left ventricular mass (LVM) was calculated from quantitative values on M-mode echocardiograms using the American Society of Echocardiography modified equation, indexed to body surface area (BSA); $\text{LV mass} = 0.8 \times \{1.04[(\text{LVIDd} + \text{PWTd} + \text{SWTd})^3 - (\text{LVIDd})^3]\} + 0.6 \text{ g}$ (LVIDd, left ventricular internal dimension in diastole; PWTd, posterior wall thickness at end diastole; SWTd, septal wall thickness in end diastole).¹⁹ LV mass calculated with this

method correlates well with measurements made at autopsy.²⁰ LVH was defined as $\text{LVM/BSA} > 134 \text{ g/m}^2$ for men and $> 110 \text{ g/m}^2$ for women.^{20–22} Analysis was restricted to subjects with LVH, who had QTc and QRS duration measurements available and echocardiogram performed. Subjects with hypertrophic cardiomyopathy were excluded from the analysis. Severe LV dysfunction was defined as a left ventricular ejection fraction less than 35% measured by echocardiogram, multigated acquisition scan (MUGA), or LV angiogram.

Measurement of QT and QRS Intervals from the 12-Lead EKG

Measurement of these intervals was made from EKGs with sinus rhythm. The standard 12-lead EKG tracing at 10 mm/mV amplitude and 25 mm/s paper speed was used for analysis. QT and JT intervals were measured manually, QRS duration as recorded by the computer. The most recent EKG available in medical records, before and unrelated to the cardiac arrest, was used in cases of SCD. For controls, we used an EKG prior to ascertainment if available; if unavailable, an EKG available following ascertainment was utilized. The end of the T wave was defined as the intersection of the tangent to the down slope of the T wave and the isoelectric line when not followed by a U wave or if distinct from the following U wave.²³ If a U-wave followed the T wave, the T-wave offset was measured as the nadir between the T and U waves. If the T-wave amplitude was less than 1.5 mm in a particular lead, that lead was excluded from the analysis. The QT interval was measured from the beginning of the earliest onset of the QRS complex to the end of the T wave. After measurements in all precordial and limb leads, the longest QT interval was recorded. The QT interval was corrected for heart rate using Bazett's formula.²⁴ EKG readers were blinded to all details of subjects. The study was approved by the Institutional Review Boards of Cedars-Sinai Medical Center, Oregon Health and Science University, and all participating hospitals and health systems.

Statistical Analysis

Analysis was conducted using SPSS 18 (SPSS Inc, Chicago, IL) and SAS 9.1 (SAS Institute, Cary, NC) statistical software. Univariate case control comparisons were done using independent-samples

Table 1. Patient Characteristics of Subjects with LVH by Echocardiographic LV Mass Criteria (n = 158)

Categories	Cases (n = 109)	Controls (n = 49)	P-Value ^a
Age (years)	70.6 ± 13.9	68.5 ± 13.2	0.38
Male	62 (56.9%)	26 (53.1%)	0.65
BMI	29.2 ± 10.2	31.3 ± 6.7	0.12
Hypertension	90 (82.6%)	40 (81.6%)	0.89
Diabetes	57 (52.3%)	22 (44.9%)	0.39
Severe LV dysfunction ^b	35 (32.4%)	10 (32.3%)	0.99
Missing ^c	1	18	
LV mass index	161.2 ± 35.1	154.2 ± 30.4	0.22

Results presented as n (%) or mean ± SD.

^aP-value from Pearson's chi-square test for categorical variables and *t*-test for continuous variables.

^bSevere LV dysfunction was defined as a left ventricular ejection fraction less than 35% measured by echocardiogram, MUGA, or LV angiogram.

^cFor variables with missing values, proportions and P values are calculated using the nonmissing data as the denominator. BMI, body mass index; LV, left ventricle.

t-tests and Pearson's chi-square tests. Multiple logistic regression was used to estimate the odds ratio (OR) for SCD associated with abnormal QTc and QRS duration adjusted for age and gender. ORs for each measurement for an estimated one standard deviation increase in that interval among controls were calculated. A P value of less than 0.05 was considered significant for all the statistical analysis.

RESULTS

Univariate Analysis

There were 109 cases and 49 controls that met study criteria. All the controls and 97.3% (106) of the cases had evidence of CAD (P = 0.24). The mean age and gender were not significantly different among cases and controls. Systemic hypertension, diabetes, body mass index were not significantly different among cases and controls. Left ventricular dysfunction was not observed to be a significant predictor of SCD (Table 1). The mean LV mass index, though higher in cases, was also not identified as a significant predictor of SCD.

EKG Predictors

The heart rate was similar in cases and controls and could not identify the high-risk subjects (Table 2). The mean QRS duration was significantly higher in cases when compared to controls (113.3 ± 30.0 ms vs 104.9 ± 18.7 ms; P = 0.03).

Table 2. EKG Measurements of Subjects with LVH by Echocardiographic LV Mass Criteria (n = 158)

Categories	Cases (n = 109)	Controls (n = 49)	P-Value ^a
QTc (ms) ^b	470.6 ± 53.6	440.7 ± 38.7	0.0001
JTc (ms) ^b	350.2 ± 50.9	337.0 ± 37.2	0.07
QRS (ms) ^b	113.3 ± 30.0	104.9 ± 18.7	0.03
HR (ms) ^b	74.6 ± 15.3	73.1 ± 18.0	0.60
Conduction abnormality			0.26
Normal	43 (39.4%)	16 (32.7%)	
First degree	6 (5.5%)	4 (8.2%)	
LAFB	4 (3.7%)	1 (2.0%)	
IRBBB/ILBBB	1 (0.9%)	1 (2.0%)	
IVCD	27 (24.8%)	21 (42.9%)	
RBBB	11 (10.1%)	2 (4.1%)	
LBBB	16 (14.7%)	3 (6.1%)	
Bifascicular block	1 (0.9%)	1 (2.0%)	

Results presented as n (%) or mean ± SD

^aP value from Pearson's chi-square test for categorical variables and *t*-test for continuous variables.

^bQRS duration and HR as reported on the EKG recording. QT and JT intervals were measured manually.

JTc, corrected JT interval; LV, left ventricle; HR, heart rate; QRS, QRS complex duration; QTc, corrected QT interval.

Table 3. Multivariate Odds Ratio Estimates of SCD

Categories	OR (95% CI) n = 158
Age	1.01 (0.99–1.04)
Male	1.17 (0.55–2.46)
QTc (1 SD increase)	1.72 (1.23–2.40)
QRS (1 SD increase)	1.15 (0.86–1.54)

QRS, QRS duration; QTc, corrected QT interval; SCD, sudden cardiac death.

QTc was significantly higher in cases compared to controls (470.6 ± 53.6 ms vs 440.7 ± 38.7 ms; P < 0.0001). The mean JTc was also higher in cases than controls though it was not statistically significant (350.2 ± 50.9 ms vs 337.0 ± 37.2 ms; P = 0.07).

Multivariate Analysis

Using EKG intervals as continuous variables and adjusting for age and gender, QTc was the only EKG marker that significantly predicted SCD in the logistic regression model (Table 3). A one standard deviation increase in QTc caused a 1.7-fold increase in odds of SCD (OR 1.72 [1.23–2.40]), whereas a one standard deviation increase in QRS duration was not significantly associated with increase in risk (OR 1.15 [0.86–1.54]).

DISCUSSION

Main Findings

This study was restricted to cases of SCD that underwent 12-lead EKG and echocardiograms prior to the SCD and had LVH by echo criteria, and comparisons were made with geographically matched controls that had known CAD. Age, gender, comorbidities, presence of CAD, and LV systolic dysfunction were not significantly different among the cases and controls. The LV mass index failed to predict risk of SCD. Among the EKG parameters, though both QTc and QRS duration were significant predictors of SCD in univariate analysis, only QTc was significant in the logistic regression model.

LVH has been associated with overall cardiovascular mortality as well as SCD.^{25,26} In the Framingham study each increment in LV mass of 50 g/m of height was found to be associated with 1.5-fold increase in cardiovascular disease and a 1.7- to 2.1-fold increase in risk-adjusted cardiovascular mortality.^{7,27} In the Losartan Intervention for End Point Reduction in Hypertension Study (LIFE), patients who had reduction of LVH by EKG criteria during treatment of hypertension had lower rates of sudden death. This effect was found to be independent of the treatment used and blood pressure achieved.²⁸

Morin et al. reported that prolonged QRS duration was significantly related to the risk of sudden death in the patients treated aggressively for systemic hypertension after controlling for risk factors for CAD, changes in blood pressure, severity of LVH, and left bundle branch block in the LIFE study.²⁹ However at present time there is no universally accepted risk stratification model for SCD in LVH. Prolonged QRS duration and QTc are associated with increased risk of SCD, as well as cardiovascular and all-cause mortality. Oikarinen et al. reported that among patients with LVH diagnosed by EKG in the LIFE study, QRS duration and maximum rate-adjusted QT_{apex} interval were predictive of increased cardiovascular and all-cause mortality.¹⁶ Since echocardiography has a higher sensitivity for the diagnosis of LVH than the EKG, the present findings may potentially be more relevant from the clinical perspective. Since a one standard deviation increase in QTc caused a 1.7-fold increase in the odds of SCD (OR 1.72 [1.23–2.40]), this parameter warrants

further evaluation as a predictor of SCD in LVH. None of the conduction abnormalities measured from the EKG conferred increased SCD risk. However, it has been reported that intraventricular conduction abnormalities complicating acute MI can degenerate into higher degree conduction blocks that are known to increase SCD risk.³⁰

Limitations

The difficulty in locating the T-end when the T wave is flat for multiphasic may affect the QTc measurements, but since the reader was blinded to the case control status of the subjects, such an error would have affected the cases and controls equally and is unlikely to lead to any bias on the findings of the study.

CONCLUSION

Prolonged QTc interval was significantly associated with SCD in subjects with echocardiographic LVH determined by calculation of LV mass. These findings have potential implications for clinical risk stratification and merit evaluation in larger, prospective studies.

Acknowledgments: *The authors would like to acknowledge the significant contribution of American Medical Response, Portland/Gresham fire departments, the Multnomah County Medical Examiner's office, and the emergency medicine, cardiology and primary care physicians, and allied health personnel of the 16 area hospitals.*

REFERENCES

1. Chugh SS, Reinier K, Teodorescu C, et al. Epidemiology of sudden cardiac death: Clinical and research implications. *Prog Cardiovasc Dis* 2008;51:213–228.
2. Fishman GI, Chugh SS, Dimarco JP, et al. Sudden cardiac death prediction and prevention: Report from a National Heart, Lung, and Blood Institute and Heart Rhythm Society Workshop. *Circulation* 2010;122:2335–2348.
3. Chugh SS, Jui J, Gunson K, et al. Current burden of sudden cardiac death: Multiple source surveillance versus retrospective death certificate-based review in a large U.S. community. *J Am Coll Cardiol* 2004;44:1268–1275.
4. Nichol G, Thomas E, Callaway CW, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. *JAMA* 2008;300:1423–1431.
5. Buxton AE, Lee KL, Hafley GE, et al. Limitations of ejection fraction for prediction of sudden death risk in patients with coronary artery disease: Lessons from the MUSTT study. *J Am Coll Cardiol* 2007;50:1150–1157.
6. Chugh SS, Uy-Evanado A, Teodorescu C, et al. Women have a lower prevalence of structural heart disease as a precursor to sudden cardiac arrest: The Ore-SUDS (Oregon Sudden

- Unexpected Death Study]. *J Am Coll Cardiol* 2009;54:2006–2011.
7. Haider AW, Larson MG, Benjamin EJ, et al. Increased left ventricular mass and hypertrophy are associated with increased risk for sudden death. *J Am Coll Cardiol* 1998;32:1454–1459.
 8. Schatzkin A, Cupples LA, Heeren T, et al. Sudden death in the Framingham Heart Study. Differences in incidence and risk factors by sex and coronary disease status. *Am J Epidemiol* 1984;120:888–899.
 9. Schirmer H, Lunde P, Rasmussen K. Prevalence of left ventricular hypertrophy in a general population: The Tromso Study. *Eur Heart J* 1999;20:429–438.
 10. Wolk R. Arrhythmogenic mechanisms in left ventricular hypertrophy. *Europace* 2000;2:216–223.
 11. Cooklin M, Wallis WR, Sheridan DJ, et al. Changes in cell-to-cell electrical coupling associated with left ventricular hypertrophy. *Circ Res* 1997;80:765–771.
 12. McIntyre H, Fry CH. Abnormal action potential conduction in isolated human hypertrophied left ventricular myocardium. *J Cardiovasc Electrophysiol* 1997;8:887–894.
 13. Winterton SJ, Turner MA, O’Gorman DJ, et al. Hypertrophy causes delayed conduction in human and guinea pig myocardium: Accentuation during ischaemic perfusion. *Cardiovasc Res* 1994;28:47–54.
 14. Rials SJ, Wu Y, Ford N, et al. Effect of left ventricular hypertrophy and its regression on ventricular electrophysiology and vulnerability to inducible arrhythmia in the feline heart. *Circulation* 1995;91:426–430.
 15. Oikarinen L, Nieminen MS, Viitasalo M, et al. Relation of QT interval and QT dispersion to echocardiographic left ventricular hypertrophy and geometric pattern in hypertensive patients. The LIFE study. The Losartan Intervention For Endpoint Reduction. *J Hypertens* 2001;19:1883–1891.
 16. Oikarinen L, Nieminen MS, Viitasalo M, et al. QRS duration and QT interval predict mortality in hypertensive patients with left ventricular hypertrophy: The Losartan Intervention for Endpoint Reduction in Hypertension Study. *Hypertension* 2004;43:1029–1034.
 17. Chugh SS, Reinier K, Singh T, et al. Determinants of prolonged QT interval and their contribution to sudden death risk in coronary artery disease: The Oregon Sudden Unexpected Death Study. *Circulation* 2009;119:663–670.
 18. Adabag AS, Peterson G, Apple FS, et al. Etiology of sudden death in the community: Results of anatomical, metabolic, and genetic evaluation. *Am Heart J* 2010;159:33–39.
 19. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: A report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440–1463.
 20. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: Comparison to necropsy findings. *Am J Cardiol* 1986;57:450–458.
 21. Devereux RB, Lutas EM, Casale PN, et al. Standardization of M-mode echocardiographic left ventricular anatomic measurements. *J Am Coll Cardiol* 1984;4:1222–1230.
 22. Rosa EC, Moyses VA, Sesso RC, et al. Left ventricular hypertrophy evaluation in obese hypertensive patients: Effect of left ventricular mass index criteria. *Arq Bras Cardiol* 2002;78:341–351.
 23. Perkiomaki JS, Koistinen MJ, Yli-Mayry S, et al. Dispersion of QT interval in patients with and without susceptibility to ventricular tachyarrhythmias after previous myocardial infarction. *J Am Coll Cardiol* 1995;26:174–179.
 24. Bazett HC. An analysis of the time-relations of electrocardiograms. *Heart* 1920;7:353–357.
 25. Kannel WB, Gordon T, Offutt D. Left ventricular hypertrophy by electrocardiogram. Prevalence, incidence, and mortality in the Framingham study. *Ann Intern Med* 1969;71:89–105.
 26. Kreger BE, Cupples LA, Kannel WB. The electrocardiogram in prediction of sudden death: Framingham Study experience. *Am Heart J* 1987;113:377–382.
 27. Levy D, Garrison RJ, Savage DD, et al. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990;322:1561–1566.
 28. Wachtell K, Okin PM, Olsen MH, et al. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive therapy and reduction in sudden cardiac death: The LIFE Study. *Circulation* 2007;116:700–765.
 29. Morin DP, Oikarinen L, Viitasalo M, et al. QRS duration predicts sudden cardiac death in hypertensive patients undergoing intensive medical therapy: The LIFE study. *Eur Heart J* 2009;30:2908–2914.
 30. Hindman MC, Wagner GS, JaRo M, et al. The clinical significance of bundle branch block complicating acute myocardial infarction. 2. Indications for temporary and permanent pacemaker insertion. *Circulation* 1978;58:689–699.