Received: 29 November 2017 | Revised: 11 May 2018 | Accepted: 6 June 2018

DOI: 10.1111/anec.12582

ORIGINAL ARTICLE

WILEY

Fibrosis and wall thickness affect ventricular repolarization dynamics in hypertrophic cardiomyopathy

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Funding information
Finnish Foundation of Cardiovascular Research, the special governmental subsidy for health sciences research of the University Hospital of Kuopio, Finnish Medical Foundation, the Ida Montin Foundation, and the Finnish Academy.

Abstract

Background: Hypertrophic cardiomyopathy (HCM) is characterized by ventricular repolarization abnormalities and risk of ventricular arrhythmias. Our aim was to study the association between the phenotype and ventricular repolarization dynamics in HCM patients.

Methods: HCM patients with either the *MYBPC3*-Q1061X or *TPM1*-D175N mutation (n = 46) and control subjects without mutation and hypertrophy (n = 35) were studied with 24-hr ambulatory ECG recordings by measuring time intervals of rate-adapted QT (QTe), maximal QT, and T-wave apex to wave end (TPE) intervals and the QTe/RR slope. Findings were correlated to specified echocardiographic and cardiac magnetic resonance imaging (CMRI) findings.

Results: Rate-adapted QTe interval was progressively longer in HCM patients with decreasing heart rates compared to control subjects (p = 0.020). The degree of hypertrophy correlated with measured QTe values. HCM patients with maximal wall thickness higher than the mean (20.6 mm) had longer maximum QTe and median TPE intervals compared to control subjects and HCM patients with milder hypertrophy (p < 0.001 and p = 0.014, respectively). HCM patients with late gadolinium enhancement (LGE) on CMRI had steeper QTe/RR slopes compared to HCM patients without LGE and control subjects (p = 0.044 and p = 0.001, respectively). LGE was an independent predictor of QTe/RR slope (p = 0.023, B = 0.043).

Conclusion: Dynamics of ventricular repolarization in HCM are affected by hypertrophy and fibrosis. LGE may confer an independent effect on QT dynamics which may increase the arrhythmogenic potential in HCM.

1 | INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common cause of sudden cardiac death in the young and in athletes (Maron, Doerer, Haas, Tierney, & Mueller, 2009; Maron, Haas, Murphy, Ahluwalia, & Rutten-Ramos, 2014). The disease is characterized by ventricular repolarization abnormalities arising from structural changes of cellular hypertrophy, interstitial fibrosis, and myofiber disarray and on the other hand from disturbances in the ion currents and calcium handling on the molecular and cellular level. In combination, these changes constitute the arrhythmic substrate responsible for the risk of malignant ventricular arrhythmias (Coppini et al., 2013; Maron, 2010). The stratification of risk for malignant ventricular arrhythmias in HCM is based on multiple factors, but even with current clinical guidelines gaps remain (Elliott et al., 2014).

The QT interval is prolonged in HCM and modestly correlates with maximal wall thickness (Johnson et al., 2011). The QTe/RR slope has been found steeper in higher risk patients and the QT variance index was slightly elevated in HCM patients with clinically significant arrhythmias (Orosz et al., 2015; Quinteiro et al., 2015). However, data on ventricular repolarization dynamics and their association to the HCM geno- and phenotype are limited.

Fibrosis, as measured by late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMRI), is a promising addition to the risk assessment of hypertrophic cardiomyopathy and is a predictor of sudden cardiac death (SCD)(Chan et al., 2014; Weng et al., 2016). The areas of fibrosis in the left ventricle (LV) provide a substrate for ventricular arrhythmias and affect repolarization parameters in monophasic action potential recordings (Sakamoto et al., 2015). The association of LGE to ventricular repolarization dynamics on the surface ECG is unclear. The aim of this study was to explore the dynamics of ventricular repolarization in HCM using ambulatory ECG recordings and analyze the association of hypertrophy and late gadolinium enhancement to the degree of ventricular repolarization disturbances.

2 | METHODS

2.1 | Subjects

Adult Finnish HCM patients carrying either the *MYBPC3*-Q1061X or *TPM*-D175N founder mutation for HCM were recruited prospectively during 2000–2012. HCM was defined in mutation carriers as maximal wall thickness (MWT) ≥13 mm and no other cause for significant hypertrophy. Exclusion criteria were nonsinus rhythm, bundle branch block or implanted pacemaker precluding CMR imaging. Of the screened 52 HCM patients, six were excluded on grounds of nonsinus rhythm (n = 4) or bundle branch block (n = 2). In total, 46 HCM patients were included in the study. Individuals without either of the gene mutations or hypertrophy constituted the control group (n = 35). The Ethics Committees at the Kuopio and Helsinki University Hospitals approved the study protocol. The study conforms to the principles outlined in the Declaration of Helsinki.

2.2 | Baseline data

Venous blood samples were collected and measured for creatinine and the plasma concentrations of the N-terminal portion of brain natriuretic peptide (NT-proBNP). Immunoassays utilizing antisera directed to NT-proBNP were used and the sensitivity of the assay was 40 pmol/L (Ala-Kopsala et al., 2005). As previously described, the genetic studies were performed in the Genome Center of Eastern Finland (Jääskeläinen et al., 2002). Normal 12-lead ECG recordings were obtained from subjects and measured for conventional parameters of heart rate, QT-interval duration and corrected QT-interval (using the Bazett formula).

2.3 | Ambulatory ECG analysis

Twenty-four-hour ambulatory ECGs were digitally recorded on Marquette commercial AECG systems and postprocessed with a custom software built in collaboration with Aalto University. Overall quality of the recording was assessed visually using all the available channels (2 or 3 channels). All data were processed and measured from the modified precordial lead V5. All nonsinus beats were excluded. The methodology of data processing and algorithms for determining QRS onset, offset and T-wave peak and T wave end have been previously described (Viitasalo, Oikarinen, Väänänen et al., 2002). T-wave peak was identified as the peak of the parabola fitted to the highest amplitude change after the QRS. T-wave end was defined as the time instant where the steepest tangent after the T-wave peak intersects the baseline. The recording was further processed by excluding beats with T waves of low amplitude (−0.1 to 0.1 mV) and beats where either the T-wave peak or end was not identified by the algorithm. All beats with a noise level >0.02 mV and beats with an RR interval change from the preceding beat of >30% were excluded. Data were further checked by plotting time interval values of from onset of Q wave to T-wave peak (QTp), onset of Q wave to T-wave end (QTe) and T-wave peak to T-wave end (TPE) against the preceding respective RR intervals and manually removing outliers.

Using these plots, the median QTe, QTp and TPE values were measured at 100 ms RR intervals from 600 to 1,200 ms. To assess the rate dependence of QTe and QTp intervals, we calculated heart rate-adapted values of median QTe and QTp values using periods of stable heart rate for 60 s (beat-to-beat RR interval variation ≤10% in RR steps of 10 ms) as described previously (Viitasalo, Oikarinen, Väänänen et al., 2002). The maximum values of QTe, QTp, and TPE were measured from the QTe-RR, QTp-RR and TPE-RR plotted data at 100 ms intervals from 600 to 1,200 ms. The mean of three separate measurements of maximal value were calculated for each time point, with a requisite of variance of no more than 5% between the measured data points and visual confirmation of data quality and stability of at least five consecutive beats around the measured beat. A fitted regression line to the QTe-RR plot (data from RR intervals 600 to1,200 ms) of the form $y = ax + b$ was used to measure the QTe/RR slope (a) and intercept b (Figure 4b).

2.4 | Echocardiography

Echocardiographic measurements were performed locally at Helsinki and Kuopio University Hospitals by experienced cardiologists (MJ, PJ, JK) using GE Vivid 7 and 9 ultrasound equipment (GE Vingmed Norway). Conventional echocardiographic measurements were performed according to current guidelines. Left ventricular ejection fraction (LVEF) was measured using Simpson's biplane method. Left ventricular outflow tract (LVOT) maximal flow velocity was measured by continuous wave Doppler (gradient >30 mmHg on echocardiography considered significant).

2.5 | Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging was performed using a 1.5-T clinical MR imaging unit in both Helsinki and Kuopio University Hospitals. Late gadolinium enhancement imaging was performed as part of protocol. All CMRI data were analyzed by three experienced radiologists (PS, MT, KL) blinded to clinical data and normal measurements including LV volumes and function were performed according to guidelines. Late gadolinium enhancement was assessed visually and reported as a binary variable (present/absent). Mean MWT on CMRI in the HCM patients was 20.6 mm. This was used as a cutoff value to investigate the effect of mild (<20.6 mm) and moderate (>20.6 mm) wall thickness on ventricular repolarization measurements.

2.6 | Statistics

Data are presented as mean and standard deviation for normally distributed continuous data, median and interquartile range for nonparametric data and count and percentage for categorical data. Differences between groups of normally distributed data were analyzed with independent *t* tests for two group comparisons and one-way analysis of variance (ANOVA) for three group comparisons with post hoc pairwise tests using Bonferroni correction. Nonparametric data were compared between groups with Kruskal-Wallis test with pairwise comparisons by using Bonferroni correction and Fisher's exact test for categorical data. The multiple measurements of QTe, QTp, and TPE from QT-RR plots at 100 ms intervals were analyzed with repeated measurements analysis of variance (RM-ANOVA) for statistical difference between groups and post hoc Bonferroni correction for pairwise comparisons. The subscript in QTe_{1000}, QTp_{1000}, and TPE_{1000} denotes a measurement at 1,000 ms RR interval. Univariate correlations were analyzed with Spearman rank correlation. Linear regression was used to analyze the predictive value of age, gender, beta blocker therapy, CMRI MWT and LGE on the QTe/RR slope. All statistical tests were considered significant with a two-way level of <0.05. All statistical analyses were performed with IBM SPSS Version 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.)

3 | RESULTS

3.1 | Baseline

The baseline variables are presented in Table 1. The study groups were balanced regarding age and blood pressure. No difference was observed in the sex distribution. HCM patients were mostly asymptomatic (78%). Creatinine was marginally higher in the HCM group but within normal limits. NT-proBNP values were higher in the HCM patients. Approximately, half of the HCM patients had the *MYBPC3*-Q1061X and the other half had the *TPM1*-D175N mutation. Beta blocker use was common in the HCM group. No drugs affecting the QT interval were used by the HCM patients. The mean heart rates on the ambulatory ECGs were similar. The peak heart rate in the HCM group was lower compared to the control group.

3.2 | Imaging

The imaging variables are presented in Table 2. LVEF and end-diastolic volumes were similar between groups. LV end-diastolic diameter was slightly larger in the control group. HCM patients had larger left atria and slower early diastolic filling as measured by

TABLE 1 Baseline variables

	Control (*n* = 35)	HCM (*n* = 46)	*p*-Value
Baseline			
Age (years)	43.3 ± 14.8	45.5 ± 11.7	0.456
Male	37% (13)	59% (27)	0.073
BMI	25.1 ± 3.8	27.2 ± 5.4	0.052
BP Systolic (mmHg)	131 ± 13	130 ± 15	0.859
BP Diastolic (mmHg)	77 ± 10	80 ± 10	0.187
Hypertension		22% (10)	
NYHA			
I		78% (36)	
II		22% (10)	
Beta blocker		48% (22)	
ACEi or ARB		12% (6)	
Creatinine (mmol/L)	75 ± 19	85 ± 15	0.015
NT-proBNP (pmol/L)	41 (3)	81 (194)	<0.001
Mutation			
MYBPC-Q1061X		52% (24)	
TPM-D175N		48% (22)	
ECG			
HR (bpm)	63 ± 10	62 ± 10	0.693
QRS duration (ms)	89 ± 8	92 ± 11	0.396
QT (ms)	395 ± 32	421 ± 41	0.003
QTc (ms)	404 ± 31	424 ± 25	0.002
Twenty-four-hour ambulatory ECG			
Mean HR (bpm)	67 ± 6	65 ± 6	0.106
Max HR (bpm)	139 ± 18	126 ± 19	0.003
Min HR (bpm)	44 ± 8	43 ± 5	0.461
PAB	8 (22)	8 (18)	0.828
PVB	3 (12)	14 (82)	0.004
At least one NSVT		26% (12)	
Number of NSVT		1 (1–16)	
Duration of NSVT (beats)		5 (3–14)	

Note. Data presented as mean ± *SD* or percentage (number of subjects) except for PAB and PVB as median (interquartile range) and for number and duration of NSVT as median (range).
BMI: body mass index; BP: blood pressure; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; PAB: premature atrial beat; PVB: premature ventricular beat; NSVT: nonsustained ventricular tachycardia.

TABLE 2 Imaging variables

	Control (*n* = 35)	HCM (*n* = 46)	*p*-Value
Echocardiography			
LVEDD (mm)	49 ± 5	44 ± 6	<0.001
Maximal wall thickness (mm)	9.8 ± 1.3	18.5 ± 5.6	<0.001
Septal wall thickness (mm)	9.1 ± 1.2	15.7 ± 5.9	<0.001
Posterior wall thickness (mm)	9.1 ± 1.4	10.2 ± 1.7	0.002
Left atrial diameter (mm)	33 ± 5	38 ± 6	0.001
LVOT gradient (mmHg)	7.1 ± 2.6	9.0 ± 10.7	0.737
MV E velocity (m/s)	0.80 ± 0.15	0.71 ± 0.18	0.013
MV A velocity (m/s)	0.56 ± 0.17	0.63 ± 0.23	0.350
MV Deceleration time (ms)	199 ± 58	227 ± 76	0.046
Cardiac magnetic resonance imaging			
LVEF (%)	60 ± 7	62 ± 8	0.152
LV end-diastolic volume index (ml/m^2)	77 ± 12	76 ± 15	0.906
LV mass index (g/m^2)	55 ± 15	71 ± 19	<0.001
Maximal wall thickness (mm)	10.0 ± 2.4	20.7 ± 5.2	<0.001
Location of hypertrophy			
Septal		78% (36)	
Lateral wall		17% (8)	
Concentric		2% (1)	
Apical		0	
Gadolinium late-enhancement		37% (17)	<0.001

Note. Data presented as mean ± *SD* or percentage (number of subjects).
LVEDD: left ventricular (LV) end-diastolic dimension; LVOT: left ventricular outflow tract; MV: mitral valve; LVEF: left ventricular ejection fraction.

TABLE 3 Repolarization measurements

Repolarization	Control (n = 35)	HCM (n = 46)	*p*-Value	95% CI
QTe (ms)	380 ± 30	417 ± 43	<0.001	19.6 to 54.9
HR-adapted QTe_{1000} (ms)	403 ± 26	426 ± 34	0.002	9.2 to 37.4
Maximum QTe_{1000} (ms)	440 ± 27	469 ± 40	0.001	12.9 to 45.1
QTe/RR slope	0.178 ± 0.06	0.215 ± 0.06	0.007	0.01 to 0.06
QTp (ms)	301 ± 29	323 ± 30	0.002	8.5 to 35.7
HR-adapted QTp_{1000} (ms)	320 ± 28	335 ± 27	0.017	2.8 to 28.2
Maximum QTp_{1000} (ms)	355 ± 29	370 ± 30	0.031	1.3 to 28.7
TPE (ms)	80 ± 9	94 ± 60	0.185	−7.0 to 35.7
Median TPE_{1000} (ms)	81 ± 11	87 ± 21	0.107	−1.45 to 14.5
Maximum TPE_{1000} (ms)	103 ± 20	110 ± 29	0.315	−6.2 to 19.0

Note. Data presented as mean ± *SD*. The subscript 1,000 denotes measurement at 1,000 ms RR interval duration.
HCM: Hypertrophic cardiomyopathy; QTe: Q wave to T-wave end; TPE: T-wave peak to T-wave end.

the deceleration time. As expected, the HCM patients had thicker ventricles. The location of maximal hypertrophy in HCM patients was mostly confined to the septum, with some patients having lateral wall hypertrophy and one patient had concentric hypertrophy. Of HCM patients, 37% exhibited fibrosis as measured by CMRI gadolinium late enhancement. NTproBNP-levels correlated

with both maximum QTe_{1000} (ρ = 0.390, p = 0.007) and QTe/RR – slope (ρ = 0.466, p = 0.001).

3.3 | Repolarization parameters

The ventricular repolarization dynamics are presented in Table 3 and Figure 1. Mean QTe and QTp measured from all beats, median heart rate-adapted QTe_{1000} and $QTp_{1000,}$ as well as maximum QTe_{1000} and QTp_{1000} were significantly different between study groups. In contrast, no differences in TPE measurements between groups were found (Table 3). Figure 1a,b shows the heart rate-adapted median QTe and maximum QTe in the two groups, with a significant difference between HCM and control groups in repeated measures ANOVA (p = 0.020 and p = 0.011, respectively). The heart rate-adapted median QTp and maximum QTp values followed a similar pattern as measured QTe values but the differences between study groups were not statistically significant (Figure 1c,d). The QTe/RR slopes were also significantly different between HCM and control groups (Table 3). No statistical differences were found in repolarization parameters of heart rate-adapted QTe or QTp, maximum QTe or QTp, or maximum TPE between the two mutation types (p > 0.05 for all). There was no effect of beta blocker therapy use on heart rate-adapted QTe, maximum QTe or maximum TPE in QTe-RR plots (p = 0.522, p = 0.779 and p = 0.790, respectively for repeated measures ANOVA).

3.4 | Repolarization and maximal wall thickness

In univariate Spearman rank correlation, there was a modest correlation of MWT to maximum QTe_{1000} (ρ = 0.319, p = 0.035). Assessing

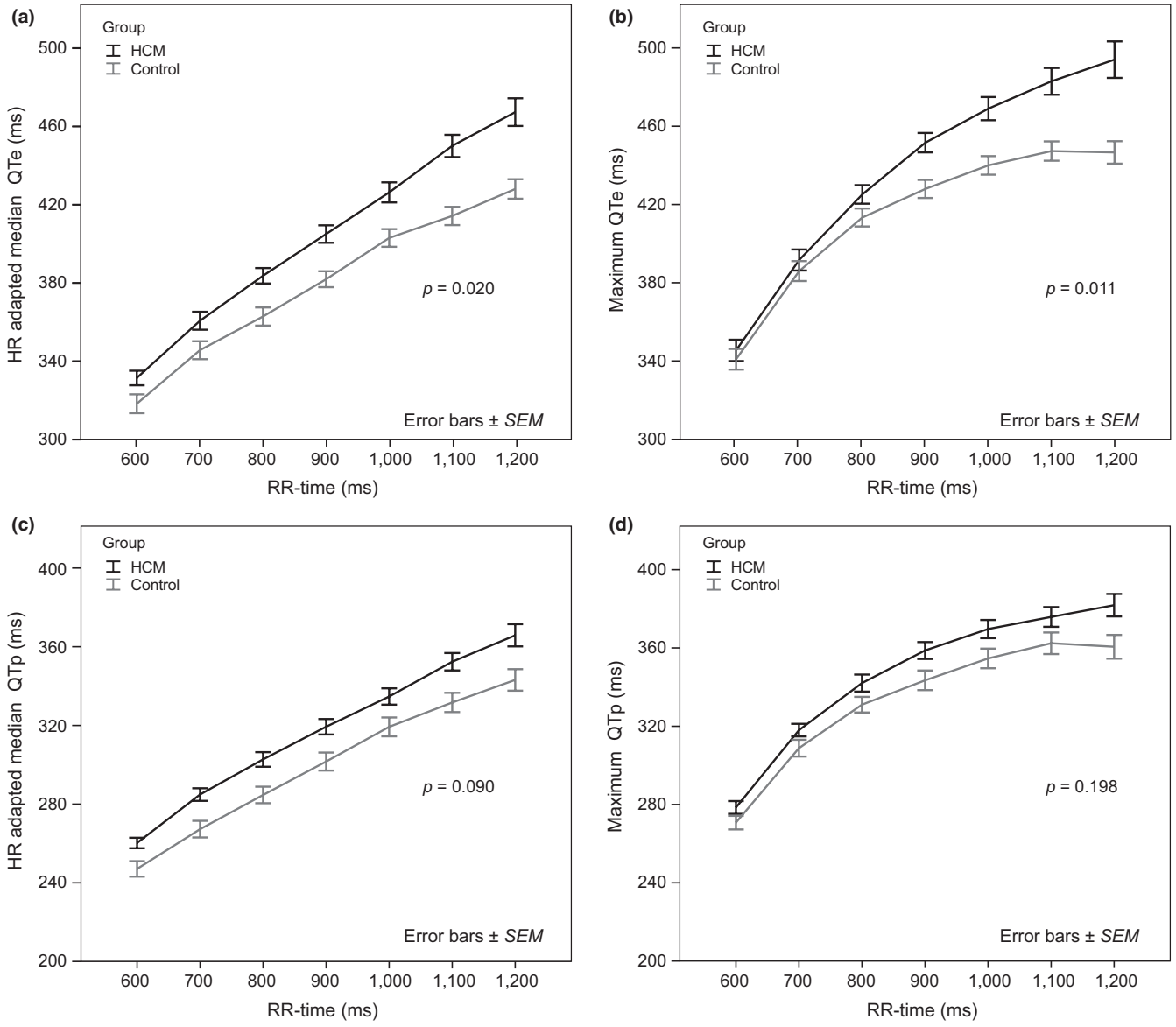

FIGURE 1 Heart rate-adapted QTe intervals (a), maximum QTe intervals (b), heart rate-adapted QTp intervals (c), and maximum QTp intervals (d) at different heart rates

the effect of MWT on ventricular repolarization, the HCM patients were divided into two groups according to MWT being below or above the mean MWT measured on CMRI (20.6 mm). The maximum QTe_{1000} was different between HCM/MWT > 20.6 mm and HCM/MWT < 20.6 mm ($p = 0.005$ for pairwise comparison) and control subjects ($p < 0.001$ for pairwise comparison). Figure 2a shows the maximum QTe values in the three groups at different RR intervals. A significant deviation of the maximum QTe curves was observed at longer RR intervals from 900 to 1,200 ms. Median TPE was significantly longer in HCM patients with thicker MWT compared to HCM patients with milder hypertrophy ($p = 0.021$) or control subjects ($p = 0.027$) in pairwise comparisons. In contrast to QTe values, the TPE measurements differed more clearly at all RR-intervals between groups (Figure 2b).

3.5 | Sex differences

MWT values were similar in HCM male (mean 21.4 ± 5.6 mm) and female (19.7 ± 4.6 mm) patients ($p = 0.301$). The mean difference in MWT between HCM patients and control subjects was 9.8 ± 1.7 mm in men and 10.6 ± 1.1 mm in women and the mean difference was not statistically significant between male and female subjects ($p = 0.071$). HR-adapted QTe_{1000} in HCM vs. control subjects was 423 ± 37 ms vs. 384 ± 24 ms among men ($p = 0.002$) and 431 ± 30 ms vs. 412 ± 21 ms among women ($p = 0.034$), respectively. Figure 3 shows the rate-adapted QTe-RR curves both for male and female control subjects and HCM patients. The ventricular repolarization dynamics were similar in both sexes. In male subjects, there was a trend toward a larger difference in HR-adapted QTe values between HCM patients and control subjects at RR intervals 900–1,200 compared to women (Figure 3a).

3.6 | Repolarization and nonsustained ventricular tachycardia

There were 12 (26%) HCM patients with at least one recorded episode of nonsustained ventricular tachycardia (NSVT, Table 1). HCM patients with NSVT did not have statistically significant differences in median or maximal measured QTe, TPE or other repolarization parameters on 24-hr ambulatory ECG in comparison to HCM patients without NSVT episodes. On a smaller note, all the HCM patients with NSVT had a maximum QTe_{1000} of at least 439 ms or higher (median 479 ms) compared to HCM patients without NSVT (minimum 373 ms and median 464 ms).

3.7 | Repolarization and fibrosis

HCM patients with fibrosis by late gadolinium enhancement (HMC/LGE+, $n = 17$) exhibited steeper QTe/RR slopes compared to HCM patients without fibrosis (HCM/LGE−, $n = 29$) or the control group (Figure 4, Table 4). No significant differences in other repolarization parameters were found between HCM/LGE+ and HCM/LGE− groups (Table 4). There was no difference in the age or sex distribution between HCM/LGE+ and HCM/LGE− patients (mean age 42.5 years and 50.8 years, $p = 0.118$, male subjects 59% in both groups, $p = 1.000$) or MWT (mean CMRI MWT 20.4 mm vs. 21.6 mm, $p = 1.000$). In linear regression of LGE, CMRI MWT, age, gender and beta blocker use to QTe/RR slope, the presence of LGE was the only independent predictor ($p = 0.023$, $B = 0.043$).

4 | DISCUSSION

The principal findings in this study are: (a) HCM patients show progressively longer heart rate-adapted QTe interval with decreasing

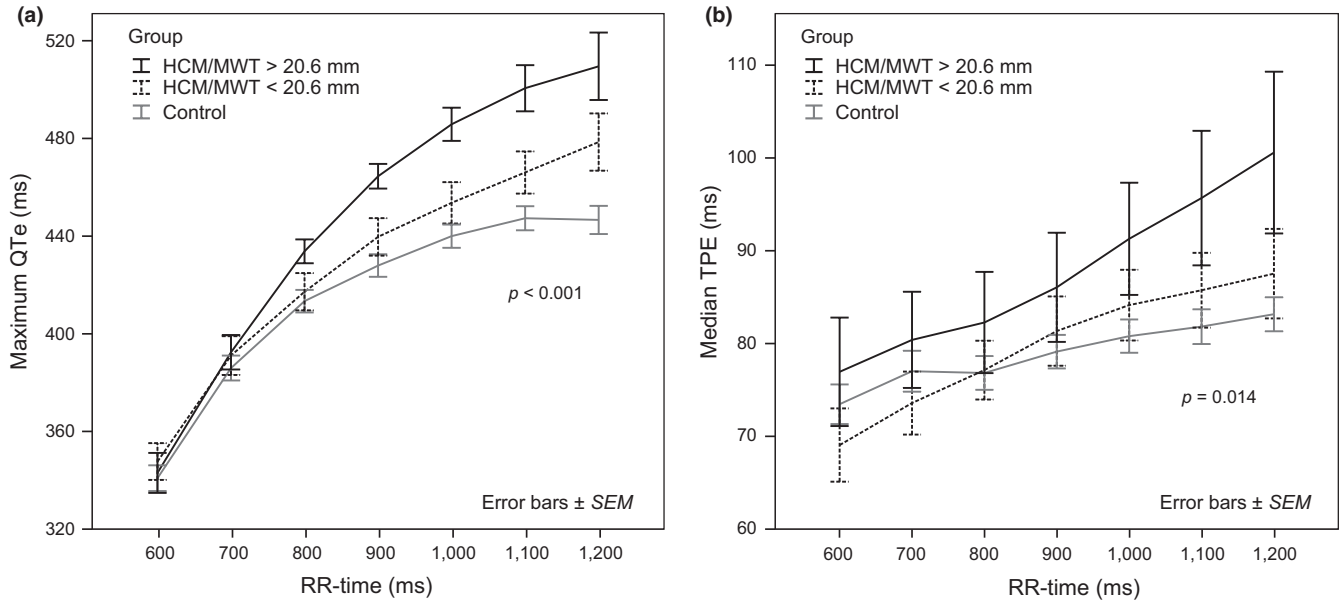

FIGURE 2 Maximum QTe intervals (a) and median TPE (b) at different heart rates in three groups according to maximal wall thickness

heart rates than normal subjects; (b) In HCM, the degree of hypertrophy prolongs the maximal QTe interval; (c) The QTe/RR slope is steeper in HCM than control subjects; (d) HCM patients with LGE show steeper QTe/RR slopes than HCM patients without LGE and LGE is an independent predictor of QTe/RR slope.

We found that the QTe/RR slope was steeper in HCM patients with LGE than those without LGE. In addition, the presence of LGE was the only independent predictor for the steepness of the QTe/RR slope. Previously, a steeper QTe/RR slope has been associated with increased risk of SCD in ischemic patients (Chevalier et al., 2003; Milliez et al., 2005) and overall mortality in heart failure (Cygankiewicz et al., 2008; Pathak et al., 2005; Watanabe et al., 2007). In a study of HCM patients, Quinteiro et al. found the QTe/RR slope steeper in individuals classified as high risk based on conventional risk criteria. Notable in that study was the significant difference in MWT between low and high risk patients (20 mm vs. 25 mm). Although in this study, MWT was associated to prolongation of the QTe, in linear regression the only independent predictor of QTe/RR slope was LGE. In a large cohort of nearly 1,300 HCM patients, an LGE extent of ≥15% of the LV mass was associated with a twofold risk of SCD in HCM patients otherwise classified as low risk (Chan et al., 2014). The fibrosis quantified with LGE may have an additional

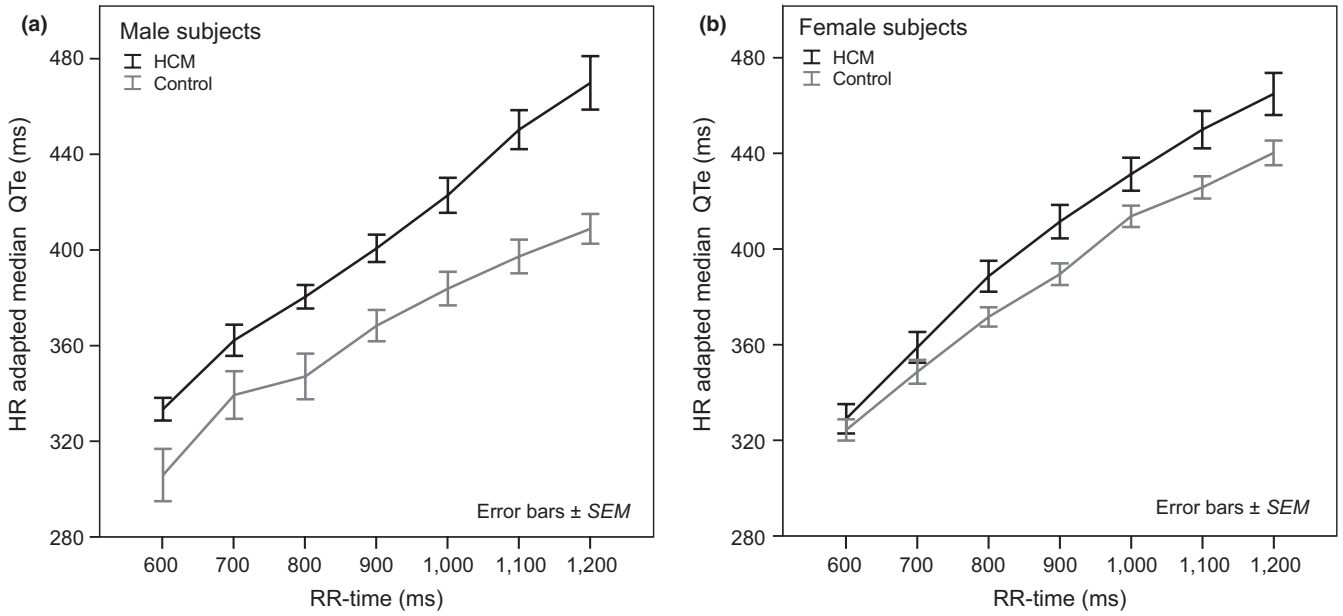

FIGURE 3 Heart rate-adapted QTe intervals for male (a) and female (b) subjects at different heart rates in the two study groups

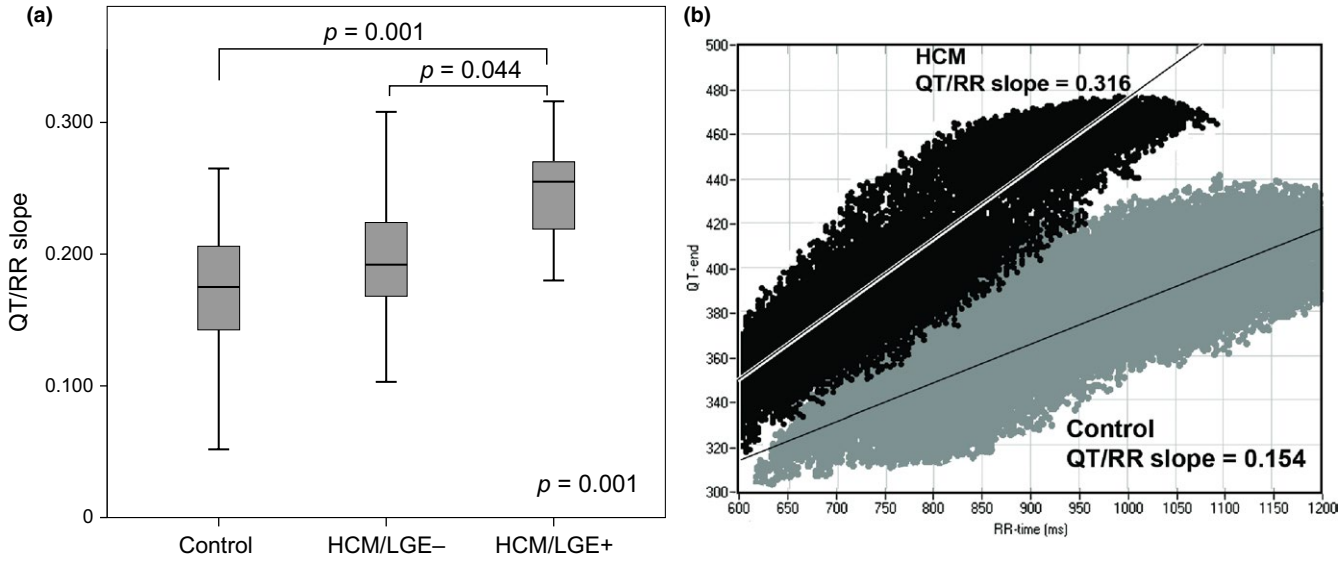

FIGURE 4 (a) Boxplot of QTe/RR slope in the control group and HCM patients with and without late gadolinium enhancement (LGE). (b) Example of a HCM/LGE+ patient with a QTe/RR slope = 0.316 (black) and a control subject with a QTe/RR slope = 0.154 (gray)

TABLE 4 Repolarization measurements in HCM patients with and without late gadolinium enhancement

Repolarization	HCM/LGE− (*n* = 29)	HCM/LGE+ (*n* = 17)	*p*-Value
QTe (ms)	422 ± 46	410 ± 38	0.367
HR-adapted QTe_{1000} (ms)	424 ± 36	431 ± 32	0.545
Maximum QTe_{1000} (ms)	468 ± 43	470 ± 36	0.886
QTe/RR slope	0.199 ± 0.06	0.242 ± 0.06	0.001
QTp (ms)	324 ± 26	322 ± 38	0.856
HR-adapted QTp_{1000} (ms)	324 ± 26	322 ± 38	0.457
Maximum QTp_{1000} (ms)	368 ± 26	374 ± 38	0.578
TPE (ms)	99 ± 73	85 ± 16	0.478
Median TPE_{1000} (ms)	84 ± 18	94 ± 20	0.168
Maximum TPE_{1000} (ms)	106 ± 24	117 ± 37	0.263

Note. Data presented as mean ± *SD*. The subscript 1,000 denotes measurement at 1,000 ms RR interval duration.
HCM: Hypertrophic cardiomyopathy; LGE: late gadolinium enhancement; QTe: Q wave to T-wave end; TPE: T-wave peak to T-wave end.

role in increasing an HCM patient's risk for ventricular arrhythmias through effects on the propagation of the repolarization current in the myocardium resulting in a steeper QTe/RR slope.

In this study, we found the QTe systematically prolonged in HCM patients, although to a lesser degree than in some previous reports. The reason for this may be, that the patients in this study were relatively asymptomatic and had a mean MWT of 20.6 mm on CMRI compared to, for example, a mean MWT of 24.1 mm in HCM patients with a pathological QTc of ≥480 ms (13% of HCM patients) in a study by Johnson et al. (2011). Prolonged QT interval is associated to increased risk for ventricular arrhythmias (Debonnaire et al., 2015) and independently of hypertrophy predicts ICD therapy in HCM (Gray, Ingles, Medi, & Semsarian, 2013). In healthy individuals, the QT interval is dependent on heart rate in a curvilinear fashion. In this study, the heart rate-adapted QTe in HCM patients prolonged with decreasing heart rates compared to control subjects, resulting in an increasing separation of the QTe curves seen in Figure 1a. This phenomenon is not related to the differences in distribution of RR intervals in the studied ambulatory ECGs. The methodology of using stable heart rates also diminishes the effect of sudden changes in RR intervals to the QTe. The measured maximal and heart rate-adapted median QT peak values followed a very similar pattern to the QTe values and did not offer additional information to the established QTe measurements.

The patterns of ventricular repolarization dynamics were similar between male and female patients with a slight trend for longer QTe values in the female HCM and control subjects. On the other hand, the differences in HR-adapted QTe values between HCM and control subjects were larger in men as compared to women at RR intervals 900–1,200 ms (Figure 3). This was not explained by differences in distribution of maximal wall thickness in male and female HCM patients.

Median TPE was significantly longer in HCM patients with MWT > 20.6 mm compared to the control group in this study. Previously, TPE has been found prolonged in HCM but without analysis of the association to structural changes (Shimizu et al., 2002). The TPE interval has been considered a measure of the global dispersion of ventricular repolarization (Gupta et al., 2008; Opthof et al., 2007) and based on our results is more evident with advanced HCM.

In experimental studies, the prolongation of ventricular repolarization in HCM is the result of pathologies on many levels. The action potential is prolonged as the net repolarizing current is diminished by increased late-type Na and Ca^{2+} currents (I_{NaL} and I_{CaL}) and selective down regulation of the outward rectifying current (I_{Kr}) (Coppini et al., 2013; Crocini et al., 2016; Passini et al., 2016). The repolarization in the myocardium is also delayed due to hypertrophy (Badran et al., 2012) and global repolarization is spatially dispersed due to the asymmetric location of hypertrophy (Sakata et al., 2003). The pathophysiological abnormalities in potassium-currents, especially the reduction in I_{Kr}, resemble those found in type 2 LQTS patients and in agreement we found the prolongation of heart rate-adapted QTe and the prolongation of TPE interval mimicking the findings in type 2 LQTS patients (Viitasalo, Oikarinen, Swan et al., 2002; Viitasalo, Oikarinen, Väänänen et al., 2002).

Approximately, 20%–27% of ICD therapies in HCM patients occur during rest (Maron et al., 2009; O'Mahony et al., 2012). The repolarization alterations in this study increased with lower heart rates and may thus have a role in the ventricular arrhythmias occurring during phases of bradycardia in HCM patients.

4.1 | Limitations of the study

The study was limited in sample size resulting in part from the decision to include only carriers of the two founder mutations. Because of the sample size, the possible effect of sex cannot be definitively ruled out in this study. We did not study the effect of location of hypertrophy on ventricular repolarization parameters, as the absolute number of patients with MWT not localized in the septal segments was relatively small. The assessment of LGE was limited due to different acquisition protocols of CMR imaging and therefore the presence of LGE was assessed only visually with a binary scale because no reliable quantification of LGE extent was possible. The echocardiographic evaluation did not include comprehensive measurements of diastolic function. A number of HCM patients were on beta blocker therapy, which was not discontinued for this study. Beta blocking agents affect the heart rate and may have an influence on the QT to the heart rate relationship. In this study, the mean heart rates were similar between the two study groups and there was no difference in QTe values between HCM patients with and without beta blocker therapy.

5 | CONCLUSIONS

The QTe/RR slope is steeper in HCM patients with LGE independently of hypertrophy. The degree of QTe prolongation is associated to MWT. Overall, the heart rate-adapted QTe is prolonged in HCM patients compared to control subjects. The repolarization dynamics in HCM reflect the underlying changes in the myocardium.

ACKNOWLEDGMENTS

The authors would like to thank Sini Weckström, RN, and Satu Nenonen, RN for data collection.

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How to cite this article: Jalanko M, Väänänen H, Tarkiainen M, et al. Fibrosis and wall thickness affect ventricular repolarization dynamics in hypertrophic cardiomyopathy. *Ann Noninvasive Electrocardiol*. 2018;23:e12582. https://doi.org/10.1111/anec.12582