Early Repolarization Pattern and Left Ventricular Mass in Hypertrophic Cardiomyopathy

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Keywords

Early repolarization · Electrocardiogram · Hypertrophic cardiomyopathy · Magnetic resonance imaging · Left ventricular mass

Abstract

Background: J-point elevation in the inferior and/or lateral leads is associated with an increased incidence of sudden cardiac death (SCD) in hypertrophic cardiomyopathy (HCM), although the exact underlying mechanism is not known. As severe left ventricular hypertrophy and late gadolinium enhancement (LGE) are important risk factors for SCD in this population, we aimed to assess whether there was an association between an early repolarization pattern (ERP) and greater left ventricular mass (LVM) and LGE extent among patients with HCM. **Methods:** This was a retrospective cohort study of 85 consecutive patients with HCM who underwent cardiac magnetic resonance (CMR) and had an electrocardiogram without confounders (intraventricular conduction delay, complete left or right bundle branch block, or ventricular paced rhythm). Baseline characteristics and MRI-derived LVM and LGE extent were compared between patients

with and without ERP. **Results:** ERP was present in 9 out of 85 patients (10.6%). Patients with ERP had greater indexed LVM compared to those without (112.5 ± 26.3 vs. 87.8 ± 24.6 g/m², $p = 0.006$). Logistic regression analysis revealed a 4.2-fold increase in the odds of prevalent ERP per standard deviation increase in body surface area-indexed LVM (odds ratio 4.2; 95% CI 1.54–11.4, $p = 0.005$). There were no statistically significant differences regarding LGE extent between groups. **Conclusion:** ERP is associated with greater CMR-derived LVM among patients with HCM. This finding could partially explain the association between J waves and a higher risk of SCD in this population. There were no differences in LGE extent. Further studies are needed to confirm this association and evaluate the importance of ERP as a marker of increased risk of SCD in HCM.

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Introduction

Sudden cardiac death (SCD), although infrequent (approx. 1% per year), remains the most visible complication of hypertrophic cardiomyopathy (HCM) [1]. Risk strati-

fication relying on noninvasive clinical parameters is recommended to identify high-risk patients suitable for an implantable cardioverter defibrillator [2]. Several electrocardiographic (ECG) parameters have been reported as potential predictors of SCD in patients with HCM, including QRS fragmentation [3] and T-peak to T-end interval [4]. Recently, J-point elevation in the inferior and/or lateral leads was shown to be associated with an increased incidence of SCD or ventricular arrhythmias in patients with HCM, and its presence improved prediction of future arrhythmic events in addition to established SCD risk factors [5]. However, the mechanism underlying this association remains to be elucidated and the authors provided no information regarding cardiac magnetic resonance (CMR) data. Early repolarization has been traditionally linked to the absence of structural heart disease, which contrasts significantly with the markedly abnormal myocardial substrate in HCM. Nevertheless, in the multiethnic, population-based, Dallas Heart Study, those with an early repolarization pattern (ERP) had greater CMR-derived left ventricular mass (LVM), which could partially explain the association between early repolarization and SCD [6]. In HCM, both the severity of left ventricular hypertrophy [7] and the extent of late gadolinium enhancement (LGE) [8] are associated with an increased risk of fatal arrhythmic events. We hypothesize that among patients with HCM, those with an ERP have greater LVM and LGE compared to those without early repolarization, possibly explaining the link between early repolarization and SCD.

Materials and Methods

Study Population

We conducted a retrospective study of all consecutive patients referred for CMR between January 2010 and December 2018 in a tertiary care hospital. All patients who had CMR-confirmed HCM and an ECG performed at the time of CMR or at a maximum of a 3-month interval before or after CMR were considered for inclusion. We excluded patients with ECG confounders, which were defined as nonspecific intraventricular conduction delay, complete left or right bundle branch block, or ventricular pacing rhythm. The classification of bundle branch block type and nonspecific intraventricular conduction delay was made according to published criteria [9]. Written informed consent was obtained from all patients in accordance with requirements of the local institutional ethics committee. The study observed the principles outlined in the 1975 Declaration of Helsinki. The final study cohort consisted of 85 HCM patients who were divided into two groups: one including patients with inferior and/or lateral early repolarization (9 patients), and the other including patients without an ERP (76 patients).

ECG and CMR Analysis

A standard 12-lead ECG was recorded at a paper speed of 25 mm/s with amplification of 10 mm/mV in all patients. The ECGs were analyzed by 2 independent cardiologists blinded to the patients' characteristics and CMR data. ERP was defined according to previously published criteria [10]. Specifically, we identified patients who had an end-QRS notch or slur on the downslope of a prominent R-wave and measured the J-point amplitude at the peak of the notch (*J peak*) or at the onset of the slur (*J peak*). ERP in inferior and/or lateral leads was considered when there was J-point (*J peak*) elevation ≥ 0.1 mV above the baseline in at least 2 contiguous inferior (II, III, aVF) and/or lateral (I, aVL, V5, and V6) leads and the QRS duration was < 120 ms. An example of an ECG with early repolarization is shown in Figure 1. LVM was calculated from the short-axis CMR cine images using steady state free precession sequences in a 1.5-T scanner (Magnetom Symphony, Siemens, Erlangen Germany) and indexed to body surface area (BSA). All CMR measurements were completed using dedicated software (CVI42, Circle Cardiovascular Imaging, Calgary, AB, Canada). LGE was quantified using a visual subsegmental analysis [11] and expressed as the total percentage of left ventricular scar volume.

Statistical Analysis

Clinical characteristics, CMR, and ECG findings were compared between the two groups. The baseline patient characteristics are presented as the mean $\pm$ standard deviation or median and interquartile range (IQR) for normally and non-normally distributed continuous variables, respectively. They were compared using the two-sample Student *t* test if normally distributed, otherwise by the Mann-Whitney U test. Categorical variables are reported as absolute number of patients and corresponding percentage, and were compared using Pearson's χ^2 or Fisher's exact test. We used a logistic regression model to assess the association between early repolarization and indexed LVM after adjusting for age, gender, hypertension, QRS duration, corrected QT interval (cQT) using the Fridericia formula, and the amplitude of R wave in lead V5 or V6 (in mm), whichever was greater. All statistical tests are two-tailed, and $p < 0.05$ was considered statistically significant. Statistical analysis was performed using Stata version 15.1 (StataCorp, College Station, TX, USA).

Results

A total of 85 patients with CMR-confirmed HCM were included in our study. The most common morphology of HCM was asymmetric septal hypertrophy in 50 patients (58.8%), followed by focal in 17 (20%), apical in 12 (14.1%), and concentric in 6 (7.1%) patients. Early repolarization was present in 9 out of 85 patients (10.6%). Patients with early repolarization had greater BSA-indexed LVM compared to those without (112.5 ± 26.3 vs. 87.8 ± 24.6 g/m², $p = 0.006$ for comparison, Fig. 2), as well as higher indexed left ventricular end-diastolic volume and lower left ventricular ejection fraction. No differences were seen in age, gender, and other baseline character-

Fig. 1. A 12-lead ECG of a patient with HCM and early repolarization in the inferior leads (II, III, and aVF). Note the elevation of the J-point (where the QRS ends and the ST segment begins) ≥ 1 mm above the isoelectric baseline.

istics (Table 1). There was also no association between ERP and the morphology of HCM. The logistic regression analysis showed a 4.2-fold increase in the odds of prevalent early repolarization per standard deviation increase in BSA-indexed LVM (odds ratio 4.2; 95% CI 1.5–11.4, $p = 0.005$). The LGE extent was 14.7% (IQR 8.8–45.6) in patients with early repolarization compared to 8.8% (IQR 3.7–14.7) in those without ($p = 0.11$ for comparison).

Discussion

In this study, we investigated whether greater LVM could be associated with the presence of early repolarization among patients with HCM. Our main finding is that early repolarization is associated with greater CMR-derived indexed LVM in patients with HCM after adjusting for confounding variables. We found no statistically significant difference in LGE extent between the groups. The mechanisms responsible for the J-point elevation have long been a matter of debate, but two main hypotheses –

Fig. 2. Box-and-whisker plots of BSA-indexed LVM stratified by to the presence of ERP in inferior and/or lateral leads. Patients with ERP had greater BSA-indexed LVM compared to those without (112.5 ± 26.3 vs. 87.8 ± 24.6 g/m², $p = 0.006$).

the repolarization and depolarization hypotheses – have been advanced, particularly in the case of Brugada syndrome (BrS) [12]. The repolarization hypothesis states that J-point elevation occurs due to an outward Ito-me-

Table 1. Baseline, ECG, and CMR characteristics of participants stratified by presence of ERP

	Individuals without ERP (<i>n</i> = 76)	Individuals with ERP (<i>n</i> = 9)	<i>p</i> value
Baseline characteristics			
Age, years	56±15	58±13	0.8
Male	46 (61)	7 (78)	0.3
BMI	28.6±5	28.9±4	0.89
Unexplained syncope	7 (9)	0	0.34
NSVT	10 (13)	1 (11)	0.86
ICD	8 (11)	1 (11)	0.96
Atrial fibrillation	18 (24)	0	0.1
Hypertension	47 (62)	8 (89)	0.11
NYHA II or higher	1 (1)	1 (11)	0.11
Hypertrophic cardiomyopathy morphology			
Asymmetric septal	45 (59.2)	5 (55.6)	0.84
Focal	16 (21.1)	1 (11.1)	0.48
Apical	11 (14.5)	1 (11.1)	0.78
Concentric	4 (5.3)	2 (22.2)	0.06
CMR findings			
LA area, cm ²	28.9±6.3	30.1±4.3	0.57
LVEDV/BSA, mL/m ²	78.4±15.3	99.8±28.4	<0.001
LVEF, %	65.4±9.1	57±12.7	0.014
Maximum septal thickness, mm	19.7±4.3	21.5±5.3	0.28
LVM/BSA, g/m ²	87.8±24.6	112.5±26.3	0.006
LGE extent, %	8.8 (3.7–14.7)	14.7 (8.8–45.6)	0.12
ECG findings			
Heart rate, bpm	67.6±15.3	63.7±15	0.47
QRS duration, ms	102.3±11.2	107.9±11.2	0.16
QTc interval, ms	415.4±41.9	438.3±31.9	0.72
LVH-SL	30 (39)	4 (44)	0.77
LVH-CL	29 (38)	5 (56)	0.31

Values are expressed as *n* (%), mean ± SD, or median (IQR). BSA, body surface area; CL, Cornell-voltage criteria; CMR, cardiac magnetic resonance; ECG, electrocardiographic; ERP, early repolarization pattern in inferior and/or lateral leads; ICD, implantable cardioverter defibrillator; LA, left atrial; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVH, left ventricular hypertrophic; LVM, left ventricular mass; NSVT, non-sustained ventricular tachycardia; QTc, corrected QT; SL, Sokolow-Lyon criteria.

diated current. The depolarization hypothesis, on the other hand, suggests that conduction delay plays a primary role in the development of the ECG and the arrhythmic manifestations of BrS. Fibrosis and fatty infiltration can result in marked activation delay and create a potential gradient responsible for the ECG pattern [13]. These findings suggest that structural abnormalities are probably intrinsic to J-wave syndromes, which could explain the association between J-waves and SCD in different cardiac abnormalities, including ischemic heart disease [14] and recently HCM [5].

Our study raises the hypothesis that greater LVM may represent a pathophysiological link between early repolarization and an increased risk of SCD among patients

with HCM [5]. Greater LVM is associated with increased interstitial myocardial fibrosis, which may cause both depolarization and repolarization abnormalities, possibly explaining the appearance of J-waves and its association with SCD. However, this assumption could not be verified in our study due to the absence of T1 mapping analysis.

The prevalence of early repolarization in our study (10.6%) is higher than that reported in the general population (approx. 5.8%) [15]. There is some discrepancy in the reported prevalence of ERP in patients with HCM, but our results are similar to those of Tsuda et al. [5] (46 out of 338 HCM patients, 13.6%) and higher than those reported by Lin et al. [16] (8 out of 128 patients, 6.3%).

Overall, our findings are of interest and raise the question of whether the abnormal substrate in HCM can favor the appearance of J-waves, which would then act as a surrogate marker for an increased risk of SCD in this population [5].

Study Strengths and Limitations

Our study's strengths include utilization of CMR, which is a highly accurate and reproducible method for evaluation of LVM and LGE. We also complied with the 2016 expert consensus of the American Heart Association on ECG early repolarization to avoid any bias related to the terminology and definition of early repolarization. There are, however, some limitations to our study worth discussing. First, it is an observational study and thus there is the possibility of residual confounding. Second, the small sample size may have limited our ability to detect a difference in LGE extent. Because none of our patients suffered SCD, we opted not to report outcomes. Third, patients with HCM often have intraventricular conduction delay which is known to give rise to notching of the QRS complex and can make the assessment of J-point elevation difficult. To prevent this, we deliberately excluded patients with abnormal intraventricular conduction. Fourth, we did not perform T1 mapping analysis, which would have been useful for a better assessment of myocardial fibrosis.

Statement of Ethics

This study was carried out according to the principles of the Declaration of Helsinki and was approved by relevant local institutional ethics committee. All patients provided written informed consent.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

The first two authors (P.M.O.A. and C.G.) equally contributed to the concept, design, analysis, and interpretation of the data, including ECG measurements, and drafted the entire manuscript. Authors R.L.-L., N.F., R.F., and R.B. provided most CMR analysis and critical revision of the article. Authors J.P. and J.B. provided important critical revision of the article.

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