Electrocardiographic versus echocardiographic left ventricular hypertrophy and sudden cardiac arrest in the community

Kumar Narayanan, MD,[*] Kyndaron Reinier, PhD,[*] Carmen Teodorescu, MD, PhD,[*] Audrey Uy-Evanado, MD,[*] Harpriya Chugh, BS,[*] Karen Gunson, MD,[†] Jonathan Jui, MD, MPH,[†] Sumeet S. Chugh, MD, FHRS[*]

From the [*]Cedars-Sinai Medical Center, Los Angeles, California, and [†]Oregon Health and Science University, Portland, Oregon.

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

OBJECTIVE The purpose of this study was to compare the association between ECG vs echocardiographic LVH and SCA in the community.

METHODS In a large, prospective population-based study (The Oregon Sudden Unexpected Death Study; population approximately 1 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 vs echocardiogram.

RESULTS Cases (n = 132, age 66.9 ± 13.5 years, 58.3% male) compared to controls (n = 211; age 66.2 ± 12 years, 59.2% male) were more likely to have both ECG LVH (12.1% vs 5.7%, $P = .03$) and echocardiographic LVH (35.0% vs 15.5%, $P < .001$). 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 (odds ratio [OR] 2.5, 95% confidence interval [CI] 1.1–6.0, $P = .04$). When echocardiographic LVH was added to the model, this association was only mildly attenuated (OR 2.4, 95% CI 1.0–6.0, $P = .05$), and echocardiographic LVH was also independently associated with SCA (OR 2.7, 95% CI 1.5–4.9, $P = .001$).

CONCLUSION 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

ABBREVIATIONS **ARB** = angiotensin receptor blocker; **CAD** = coronary artery disease; **CI** = confidence interval; **EF** = ejection fraction; **HCM** = hypertrophic cardiomyopathy; **ICD** = implantable cardioverter-defibrillator; **LV** = left ventricle; **LVH** = left ventricular hypertrophy; **OR** = odds ratio; **SCA** = sudden cardiac arrest; **SUDS** = Sudden Unexpected Death Study

(Heart Rhythm 2014;11:1040–1046)

Introduction

Sudden cardiac arrest (SCA) is a major cause of cardiovascular mortality, with an estimated 300,000–350,000 cases annually in the United States.[1] Although coronary artery disease (CAD) is likely to be responsible for the majority of SCA cases in the general population,[2] in more than half, SCA may be the first manifestation of heart disease.[3] The unexpected nature of the event and poor survival rates (nationally <5%) cause a devastating societal impact. Therefore, prediction of risk for SCA has been an important area of research, made even more relevant with the advent of the implantable cardioverter-defibrillator (ICD). 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 implantation.[4] However, population-based studies have highlighted that only a minority of SCA victims have severe LV dysfunction.[3,5] Furthermore, among patients who undergo ICD placement based on current guidelines, only a small fraction receive appropriate therapies,[6] suggesting that 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.

Funded in part by National Heart, Lung, and Blood Institute Grants R01HL088416 and HL105170 to Dr. Chugh. Dr. Chugh holds the Pauline and Harold Price Chair in Cardiac Electrophysiology Research at the Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA. **Address reprint requests and correspondence:** Dr. Sumeet S. Chugh, The Heart Institute, Advanced Health Sciences Pavilion Suite A3100, Cedars-Sinai Medical Center, 127 S. San Vicente Blvd, Los Angeles, CA 90048. E-mail address: sumeet.chugh@cshs.org.

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 (SUDS), we previously reported that increased LV mass measured by echocardiogram is an important risk predictor for SCA independent of the EF.[9] Similarly, LVH diagnosed by 12-lead ECG has been shown to increase SCA risk[10] and regression of LVH by medical therapy to reduce this risk.[11] Whether assessment of LVH by ECG adds any benefit over echocardiogram for SCA risk assessment remains to be evaluated, because the ECG is generally considered to be a less sensitive technique for identification of LVH.[12] 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 cardiac 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] In brief, 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 noncardiac causes of sudden death (e.g., drug overdose) were 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 in unwitnessed cases. SCA is diagnosed based on an in-house adjudication process involving 3 physicians. Survivors of sudden cardiac arrest were 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 1 of the region's major participating health systems, those who were transported by the emergency medical system 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 the 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 V1 + R V5 or V6 $\geq$ 35 mm) were used to diagnose LVH by ECG.[16] LV mass was calculated using the American Society of Echocardiography recommended formula using LV linear dimensions: $0.8 \times (1.04\ [(\text{LVIDD} + \text{PWTD} + \text{IVSTD})^3 - (\text{LVIDD})^3]) + 0.6$ g, where LVIDD is left ventricular internal diameter in diastole, PWTD is posterior wall thickness in diastole, and IVSTD is interventricular septal thickness in diastole. LV mass index was calculated as LV mass divided by body surface area (in m^2). Echocardiographic LVH was defined as LV mass index >134 g/m^2 for men and >110 g/m^2 for women.[17] LV EF measurements were also obtained from the same echocardiograms. In addition, we assessed the association of ECG vs echocardiographic LVH with SCA by using alternative ECG criteria, including the gender-specific Cornell voltage criteria (S in V3 + 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 χ^2 test for categorical variables. Agreement between the diagnosis of LVH by ECG vs 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 Corp, Armonk, NY.).

Results

Demographic and clinical characteristics

A total of 343 subjects (132 cases, 211 controls) were analyzed. Table 1 lists 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 $\pm$ 13.5 years vs 66.2 $\pm$ 12.0 years, $P = .61$), proportion of males (58.3% vs 59.2%, $P = .87$), prevalence of hypertension (78.0% vs 75.4%, $P = .57$), cholesterol level (179.1 $\pm$ 50.5 mg/dL vs 177.2 $\pm$ 52.5 mg/dL, $P = .77$), and smoking status ($P = .14$). A definite diagnosis of CAD was established in 91.5% of the controls and 90.1% of the cases who had adequate information. Cases