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Myocardial Repolarization Dispersion and Late Gadolinium Enhancement in Patients With Hypertrophic Cardiomyopathy

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Background: Growing evidence suggests that late gadolinium enhancement (LGE) at cardiac magnetic resonance (CMR) is an additive marker of disease severity, and possibly of arrhythmic risk, in hypertrophic cardiomyopathy (HCM). We investigated the possible relationship between LGE and markers of myocardial repolarization dispersion in HCM.

Methods and Results: Eighty-five HCM outpatients underwent CMR and short-period electrocardiogram analysis to calculate the temporal myocardial repolarization dispersion through the QT variance normalized for QT mean (QTVN) and the QT variability index (QTVI). The QT dispersion in the spatial domain was also obtained. Patients with LGE (62%) had higher left atrial volume, maximum wall thickness, and left ventricular mass (P<0.0001), as well as a greater prevalence of non-sustained ventricular tachycardia (P<0.0001) and hypotensive blood pressure response (P=0.044). Both QTVN and QTVI were higher in the group with LGE (P<0.0001). At multivariate analysis, using QTVI as the dependent variable, %LGE (P<0.0001), age (P<0.0001), left ventricular outflow obstruction (P=0.038), and sudden cardiac death risk factor burden (P=0.020) reached statistical significance. Otherwise, only %LGE (P=0.005) and left ventricular mass index (P=0.015) remained associated with QTVN.

Conclusions: Temporal myocardial repolarization dispersion correlates with LGE extent. Whether these variables could be useful in HCM clinical management warrants confirmation by larger prospective studies. (*Circ J* 2014; **78:** 1216–1223)

Key Words: Cardiac magnetic resonance imaging; Hypertrophic cardiomyopathy; QT variability; Ventricular arrhythmia

Hypertrophic cardiomyopathy (HCM), the most common inherited heart disease, still represents one of the leading cause of sudden cardiac death (SCD) in young people and athletes.[1,2] Indeed, despite a number of useful clinical variables currently adopted,[2–4] further improvement in risk stratification in this specific patient setting remains challenging.[2,5–7]

In HCM, as well as in many other cardiomyopathies, most malignant ventricular arrhythmias are thought to emanate from regions of structurally abnormal myocardium.[8–10] Given that myocardial fibrosis represents an important underlying arrhythmogenic substrate in HCM, there has been growing interest in investigating a possible association between arrhythmic risk and late gadolinium enhancement (LGE) at contrast-enhanced cardiac magnetic resonance (CMR). Indeed, the ability of LGE to detect, non-invasively, the presence of myocardial fibrosis is well known,[11] and several investigations have already reported a significant relationship between this radiological feature and the occurrence of ventricular arrhythmias in HCM patients.[7,11–13] The usefulness of LGE as a marker of disease severity and, specifically, of arrhythmic risk, however still remains as a matter for debate.[14,15] In this context, a somewhat unexplored but

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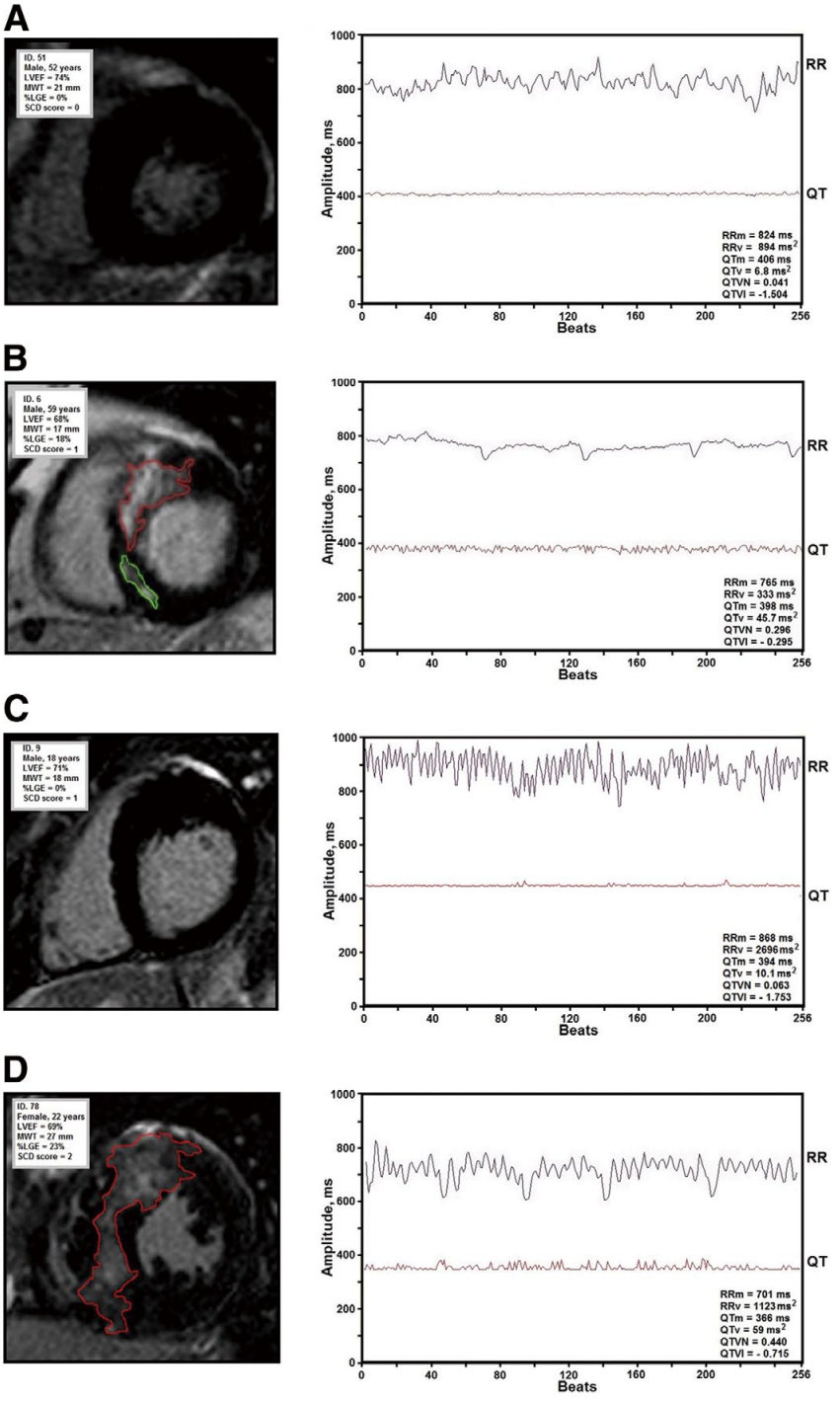

Figure 1. (**Right**) Representative short-term beat-to-beat RR and QT electrocardiogram recordings coupled with (**Left**) cardiac magnetic resonance imaging in (**A**,**B**) 2 middle-aged and (**C**,**D**) 2 young HCM patients. (**A**) Man, 52 years old, without risk factor for sudden cardiac death (SCD) and no late gadolinium enhancement (LGE). Both QT variance normalized for QT mean (QTVN) and QT variability index (QTVI) appeared normal due to a good RR variability (high RR variance, RR_V) and QT variability (low QT variance, QT_V). (**B**) Man, 59 years old, with 1 SCD risk factor (recent unexplained syncope) and a large percentage of LGE. Both QTVN and QTVI were significantly worse than those in (**A**) due to lower RR_V and higher QT_V. (**C**) Man, 18 years old, with 1 SCD risk factor (hypotensive blood pressure response during exercise test) and without LGE. RR_V and QT_V were normal, leading to normal QTVN and QTVI. (**D**) Woman, 22 years old, with 2 SCD risk factors (nonsustained ventricular tachycardia and hypotensive blood pressure response during exercise test) and diffuse LGE. Both QTVN and QTVI appeared significantly worse than those in (**C**). LVEF, left ventricular ejection fraction; MWT, maximum wall thickness.

intriguing aspect is represented by the relationship of LGE to temporal myocardial repolarization dispersion markers, predictors of arrhythmic risk in cardiovascular[16–20] and non-cardiovascular disease.[21–23] Specifically, to our knowledge no study has investigated the behavior of the QT variance indexed for the QT mean (QTVN) and the QT variability index (QTVI) in HCM patients and its possible link to LGE presence and extent.

Therefore, the present study analyzed the possible relationships between some markers of spatial and temporal myocardial repolarization dispersion and CMR-derived data in a selected cohort of HCM outpatients, mainly focusing on the LGE presence and extent. Moreover, all aforementioned experimental variables were challenged with standard clinical and instrumental data widely accepted as predictors of poor outcome and, overall, of arrhythmia risk in HCM.

Methods

Subjects

We evaluated 108 consecutive outpatients diagnosed with HCM

who were referred to the HCM Center of Sant'Andrea Hospital, "Sapienza" University of Rome, between January and April 2013. The diagnosis of HCM was derived from 2-D echocardiographic demonstration of hypertrophied, non-dilated left ventricle (LV) in the absence of any other cardiac or systemic disease capable of producing a similar magnitude of wall thickening.[2] Left ventricular outflow tract (LVOT) obstruction was considered present when the peak instantaneous outflow gradient estimated on continuous-wave Doppler was ≥30 mmHg under baseline conditions.[2,24]

Patients with a history of septal myectomy were a priori excluded from the current analysis, as well as those patients who were receiving any anti-arrhythmic therapy. Other exclusion criteria were: history and/or clinical documentation of significant comorbidity, such as known coronary artery disease, pulmonary embolism or valvular heart disease, pericardial disease, primary pulmonary hypertension, moderate–severe renal failure (serum creatinine >2 mg/dl), moderate–severe anemia (hemoglobin <11 g/dl), and severe obstructive lung disease. All patients with complete left bundle branch block, atrial fibrillation, pacemaker-dependent atrial rhythm, frequent extrasystoles (1 extrasystole/min was permitted) or other arrhythmias likely to interfere with assessment were also excluded.

Each HCM patient who fulfilled the initial inclusion criteria underwent complete clinical assessment, including New York Heart Association (NYHA) classification, systemic blood pressure measurement, CMR, standard 12-lead surface electrocardiogram (ECG) at 25 mm/s, and conventional Doppler echocardiography. Furthermore, SCD risk stratification was performed according to the established risk factors:[2,4] (1) history of HCM-related SCD in at least 1 first-degree relative or other relative younger than 50 years old; (2) massive LV hypertrophy (LVH; maximum wall thickness ≥30 mm); (3) at least 1 run of non-sustained ventricular tachycardia on 24-h Holter ECG monitoring; (4) unexplained syncope judged inconsistent with neurocardiogenic origin; and (5) hypotensive blood pressure response to exercise test. A variable was obtained by adding 1 point for each of the aforementioned SCD risk factors (SCD risk factor burden, from 0 to 5). With the exception of CMR, all sessions of the present research protocol were performed with HCM patients off β-blocker and/or calcium channel blocker treatment for at least 72 h.

All participants gave informed written consent and the study was approved by the internal review board of the S. Andrea Hospital – "Sapienza" University of Rome. The authors had full access to and took full responsibility for data integrity.

RR and QT Interval Data Analysis

After a 15-min rest in the supine position, each HCM patient underwent a 15-min simultaneous recording of a single ECG lead and respiratory rate (strain-gauge belt). During the last 5 min of this recording, subjects were required to breathe at 15 breaths/min (0.25 Hz) in time with a metronome. The 2 analog signals (ECG and respiratory rate) were acquired simultaneously and digitally converted with a custom-designed card (Keithley Metrabyte – DAS 1200 Series; Keithley Instruments, Munich, Germany) at a sampling frequency of 500 Hz per channel. All digitalized ECG recordings were analyzed by a single physician (D.M.) blind to patient clinical features. Software for data acquisition, storage, and analysis were designed and produced by our research group and are described in detail elsewhere.[19–22,24,25]

To calculate the RR and QT intervals and to make the end of the T wave easier to identify, we used software that our laboratory developed based on the algorithm for quantification of beat-to-beat fluctuations in QT interval variability proposed by Berger et al.[26] To avoid probable confounding from the influence of respiration on RR interval and QT variables,[24,25] we analyzed RR and QT intervals only from the last 5-min beat segments recorded during the controlled breathing. QT and RR mean (QT_m and RR_m), as well as their variances (QT_v and RR_v), were automatically calculated in order to obtain QT_v normalized for QT_m (QTVN) and QTVI according to the following 2 standard formulas (Figure 1):[17,26] $QTVN=\log_{10}(QT_v)/(QT_m)^2$; $QTVI=\log_{10}\{[(QT_v)/(QT_m)^2]/[(RR_v)/(RR_m)^2]\}$.

Last, a standard 12-lead surface ECG at 50 mm/s was used to manually measure the QT interval length in every lead with a digital caliper. In accordance with previously published work, a single physician (F.M.C.), blinded to patient characteristics, measured the QT interval from the onset of the QRS complex to the end of the T wave and, when the latter was unclear, the QT interval was defined as the intersection of the isoelectric baseline and the maximum tangent line of the T-wave terminal limb.[22,27,28] To minimize the possible confounder of different heart rates, the corrected QT interval (QTc) was also obtained according to Bazett's classic formula ($QT/RR^{0.5}$). Thereafter the maximum and the minimum QT and QTc were determined, defining their difference as QT dispersion (QTd) and QTc dispersion (QTcd), respectively. A minimum of 8 leads was required for these two markers of spatial myocardial repolarization.

CMR

All HCM patients underwent CMR with a 1.5-T MRI scanner (Sonata and Avanto; Siemens Healthcare, Erlangen, Germany) within 6 months of enrollment in the study (111±53 days). CMR was performed using steady-state, free-precession breath-hold cines in 3 long-axis planes and sequential short-axis slices from atrioventricular ring to apex. LGE images were acquired 10–20 min after i.v. injection of 0.1 mmol/kg gadolinium (Gadovist; Bayer Schering Pharma, Berlin, Germany) with breath-hold 2-D segmented inversion-recovery turbo-FLASH sequence (TR, 8 ms; TE, 4 ms; T1, 250–320 ms; slice thickness, 8 mm).[29] Inversion time was optimized to null normal myocardial signal. In case of uncertainty or artifacts, LGE sequences were acquired twice using 2 different phase-encoding directions. A 90° presaturation pulse was also placed along the phase-encoding direction to avoid ghosting artifacts.

CMR data were transferred to a dedicated workstation and 2 experienced cardiovascular radiologists (C.N.D.C. and G.M.) analyzed the images in consensus, blinded to clinical parameters. LV volumes, ejection fraction, and mass were measured using a standard volumetric technique and analyzed with commercially available software (Syngo; Siemens Healthcare, Germany). LV epicardial and endocardial borders on cine images were manually planimetered to define the myocardium, taking care to exclude papillary muscles.

The LV short-axis stack of LGE images was initially assessed visually for the presence of LGE according to the American Heart Association 17-segment model. Subsequently, LGE quantification was performed by 1 expert reader (G.M.) on all LGE-positive scans using commercial available software (Syngo, Siemens Healthcare). Signal intensity ≥6 SD from the mean of normal myocardium was used to define LGE areas, which were manually traced on all short-axis slices, from base to apex, in the end-diastolic phase (Figure 1).[13] Small LGE areas (total LGE volume <1 g) located in the right ventricular and LV hingepoint in the absence of other LGE were not considered for the analysis, because they do not necessarily represent fibrosis and they are also frequently found in healthy sub-

Table 1. Subject Characteristics vs. Presence of LGE

	HCM without LGE (n=32)	HCM with LGE (n=53)	P-value
General characteristics			
Age (years)	45±17	47±15	NS
Male	18 (56)	34 (64)	NS
Body surface area (g/m^2)	1.9±0.2	1.9±0.2	NS
NYHA class I	17 (53)	24 (47)	NS
NYHA class II	14 (44)	26 (49)	Ns
NYHA class III	1 (3)	2 (4)	NS
LVOTO	8 (25)	14 (27)	NS
Systolic BP (mmHg)	125±13	126±15	NS
Diastolic BP (mmHg)	76±9	76±10	NS
HR (beats/min)	65±16	70±13	NS
QRS (ms)	86±14	91±18	NS
QTc (ms)	406±19	431±28	NS
QTd (ms)	48±26	59±27	NS
QTcd (ms)	50±27	62±27	0.053
SCD risk factors,			
Non-sustained VT	5 (16)	28 (53)	0.000
SCD family history	3 (9)	5 (9)	NS
Massive LVH	1 (3)	9 (17)	NS
Unexplained syncope	1 (3)	1 (2)	NS
Hypotensive blood pressure response	2 (6)	7 (13)	0.041
SCD risk factors burden (n)	0.38±0.71	0.94±0.82	0.001
Comorbidity			
Systemic hypertension	5 (16)	11 (21)	NS
Dyslipidemia	5 (16)	8 (15)	NS
Diabetes	2 (6)	2 (4)	NS
Drugs			
ACEI/ARBs	13 (41)	22 (43)	NS
β-blockers	21 (66)	40 (75)	NS
CCB	3 (9)	4 (9)	NS
Diuretics	2 (6)	9 (17)	NS

Data given as mean ± SD or n (%).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCL, calcium channel blocker; HCM, hypertrophic cardiomyopathy; HR, heart rate; LGE, late gadolinium enhancement; LVH, left ventricular hypertrophy; LVOTO, left ventricular outflow tract obstruction; NYHA, New York Heart Association; QTc, QT interval corrected; QTd, QT interval dispersion; SCD, sudden cardiac death; VT, ventricular tachycardia.

jects.[30] Summation of the planimetered areas yielded the total volume of LGE (g), also expressed as a proportion of total LV myocardial mass (%LGE).

Statistical Analysis

Unless otherwise indicated, all data are expressed as mean±SD. As a preliminary analysis, an extension of the Shapiro-Wilk test of normality was done. Categorical variables were compared using a difference in proportions test; a 2-sample t-test was used to compare the general characteristics, and other continuous data, between study groups.

In order to identify variables associated with QTVI and QTVN, we first adopted a regression approach including all possible confounders known to be associated with the outcomes. Nevertheless, most of these confounders (eg, gender, pattern of LVH, etc.) were not significant. Thus, to provide a parsimonious model, much easier to interpret, a forward–backward stepwise polynomial multivariate regression analysis was performed in order to select the final model. Variable selection was performed according to the Akaike information criterion. Polynomial regression is based on the same principles as basic linear regression, except that the relationship between the independent and dependent variables is non-linear. It is used to fit non-linear (eg, curvilinear) data into a least-squares linear regression model. It is a form of linear regression that allows prediction of an outcome by decomposing the effect of independent variables into a higher-order polynomial. Different powers of independent variables can be added to capture non-linearities. Categorical variables have been included in the linear regression analysis using dummy coding, which assigns "1" and "0" to reflect the presence and absence, respectively, of a specific category level, that is, each dummy is compared to the benchmark level, coded as "0" for dummy variables. The fit of the regression model was measured using the adjusted-R^2 index and by performing an analysis of residuals, where normality of these residuals is an indication of the correct specification of the considered model.

Statistical analysis was performed using R (R Development Core Team, 2009). $P \leq 0.05$ was considered as statistically significant.

Table 2. CMR and ECG Characteristics vs. Presence of LGE

	HCM without LGE (n=32)	HCM with LGE (n=53)	P-value
CMR data			
LAVI (ml/m²)	46±18	59±22	0.000
LVEDVI (ml)	61±16	63±19	NS
LVEF (%)	76±9	73±9	NS
MWT (mm)	16±3	21±5	0.000
LVMI (g/m²)	77±24	102±33	0.000
%LGE (% of LVM)	–	4.2 [6.8]	–
Short-term (5-min) ECG data			
RR mean (ms)	893±120	891±143	NS
RR variance (ms²)	1188 [1414]	738 [1008]	NS
QT mean (ms)	400±41	399±35	NS
QT variance (ms²)	26.9 [13.5]	35.0 [27.0]	0.011
QTVN	0.181 [0.131]	0.275 [0.197]	0.000
QTVI	–0.865 [0.623]	–0.570 [0.462]	0.000

Data given as mean±SD or median [75th–25th percentile].
CMR, cardiac magnetic resonance; ECG, electrocardiogram; LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MWT, maximum wall thickness; QTVI, QT variability index; QTVN, QT variance normalized for QT mean. Other abbreviations as in Table 1.

Table 3. Significant Predictors of Temporal Myocardial Repolarization Dispersion

	QTVI			QTVN		
	β	SE	P-value	*β*	SE	P-value
Age	0.011	0.002	0.000	–	–	–
%LGE	0.069	0.015	0.000	0.019	0.007	0.005
%LGE²	–0.002	0.001	0.009	–0.001	0.000	0.030
LVOTO presence	0.160	0.076	0.038	–	–	–
SCD risk factor burden	0.097	0.041	0.020	–	–	–
LVMI	–	–	–	0.001	0.000	0.015

LGE and LGE², linear and quadratic late gadolinium enhancement, respectively. Other abbreviations as in Tables 1,2.

Results

Of the 108 HCM patients initially screened, only 90 patients met the initial inclusion criteria. Thirteen patients were excluded due to permanent atrial fibrillation (n=7) or because of documented history of coronary artery disease (n=6); 3 patients were excluded due to evidence of left bundle branch block at standard 12-lead surface ECG; and 2 patients were unwilling to participate in this study. Three additional patients were excluded from the analysis after frequent premature ventricular beats occurred during the short-term ECG recording; 2 patients were excluded due to uninterpretable CMR data. A total of 85 HCM patients were considered and analyzed in this study and LGE was found in 53 patients, corresponding to a prevalence of 62% in the study cohort. In all cases, LGE was located in the mid-basal septum and anterior wall with a prevalent patchy intramural distribution.

Age, gender distribution, body surface area, functional capacity (NYHA class), LVOT obstruction presence, and systolic and diastolic blood pressure did not differ significantly between HCM patients with and without LGE (Table 1). Concerning standard 12-lead surface ECG data, again there was no significant difference between study groups with respect to heart rate, QTc, QTd, and QTcd, although the latter variable showed a trend to significance (P=0.053; Table 1). Similarly, distribution of comorbidities and pharmacological treatment were similar between the 2 HCM subgroups (Table 1). Conversely, the prevalence of non-sustained ventricular tachycardia (P<0.0001), hypotensive blood pressure response at exercise test (P=0.044), as well as of the SCD risk factor burden (P=0.000) was significantly higher for the HCM group with LGE than for the respective group without LGE (Table 1).

At CMR analysis the HCM group with LGE had significantly higher left atrial volume index (LAVI), maximum wall thickness, and LV mass index (LVMI) than those in the HCM group without LGE (P<0.0001), whereas no difference between groups was found in LV end-diastolic volume index and LV ejection fraction (Table 2). QTVN and QTVI were significantly higher in the group with LGE (P<0.0001), as was QT_V (P=0.012), whereas all other short-term single-lead ECG variables were not significantly different between groups (Table 2; Figure 1).

At univariate analysis, QTVI was significantly associated with %LGE (r=0.54; P=0.000) and SCD risk factor burden (r=0.37; P=0.000); similarly, QTVN was associated with LGE% (r=0.45; P=0.000) and SCD risk factor burden (r=0.13; P=0.021); finally, %LGE, besides its relationship with both QTVI and QTVN, correlated per se with the SCD risk factor burden (r=0.37; P=0.000). Moreover, we looked for possible differences in QTVI and QTVN according to the presence of each of the SCD risk factors and found that the patients with non-sustained ventricular tachycardia had higher QTVI (+0.34, P=0.000) and QTVN (+0.12, P=0.022), while those with a family history of SCD

had only higher QTVI (+0.31; P=0.000).

At multiple regression analysis, using QTVI as the dependent variable, %LGE (β=0.069; standard error, 0.015; P<0.0001), age (β=0.011; standard error, 0.002; P<0.0001), LVOT obstruction presence (β=0.160; standard error, 0.076; P=0.038), and SCD risk factor burden (β=0.097; standard error, 0.041; P=0.020) reached statistical significance (**Table 3**). Otherwise, only %LGE (β=0.019; standard error, 0.007; P=0.005) and LVMI (β=0.001; standard error, 0.000; P=0.015) remained significantly associated when QTVN was used as the dependent variable (**Table 3**). Coefficients of the squared term in both equations for %LGE were also significant, suggesting that the quadratic model more closely fitted the data (**Figure 2**). A parametric approach (ie, a quadratic polynomial) has been considered to model the non-linear relationship between %LGE and the analyzed outcomes. Of course, more complex approaches (eg, based on non-parametric methods) can be used if such a relationship cannot be easily approximated by a polynomial curve.

Discussion

Detailed exploration of non-invasive spatial and temporal myocardial repolarization dispersion and its possible relationship with the extent of myocardial LGE at CMR has not previously been done in HCM patients. The present data show a correlation between a worsening of temporal myocardial repolarization dispersion and LGE extent, thus supporting LGE presence as a reliable marker of disease severity and, possibly, of arrhythmic risk in HCM.

Postmortem studies in young HCM patients who experienced SCD reported large areas of myocardial disarray and intramyocardial fibrosis,[8,9] thus supporting an arrhythmogenic nature of these cardiac lesions.[8–10] Accordingly, during the last decade some authors suggested LGE per se as a useful tool in the SCD risk stratification in addition to the other established risk factors. In line with this proposal, several papers found a significant relationship between LGE and the standard SCD risk factors.[7,11–14,31,32] Likewise, the present HCM patients with LGE had a greater prevalence of non-sustained ventricular tachycardia, hypotensive blood pressure response to exercise, as well as a higher SCD risk factor burden than those without LGE. It is of note, however, that the present investigation found a nearly two-thirds prevalence of LGE at CMR analysis, a result that is in line with that reported in other series.[14,15,31–34] Moreover, many other variables have been correlated with presence of LGE and, for most of them, an association with a significant arrhythmic risk has not been found (ie, LAVI, LVMI, maximum wall thickness, age, etc.).[12,15,31–35] Hence, owing to its high prevalence and multiple confounders, LGE presence per se is considered as a composite predictor of poor outcome without specifically predicting SCD.[15]

In the present study there was a significant relationship between increase in LGE extent and temporal myocardial repolarization worsening, thus suggesting a quantitative (ie, %LGE) rather than a qualitative (ie, LGE presence/absence) approach in interpreting LGE in this setting. The underlying mechanisms of this novel finding could be only hypothesized. One possible explanation, albeit merely speculative, could be that large areas of fibrosis not homogeneously distributed within the 3 myocardial layers (epicardial, M-cell, endocardial) directly lead to a greater beat-to-beat myocardial repolarization lability, thus increasing risk of arrhythmia. Indeed, given that the duration of a single QT-interval represents the sum of the duration of myocardial cell repolarizations, it is likely that the myocardial

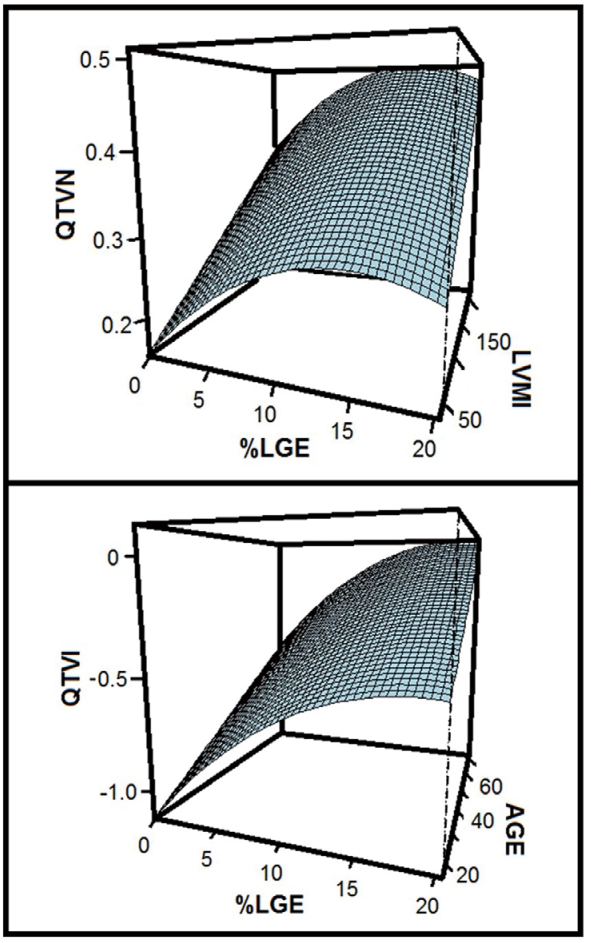

Figure 2. Relationship of proportion of late gadolinium enhancement (%LGE) to (**Upper**) QT variance normalized for QT mean (QTVN) and left ventricular mass index (LVMI), and to (**Lower**) QT variability index (QTVI) and age (the data refer to the covariate profile with sudden cardiac death risk burden equal to zero and an absence of left ventricular outflow obstruction). Both panels show a significant flattening of the relationship between %LGE and QT indices beginning at %LGE=18–20% (see **Table 3** for all regression analysis data). Note that plots are obtained from the multivariate parameters estimates. For each combination of %LGE and AGE/LVMI, the value of QTVI and QTVN are predicted (not simply described).

structural abnormalities, such as disarray and fibrosis, affect the beat-to-beat variation of cardiac action potential.[16,21,26] Nonetheless, myocardial repolarization is a highly complex electrophysiological phenomenon that involves ventricular myocardial ion channel function and, indirectly, reflects autonomic nervous system balance, the latter highly susceptible to many other factors. Last, experimental studies reported that myocardial cell electrophysiological activity may change, thus altering the action potential phase, even before myocyte hypertrophy and fibrosis develop.[36] Hence, as well as LGE, it is reasonable that also QTVN and, mainly, QTVI might be interpreted as multidimensional indexes of disease severity. Conversely, none of the QT indices derived from the spatial domain approach (ie, QTd and QTcd) correlated with LGE, a possible explanation being the great influence of the altered ventricular hypertrophy geometry on these variables.[28,37] It should be noted, how-

ever, that the same approach has been shown to be useful in specific genotyped HCM subgroups, even in the absence of LVH.[28] Unfortunately, due to lack of data on presence and/or prevalence of gene mutations in the present subjects, the present study cannot clarify this intriguing aspect.

Interestingly, we observed a flattening in both QTVN and QTVI trend for %LGE >18–20% (**Figure 2**). A possible explanation for this paradoxical finding could be related to the physiological implications of such a large LGE extent. Besides those HCM patients with a history of septal myectomy (a priori excluded from the analysis), the highest %LGE is usually found in end-stage HCM as well as in restrictive HCM phenotypes.[31,32,38–40] Thus, also the progression of heart failure or ischemic stroke due to atrial fibrillation could be possible alternative modes of death in these settings.[34,38,40] Clearly, the small number of HCM patients enrolled with %LGE >18–20%, along with the lack of prospective data concerning hard endpoints enables us only to speculate.

Finally, a few considerations regarding temporal myocardial repolarization dispersion behavior with respect to other clinical variables should be discussed. Indeed, besides the relationship with %LGE, 3 other variables have been found to be significant predictors of QTVI. While the relationship between QTVI and SCD risk factor burden might support its use in identifying specific arrhythmic risk, its relationship to LVOT obstruction and aging might raise some concerns.[41] It is most likely that an altered autonomic nervous system activity (ie, decreased heart rate variability) represents the major underlying reason for this conflicting finding, being that it worsens with diastolic dysfunction, microvascular ischemia and, physiologically, with aging.[24,25,42] Accordingly, it is possible that the prognostic value of QTVI might be strongest in young and middle-aged HCM patients, in whom reduced heart rate variability could be interpreted as a marker of autonomic nervous system imbalance (**Figure 1D**).[43,44] Conversely, it could be hypothesized that the most likely usefulness of QTVN, slightly influenced by LVMI, resides in the context of elderly HCM patients. Again, as acknowledged, the present study design enables us only to hypothesize such a clinically oriented interpretation of the findings.

Study Limitations

The small study sample together with the non-prospective study design represent obvious limitations that allows us to support, rather than conclude, that %LGE might be useful in risk stratification in HCM patients. The present pathophysiological study, however, was not intended to investigate the effectiveness of LGE as an outcome predictor but only to explore its relationship with other non-invasive markers known to stratify prognosis in other clinical settings.

Currently, we cannot supply data on the prevalence as well as the possible impact on the studied variables of sarcomere gene mutations. To our knowledge, only 1 single study on a small cohort of patients with HCM noted a significant relationship between temporal ventricular repolarization dispersion (QTVI) and a specific β-myosin heavy-chain (MYH7) gene mutation ($Arg^{403}Gln$).[45] But, although determination of the pathogenicity of a gene mutation or even of a single-nucleotide variant remains a major clinical challenge,[46,47] there is now consensus that routine screening for specific mutations cannot be designated either "benign" or "malignant" or reliably predict clinical outcome.[2,46] Conversely, we should recognize that double or compound pathogenic mutations have been recently associated with more severe disease expression and sudden death.[48]

A third possible limitation is represented by a technical problem that hampers more widespread use of QT, namely the difficulty in computing the end of the T wave. Many studies, however, have examined beat-to-beat QT variability, and new methodology[26] has enabled investigators to better assess ventricular repolarization lability.[16–22,27] Unfortunately, none of the commercially available software guarantees reliable estimates in this ECG zone and evaluation errors (also lasting few thousandths of a second) tend exponentially to increase QT_V. Notwithstanding, our expertise allows us to recommend the use of the method based on the template of Berger, possibly on short-term ECG recording.

Finally, we should acknowledge the lack of data on the possible relationship between the present study variables and the presence of a midventricular obstruction, a distinct HCM phenotype recently shown to be associated with unfavorable prognosis in terms of lethal arrhythmic events.[49]

Conclusions

Temporal myocardial repolarization dispersion independently correlates with LGE presence and extent. The present findings warrant prospective and, most likely, multicenter studies to investigate a possible role of these non-invasive variables in clinical management of HCM and, possibly, to identify those patients with a significantly increased risk of arrhythmia, although not yet considered eligible for cardioverter defibrillator implantation.

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