ORIGINAL ARTICLE

The relationship between myocardial fibrosis detected by cardiac magnetic resonance and Tp-e interval, 5-year sudden cardiac death risk score in hypertrophic cardiomyopathy patients

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Abstract

Background: The aim of this study was to investigate the relationship between QT (QTc) interval, Tp-e interval, Tp-e/QTc ratio, 5-year sudden cardiac death (SCD) risk score, and late gadolinium enhancement (LGE) detected by CMR in hypertrophic cardiomyopathy (HCM) patients.

Method: A total of 74 consecutive patients who underwent CMR with HCM diagnosis were included in the study. These patients were divided into two groups according to the presence of LGE on CMR. All patients underwent detailed echocardiography and QTc interval, Tp-e interval, and Tp-e/QTc ratios and 5-year SCD risk scores were calculated. These parameters were compared for two groups.

Results: CMR revealed LGE in 32 (43.2%) of 74 HCM patients. In the group with LGE, significantly higher QTc interval ($p = 0.002$), Tp-e interval ($p < 0.001$), Tp-e/QTc ratio ($p = 0.004$), and 5-year SCD risk score were detected. In addition, QTc interval, Tp-e interval, Tp-e/QTc ratio, maximum wall thickness, left ventricular mass index, 5-year SCD risk score, and cardiac fibrosis index were found to be correlated with various degrees in correlation analysis. Also, Tp-e interval is found to be an independent predictor of LGE detected by CMR in HCM patients ($p = 0.017$, OR [%95 CI] = 1.017 [1.001–1.034]). In addition, the Tp-e interval can detect the LGE with a sensitivity of 64.3% and a specificity of 84.2% at 99.4 ms. ($p < 0.001$, AUC [95% CI] = 0.790 [0.676–0.905]).

Conclusion: The Tp-e interval can be used to optimize SCD risk stratification in HCM patients and determine which patients will benefit from implantable cardioverter-defibrillator (ICD) treatment.

KEYWORDS

cardiac magnetic resonance, hypertrophic cardiomyopathy, late gadolinium enhancement, sudden cardiac death, Tp-e interval

1 | INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiomyopathy. More than 600 mutations associated with sarcomeric genes have been identified which are autosomal dominant and cause the development of the disease (Bos, Towbin, & Ackerman, 2009). The pathophysiology of the disease includes cardiac hypertrophy, disruption in the alignment of myocytes, fibrosis in the interstitial space, and dysplasia of intramyocardial arterioles. The most important clinical course of HCM is sudden cardiac death (SCD) (Gersh et al., 2011). High-risk individuals with risk of SCD are treated with implantable cardioverter-defibrillators (ICD). Currently, clinical studies on HCM are focused on the selection and treatment of high-risk patients. The classical risk factors have low positive predictive values. For these reasons, researches for new markers are ongoing.

Comprehensive examination of cardiac structure and function including severity of dynamic obstruction, mitral valve abnormalities, myocardial ischemia, myocardial fibrosis, and myocardial metabolism can be evaluated with newly developed imaging modalities (Maron, 2010). Cardiac magnetic resonance (CMR) is the most promising imaging modality of HCM research. CMR allows accurate and precise characterization of both ventricular functions, wall thickness, and myocardial tissue characterization. Recently, new perspectives have been developed in HCM by CMR and new markers which show poor prognosis have been found (Kwon et al., 2009; To, Dhillon, & Desai, 2011). CMR is superior to transthoracic echocardiography (TTE) for the determination of endocardial borders and for the evaluation of hypertrophic myocardial segments. CMR is recommended with class I indication in HCM suspected patients whose diagnosis cannot be cleared by echocardiography. CMR is the best method for evaluating myocardial fibrosis which is a poor prognostic factor (O'Hanlon et al., 2010).

Myocardial fibrosis is thought to cause predisposition to arrhythmias in patients with HCM. In fact, there is a proven relationship between late gadolinium enhancement (LGE) and ventricular arrhythmias from 24-hr Holter electrocardiography (ECG) records (Adabag et al., 2008; Fluechter et al., 2010). Abnormalities of myocardial repolarization are also associated with increased ventricular arrhythmia and cardiovascular mortality. The most frequently used indicators of myocardial repolarization are QT and corrected QT (QTc) intervals (Antzelevitch et al., 2007). In some studies, the time between the peak of the T wave and the endpoint (TP-e interval) and the duration of the TP-e time to QTc time can be used as a new marker for the evaluation of ventricular repolarization, and even these markers are found to be more reliable in evaluating ventricular repolarization as they are not affected by heart rate changes (Gupta et al., 2008).

In this study, we aimed to investigate the relationship between LGE in HCM patients and QTc interval, TP-e interval, TP-e/QTc ratio, and 5-year SCD risk score that the European Cardiology Association (ESC) suggested in the latest HCM guideline.

2 | METHODS

2.1 | Study population

Our study has retrospective design and enrolled in a single, tertiary heart center. We evaluated 87 patients with HCM who underwent CMR between January 2016 and September 2018. Diagnosis of HCM, according to the ESC guidelines, was based on the presence of LV wall thickness of at least 15 mm without any other cause that could lead to ventricular hypertrophy (Authors/Task Force members, 2014). The exclusion criteria were prior myocardial infarction ($n = 1$), symptoms suggestive of coronary artery disease ($n = 2$), class IV New York Heart Association (NYHA) functional classification of heart failure ($n = 2$), connective tissue disease ($n = 2$), renal dysfunction defined as an estimated glomerular filtration rate <50 ml/min/1.73 m² ($n = 1$), and infection ($n = 1$). Subjects with a history of alcohol septal ablation ($n = 3$) or septal myectomy ($n = 1$) were not included in the study. After exclusion criteria, 74 patients were included in the study. All patients underwent routine evaluation including medical history, physical examination, 12-lead electrocardiography, Holter electrocardiography, two-dimensional echocardiography, and blood tests. The study was approved by the Ethics Committee (date: October 9 2018; decision no: 2018/37) of Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training Research Hospital. This study was performed in accordance with the requirements of the Declaration of Helsinki.

2.2 | Echocardiography

Transthoracic echocardiographic study was performed using a Vivid S5 3S-RS probe (General Electric Vivid S5; GE Vingmed Ultrasound AS) with a 1.7/3.4 MHz phased-array transducer. All patients underwent clinical TTE according to the recommendations from the European Association of Cardiovascular Imaging (Lang et al., 2015). Those variables included in the risk-stratification model were collected. Maximum left ventricular wall thickness (LVWT) was defined as the greatest thickness using parasternal short-axis plane in 2D echocardiography. Left atrial (LA) diameter was determined by M-mode or 2D echocardiography in the parasternal long-axis plane. The maximum left ventricular outflow tract (LVOT) gradient was determined at rest and with Valsalva provocation using pulsed and continuous wave Doppler from the apical 3- and 5-chamber view. Peak LVOT gradients were determined using the modified Bernoulli equation (pressure gradient = $4v^2$, where v is the peak aortic outflow velocity).

2.3 | Electrocardiography

Twelve-lead ECG was performed at paper speed of 25 mm/s with the patient at rest in supine position. Resting heart rate was then measured from ECG data. All ECG data were scanned and transferred to personal computer and used for x400% magnification with Adobe Photoshop software (Adobe Systems, Inc.). ECG measurements of

QTc and Tp-e intervals were performed by two cardiologists who were blinded to patient data. Subjects with U wave on their ECG were excluded from the study. Average value of three examinations was calculated for each lead. QT interval was measured from beginning of QRS complex to end of T wave and corrected for heart rate, using Bazett's formula ($cQT = QT\sqrt{[R-R \text{ interval}]}$). Tp-e interval was defined as interval from peak of T wave to end of T wave. Measurements of Tp-e interval were performed from precordial leads. Tp-e/QT ratio was calculated from these measurements. The intra- and inter-observer differences for Tp-e interval, QT interval, and cQT were <5%.

2.4 | Holter electrocardiography

Holter electrocardiography analyses were performed using 12-channel recordings obtained from the ambulatory Holter monitors. Ambulatory electrocardiographic recordings (DMS 300-7 Holter Reader; DSM) were obtained for a period of 24 hr in all the patients. Before automatic analysis, the tapes were analyzed using the Holter program (CardioScan 12.0 DM software, DSM). The recordings were evaluated for rhythm, premature atrial contraction (PAC), supraventricular tachycardia (SVT), ventricular extra-systole (VES), paroxysmal atrial fibrillation (PAF), non-sustained and/or sustained ventricular tachycardia (NSVT), and atrioventricular (AV) block with pauses.

2.5 | ESC risk score

ESC risk score was calculated according to the following formulas: Prognostic index = $[0.15939858 \times \text{maximal LVWT (mm)}] - [0.00294271 \times \text{maximal LVWT}^2 \text{ (mm}^2\text{)}] + [0.0259082 \times \text{LA diameter (mm)}] + [0.00446131 \times \text{maximal(rest/Valsalva) LVOT gradient (mm Hg)}] + [0.4583082 \times \text{family history SCD}] + [0.82639195 \times \text{NSVT}] + [0.71650361 \times \text{unexplained syncope}] - [0.01799934 \times \text{age at clinical evaluation (years)}]$ and Probability of SCD at 5 years = $1 - 0.998\exp^{(\text{Prognostic index})}$ (14). A risk of SCD at 5 years < 4% was considered as low, ≥ 4 –<6% as intermediate, and ≥ 6 % as high risk (Authors/Task Force members, 2014).

2.6 | Image acquisition

Images were acquired using 1.5 T scanners (MAGNETON Aera, Siemens) with full myocardial coverage. Balanced steady-state free-precession sequences were used to obtain breath-hold cine images in three long-axis planes, followed by a contiguous stack of short-axis slices from the atrioventricular ring to the apex (Kramer, Barkhausen, Flamm, Kim, & Nagel, 2008). Late enhancement images were acquired ~10 min after the administration of 0.1 mmol/kg intravenous gadolinium contrast agent (gadopentetate dimeglumine/gadobutrol, Bayer) with an inversion recovery-prepared gradient-echo sequence (Simonetti et al., 2001). Inversion times were optimised to null normal myocardium with images acquired in two orthogonal phase-encoding directions to exclude artifact.

2.7 | Image analysis

Images were transferred to a workstation (Leonardo, Siemens Medical Solutions) for analysis. For the functional analysis, commercially available software program, Argus (Siemens Healthcare), were used.

2.8 | CMR data analysis

The endocardial and epicardial borders were traced manually using both software systems and functional analysis was performed.

Using Argus (Siemens Healthcare) Software for each study, the end-diastolic and end-systolic phases were determined. For the detection of each phase, the largest and narrowest diameters of the ventricular cavity at the middle of the ventricle were used. The endocardial and epicardial borders were traced manually in short-axis images in both phases. The borders of the endocardium were traced by using the intensity difference between the chamber when filled with blood and the moderate intensity of the myocardium.

The papillary muscles were included in the LV volumetric analysis. While the epicardial border was being detected, the interventricular septum was included in the LV volume. The most basal slice that was surrounded by at least 50% of the myocardium with filled blood was defined as the basal segment of the left ventricle. This was included in the LV chamber volume. The apex was defined as the last slice with a visible lumen throughout the entire cardiac cycle. The end-systolic volume (ESV), end-diastolic volume (EDV), ejection fraction (EF), and LV myocardial masses were determined according to Simpson's rule. The elapsed time from inputting of the data to obtaining the results was calculated for each patient.

CMR images were reanalyzed and documented using the 17-segment cardiac model recommended by the American Heart Association to improve standardization of the results. The left ventricle was evaluated from the short-axis images from basal, mid, and apical segments. The basal and mid-cavity were divided into six equal segments: anterior, anteroseptal, inferoseptal, inferior, inferolateral, and anterolateral. The apical segment was divided into four segments: anterior, septal, inferior, and lateral. The apical cap was termed the apex and constituted the 17th segment. The contrast-enhanced images were analyzed visually by two experienced observers who were blinded to other MRI, echocardiographic, and clinical data. Late gadolinium enhancement was rated by visual assessment, and each segment was graded on a 2-point scale (segmental fibrosis score; 0 = absence of late gadolinium enhancement and 1 = presence of late gadolinium enhancement), using the method of Kaandorp et al because of the frequency of linear and patchy enhancement in patients with NDCM. A cardiac fibrosis index was calculated as $17 / (17 - \text{sum of fibrotic segments})$.

2.9 | Statistics

Statistical analysis of the study was performed with SPSS Version 24.0 program (SPSS Inc.). If the variables show normal distribution;

visual (histograms, probability curves) and analytical methods (Kolmogorov–Smirnov and Shapiro–Wilk) were evaluated. Numerical variables showing normal distribution were mean $\pm$ standard deviation (SD), and numerical variables not showing normal distribution were expressed as median (minimum - maximum) and categorical variables as percentage (%). Statistical analysis of numerical variables such as inter-group Tp-e interval and 5-year SCD risk score were analyzed by Student *t* test or Mann–Whitney *U* test and categorical variables were analyzed by chi-square or Fisher exact test. The correlation between Tp-e interval, QTc interval, and Tp-e/QTc ratio among the other numerical variables was evaluated by Pearson or Spearman analysis. Logistic regression analysis was used to

determine if Tp-e interval is an independent predictor of myocardial fibrosis. In order to determine the threshold value, ROC curve is used and the area below the ROC curve is above 0.5 and *p* value < 0.05 is considered statistically significant.

3 | RESULTS

The mean age of 74 HCM patients included in our study was 51.2 ± 11.9 . A total of 47 patients (63.5%) were male, and 27 patients (36.5%) were female. We divided our patients into two groups according to the presence of LGE in CMR. LGE was detected in 32

N = 74	HCM without LGE (n = 42)	HCM with LGE (n = 32)	p-value
Age, years	51.98 $\pm$ 11.69	50.22 $\pm$ 12.36	0.534
Male, n (%)	26 (61.9%)	21 (65.6%)	0.742
Body mass index, kg/m ²	29.92 $\pm$ 4.55	30.11 $\pm$ 5.08	0.866
Diabetes mellitus, n (%)	10 (24.4%)	3 (9.4%)	0.096
Hypertension, n (%)	17 (41.5%)	14 (43.8%)	0.845
Coronary artery disease, n (%)	4 (9.8%)	8 (25%)	0.081
Hyperlipidemia, n (%)	7 (17.1%)	6 (18.8%)	0.853
Systolic blood pressure, mm Hg	133.7 $\pm$ 15.0	133.1 $\pm$ 12.9	0.843
Diastolic blood pressure, mm Hg	77.3 $\pm$ 10.5	78.4 $\pm$ 9.8	0.661
Max HR, bpm	113.3 $\pm$ 18.6	115.6 $\pm$ 15.8	0.651
Min HR, bpm	53.7 $\pm$ 8.6	52.3 $\pm$ 8.7	0.570
Mean HR, bpm	69.9 $\pm$ 10.1	71.2 $\pm$ 11.2	0.666
Atrial Fibrillation, n (%)	3 (9.1%)	3 (11.1%)	1.0
NYHA class I, n (%)	23 (54.8%)	12 (37.5%)	0.141
NYHA class II, n (%)	13 (31.0%)	10 (31.3%)	0.978
NYHA class III, n (%)	6 (14.3%)	10 (31.3%)	0.079
Hemoglobin, g/dl	13.55 $\pm$ 2.05	13.91 $\pm$ 1.97	0.465
White blood cells, 10 ³ /μl	7.72 $\pm$ 1.72	8.42 $\pm$ 2.15	0.133
Neutrophil, 10 ³ /μl	4.50 $\pm$ 1.51	5.11 $\pm$ 1.88	0.139
Lymphocyte, 10 ³ /μl	2.24 (1.25–4.70)	2.37 (1.69–4.10)	0.943
Neutrophil/Lymphocyte	1.86 $\pm$ 0.79	2.07 $\pm$ 0.68	0.252
Monocyte, 10 ³ /μl	0.65 $\pm$ 0.20	0.69 $\pm$ 0.19	0.453
Creatinine, mg/dl	0.82 (0.52–1.38)	0.88 (0.60–1.30)	0.461
Glomerular filtration rate, ml/dl	93 (49–122)	97 (51–119)	0.646
Beta blockers, n (%)	35 (85.4%)	30 (93.8%)	0.453
Calcium channel blockers, n (%)	4 (9.8%)	3 (9.4%)	1.0
ACEi or ARB, n (%)	4 (9.8%)	8 (25%)	0.081

TABLE 1 Baseline demographic, clinical, and laboratory characteristics of the study groups

Note: Data are presented as percentage, mean $\pm$ SD, or median (min-max).

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; Max HR, maximum heart rate; Min HR, minimum heart rate; NYHA, New York Heart Association.

(43.2%) patients. Table 1 shows basal demographic characteristics and laboratory values of two groups. There were no significant differences between two groups in terms of demographic characteristics and laboratory values.

In Table 2, two groups were compared for the parameters used to calculate the 5-year SCD risk score. The variables such as age, syncope history, and family history of sudden cardiac death did not show significant difference between two groups, and the maximum LVWT ($p = 0.005$), LA diameter ($p = 0.019$), maximum LVOT gradient ($p = 0.009$), 24-hr ambulatory ECG at NSVT ($p = 0.037$) were significantly higher in LGE group. The 5-year SCD risk score was also significantly higher in the group with LGE ($p < 0.001$).

Table 3 shows the comparison of ECG parameters and CMR variables for two groups. QTc, Tp-e interval, and Tp-e/QTc ratio, which are reflections of repolarization on ECG, were significantly higher in LGE group. LV mass index was also found to be higher in the LGE group with borderline level of significance.

The correlation of QTc, Tp-e interval, and Tp-e/QTc ratio with other variables are shown in Table 4. All three parameters were significantly correlated with maximum LVWT, LV mass index, 5-year SCD risk score, and cardiac fibrosis index. QTc and Tp-e interval were found to be significantly correlated ($r = 0.445$, $p < 0.001$).

First, univariate logistic regression analysis was performed to determine the variables predicting LGE in CMR (Table 5). Maximal LVWT ($p = 0.009$), LA diameter ($p = 0.024$), presence of NSVT in a 24-hr ambulatory ECG ($p = 0.045$), 5-year SCD risk score (0.006), QTc interval ($p = 0.004$), Tp-e interval ($p < 0.001$), and

LV mass index ($p = 0.037$) reached significance level. Using these variables, two separate models were formed and multivariate regression analysis was performed. QTc interval and Tp-e interval were not included in the first model with other variables and in second model while Tp-e interval was included, QTc was excluded. Moreover, the 5-year SCD risk score was not used in both models because it included other variables (Table 6). In the first model, all variables including QTc interval ($p = 0.269$) lost their significance, while in the second model the other variables lost significance, while the Tp-e interval [$p = 0.017$, OR (95% CI) = 1.017 (1.001–1.034)] was the only variable with the significance level. The Tp-e interval was found to be an independent predictor of LGE detected by CMR in HCM patients. Figure 1 shows the receiver operator characteristic (ROC) curve of the Tp-e interval for the presence of LGE on CMR. The Tp-e interval can detect LGE with a sensitivity of 64.3% and a specificity of 84.2% at 99.4 ms [$p < 0.001$, AUC (95% CI) = 0.790 (0.676–0.905)]. Also, patients with Tp-e > 99.4 ms were significantly higher in LGE group (%69 vs. %23.7, $p < 0.001$). On the other hand, when the patients were divided into two groups according to this predictive value, the 5-year SCD risk score was significantly higher in the group with

TABLE 2 Comparison of study groups in terms of the parameters used to calculate the 5-year SCD risk score

N = 74	HCM without LGE (n = 42)	HCM with LGE (n = 32)	p-value
Age, years	51.98 ± 11.69	50.22 ± 12.36	0.534
Maximal LVWT, mm	20.49 ± 3.86	23.05 ± 3.71	0.005
Left atrial diameter, mm	40.95 ± 5.22	44.16 ± 6.27	0.019
LVOT gradient, mm Hg	15 (8–105)	18 (10–100)	0.009
Syncopal history, n (%)	1 (2.4%)	4 (12.5%)	0.159
History of family SCD, n (%)	1 (2.4%)	4 (12.5%)	0.159
NSVT, n (%)	4 (9.5%)	9 (28.1%)	0.037
HCM Risk-SCD, %	1.75 (1.18–7.19)	2.87 (1.38–17.21)	<0.001

Note: Data are presented as percentage, mean ± SD or median (min–max).

Abbreviations: HCM, Risk-SCD: predicted risk score of sudden cardiac death at five years; HCM: hypertrophic cardiomyopathy; LGE: late gadolinium enhancement; LVOT: left ventricular outflow tract; LVWT: left ventricular wall thickness; NSVT: non-sustained ventricular tachycardia; SCD: sudden cardiac death.

Bold character shows statistically significant values.

TABLE 3 Comparison of study groups in terms of some parameters calculated from CMR and ECG

N = 74	HCM without LGE (n = 42)	HCM with LGE (n = 32)	p-value
QRS duration, ms	93.16 ± 15.52	101.50 ± 21.97	0.075
PR duration, ms	155.9 ± 21.7	152.2 ± 24.3	0.537
QTc interval, ms	429.9 ± 29.0	455.0 ± 37.5	0.002
Tp-e interval, ms	84.2 ± 16.8	103.8 ± 17.6	<0.001
Tp-e/QTc ratio	0.196 ± 0.04	0.224 ± 0.04	0.004
LVEF, %	65.7 ± 3.2	64.9 ± 3.1	0.274
LVEDV index, ml/m ²	71.67 ± 21.76	64.21 ± 17.56	0.137
LVESV index, ml/m ²	21.04 ± 13.02	20.30 ± 8.11	0.405
LV mass index, g/m ²	77.9 (38.7–186.0)	99.1 (52.0–188.3)	0.026
Number of LV segments with LGE		3.13 ± 1.58	
Cardiac fibrosis index		1.24 ± 0.16	

Note: Data are presented as percentage, mean ± SD or median (min–max).

Abbreviations: HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume.

Bold character shows statistically significant values.

	QTc interval		Tp-e interval		Tp-e/QTc ratio	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Maximal LVWT	0.472	<0.001	0.475	<0.001	0.342	0.005
LVOT gradient	0.117	0.320	0.189	0.128	0.081	0.516
Left atrial diameter	0.231	0.048	0.152	0.222	0.073	0.562
LVEDV index	0.001	1.0	0.049	0.714	0.089	0.504
LVESV index	-0.037	0.778	0.070	0.619	0.135	0.342
LV mass index	0.491	<0.001	0.471	<0.001	0.316	0.019
HCM Risk-SCD	0.427	<0.001	0.432	<0.001	0.279	0.023
Cardiac fibrosis index	0.353	0.002	0.498	<0.001	0.351	0.004
Tp-e interval	0.445	<0.001				
QTc interval			0.445	<0.001		

Abbreviations: HCM Risk-SCD, predicted risk score of sudden cardiac death at five years; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVOT, left ventricular outflow tract; LVWT, left ventricular wall thickness. Bold character shows statistically significant values.

TABLE 5 Univariate regression analysis to determine the predictability of LGE in HCM patients

	Univariate analysis	
	OR (95% CI)	<i>p</i>
Age	0.988 (0.950–1.027)	0.529
Maximal wall thickness	1.196 (1.046–1.368)	0.009
Left atrial diameter	1.104 (1.013–1.204)	0.024
LVOTgradient	1.016 (0.998–1.035)	0.084
Syncopal history	5.857 (0.621–55.204)	0.123
History of family SCD	5.857 (0.621–55.204)	0.123
NSVT	3.717 (1.027–13.458)	0.045
HCM risk-SCD	1.521 (1.125–2.055)	0.006
QRS duration	1.025 (0.996–1.055)	0.087
PR duration	0.993 (0.970–1.016)	0.530
QTc interval	1.024 (1.007–1.040)	0.004
Tp-e interval	1.067 (1.031–1.105)	<0.001
LVEF	0.957 (0.909–1.008)	0.099
LVEDV index	0.979 (0.952–1.007)	0.144
LVESV index	0.994 (0.948–1.042)	0.797
LV mass index	1.017 (1.001–1.034)	0.037

Abbreviations: CI, confidence interval; HCM Risk-SCD, predicted risk score of sudden cardiac death at five years; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVOT, left ventricular outflow tract; NSVT, non-sustained ventricular tachycardia; OR, odds ratio; SCD, sudden cardiac death. Bold character shows statistically significant values.

Tp-e > 99.4ms than the Tp-e < 99.4ms group ($p = 0.004$). For the other analysis, we divided the patients into two groups according to the 5-year SCD risk score. Group with 5-year SCD risk score

TABLE 4 Correlation analysis of QTc, Tp-e interval and Tp-e /QTc ratio with other variables

less than %4 was low-risk patients group and 5-year SCD risk score more than %4 was moderate- and high-risk patient group. In moderate- and high-risk group, patients with Tp-e > 99.4 ms (%71.4 vs. %35.8, $p = 0.017$) and LGE (%66.7 vs. %37.3, $p = 0.040$) were significantly higher than low-risk group.

4 | DISCUSSION

In this study, we found significantly higher QTc interval, Tp-e interval, and Tp-e/QTc ratio in HCM patients with LGE on CMR. In addition, the 5-year SCD risk score was significantly higher in group with LGE. In addition, QTc interval, Tp-e interval, Tp-e/QTc ratio, maximum LVWT, LV mass index, 5-year SCD risk score, and cardiac fibrosis index were found to be significantly correlated in various correlations. Additionally, Tp-e interval was found to be an independent predictor of LGE detected by CMR in HCM patients.

Upon ESC guidelines patient's age ($p = 0.007$), LVST ($p < 0.001$), LVOT gradient ($p = 0.005$), LA diameter ($p < 0.001$), family history of sudden death ($p < 0.001$), NSVT attack ($p < 0.001$), and unexplained syncope ($p < 0.001$) emerged as significant factors determining SCD (O'mahony et al., 2013). With the 5-year SCD risk score calculated using these data, it can roughly evaluate the indication of ICD in HCM patients. However, in a study published immediately after this study, it has been suggested that these criteria are not predictive of sudden death (Maron et al., 2015). In this study, 1629 patients older than sixteen were evaluated retrospectively according to these criteria. According to the correct shock in patients with ICD, low-risk cases according to the ESC risk classification were not actually low risk, and significant amount of patients mentioned with high risk are actually with low risk. This situation forces researchers to find new markers. Myocyte heavy chain gene mutations in HCM patients

TABLE 6 Multivariate regression analysis to determine the independent predictor of LGE in HCM patients

	Multivariate analysis			
	QTc interval		Tp-e interval	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Maximal wall thickness	1.114 (0.939–1.323)	0.216	1.066 (0.867–1.311)	0.544
Left atrial diameter	1.088 (0.977–1.211)	0.125	1.100 (0.967–1.252)	0.149
NSVT	1.168 (0.229–5.967)	0.852	2.168 (0.361–13.019)	0.398
LV mass index	1.001 (0.980–1.022)	0.939	0.998 (0.975–1.021)	0.834
QTc–Tp-e	1.012 (0.991–1.032)	0.269	1.047 (1.008–1.086)	0.017

Abbreviations: CI, confidence interval; LV, left ventricle; NSVT, non-sustained ventricular tachycardia; OR, odds ratio.

Bold character shows statistically significant values.

disrupt the sarcomere structure, alter myocyte calcium signal, and thus lead to deterioration of cardiac relaxation (Maron et al., 2008; Rubinshtein et al., 2010). Hypertrophy is an incompatible mechanism against relaxation distortion. There are studies suggesting that reactive oxygen species resulting from hypertrophy, restricted coronary circulation, microvascular dysfunction, increased metabolic need, and abnormal physiology of the mutant sarcomere cause myocardial fibrosis (Bruder et al., 2010; O'Hanlon et al., 2010). Several recent studies have shown that myocardial fibrosis detected by LGE on CMR is associated with sudden cardiac death and cardiovascular events (Dobaczewski, Chen, & Frangogiannis, 2011; Dobaczewski et al., 2011; Teekakirikul et al., 2010). In some prospective studies, LGE was found to be more common in HCM patients who developed SCD or had appropriate ICD shock (Bruder et al., 2010). In a study conducted by Chan et al., which included a thousand three hundred cases, it was striking that LGE involvement in MRI showed doubling of sudden death, especially in asymptomatic and relatively young people (O'Hanlon et al., 2010). A meta-analysis of more than 3,000 patients with fibrosis more than %15 in myocardium doubled the risk of sudden death even if you ignore all other parameters (Weng et al., 2016). Also, the risk of development of heart failure is also directly related to the amount of fibrosis tissue (Maron & Maron, 2016). All of these studies suggest that the presence and amount of myocardial fibrosis in detecting HCM patients with high risk of SCD, although the current guidelines do not recommend ICD implantation, cannot be ruled out. In our study, the 5-year SCD risk score was significantly higher in the group with myocardial fibrosis to support this idea than the non-fibrosis group.

The electrocardiogram is commonly used for predicting arrhythmogenic risk in clinical practice. Now, the Tp-e interval and Tp-e/QTc ratio have been proposed as markers for predicting malignant ventricular arrhythmias and have been evaluated and recommended as alternatives for risk stratification of SCD in patients with several medical conditions (Castro-Torres, Robau, & Clara-Cuba, 2017).

FIGURE 1 Tp-e interval for the presence of LGE in CMR ROC curve; AUC, area under curves; CI, confidence interval; ROC, receiver operator characteristic

The duration of action potential is longer in middle myocardial M cells than in other myocytes. Repolarization begins at the earliest epicardial cells. While epicardial action potential is represented by T-wave peak, the end of the middle myocardial action potential is represented by the end of the T wave in ECG. Thus, the TP-e interval is indicative of transmural depolarization (İlgenli, Tokatlı, Akpınar, & Kılıçaslan, 2015; Yan & Antzelevitch, 1998). The prolongation of TP-e interval was previously demonstrated in patients with HCM patients with Brugada syndrome, long QT syndrome, percutaneous coronary intervention, and patients with obstructive sleep apnea (İlgenli et al., 2015; Kılıçaslan et al., 2012; Shimizu et al., 2002;

Sicouri & Antzelevitch, 1991; Yan & Antzelevitch, 1998). In addition, prolongation of TP-e interval was associated with SCD (Panikkath et al., 2011).

In Akboga et al study, Tp-e interval and Tp-e/QTc ratio were significantly longer and higher in HCM patients than healthy subjects. Furthermore, in patients with ventricular arrhythmic event (VAE) in the HCM group, the Tp-e interval and Tp-e/QTc ratio were significantly higher than patients without VAE and there was a positive correlation with the maximum LVWT and Tp-e interval and Tp-e/QTc ratio. In addition, multivariate analysis revealed that these markers were associated with a higher risk of VAE (respectively, OR: 1.060; % 95 CI: 1.005–1.117; $p = 0.012$ and OR: 1.148; % 95 CI: 1.086–1.204; $p = 0.049$) (Akboğa et al., 2017). In Shimizu et al. study with 47 HCM patients, they found higher Tp-e intervals compared to patients without SCD and VT. They also found that Tp-e interval is a more valuable parameter than QTc interval and QT dispersion in detecting SCD and VT (Shimizu et al., 2002). In our study, we showed that Tp-e interval was more valuable than QTc interval and Tp-e/QTc ratio in detecting HCM patients with LGE.

In a recent study published in patients with HCM with LGE ($n = 17$), the Tp-e interval was found to be higher than in patients without LGE ($n = 29$), but not statistically significant (Jalanko et al., 2018). In our study, we found a significantly higher Tp-e interval in the group with LGE. We also found the Tp-e interval to be the only independent variable in detecting LGE in HCM patients. In addition, we determined that LGE could be detected with a sensitivity of 64.3% and a specificity of 84.2% with a Tp-e interval of 99.4 ms.

ICD implantation is the most vital treatment step in HCM patients. Which patients will benefit from this treatment remains a current problem. In our study, the relationship between the presence of myocardial fibrosis detected by CMR and repolarization indicators determined by ECG with the 5-year SCD risk score proposed by ESC was investigated. To the best of our knowledge, our study is the first one which co-evaluated these three parameters. As a result of our study these parameters, especially the Tp-e interval calculated from the ECG which is easy to reach and interpret, can be optimized for the risk stratification of SCD.

4.1 | Limitations of the study

This study has some limitations. First of all, this study was performed in a single center and included relatively small group and designed retrospectively. Second, healthy control group was not included in the study. Third, we do not have clinical follow-up data. On the other hand, some studies have reported poor inter- and intraobserver reproducibility of manual measurements of the QT intervals (Coumel, Maison-Blanche, & Badilini, 1998; Kautzner, Yi, Camm, & Malik, 1994; Macfarlane, 1998). This shortfall applies to the measurement of the Tp-e as well. In addition, there has been some confusion as to how to measure these parameters with different configurations of the T wave. This has been clarified in recent experimental studies

(Emori & Antzelevitch, 2001), and we applied these methods in our measurements.

5 | CONCLUSION

In our study, we found a higher 5-year SCD risk score and Tp-e interval in HCM patients with myocardial fibrosis with CMR. The Tp-e interval was the only independent variable predicting myocardial fibrosis. The Tp-e interval may be the answer to the question of which patients should be implanted with ICD as one of the most current problems in the treatment of HCM patients. Of course, we are aware that a larger population of prospective, randomized studies are needed to support this view.

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