ORIGINAL ARTICLE

Indexes of Temporal Myocardial Repolarization Dispersion and Sudden Cardiac Death in Heart Failure: Any Difference?

Gianfranco Piccirillo, M.D., Ph.D.,* Pietro Rossi, M.D.,† Marilena Mitra, M.D.,* Raffaele Quaglione, M.D.,* Annalaura Dell'Armi, M.D.,* Daniele Di Barba, M.D.,* Damiana Maisto, M.D.,* Andrea Lizio, M.D.,* Francesco Barillà, M.D.,* and Damiano Magrì, M.D., Ph.D.‡

*From the *Department of Cardiovascular, Respiratory, Nephrologic, and Geriatric Sciences, "Sapienza" University of Rome, Rome, Italy; †Division of Cardiology, S. Giovanni Calibita Fatebenefratelli Hospital, Rome, Italy; and ‡Department of Clinical and Molecular Medicine, "Sapienza" University of Rome, Rome, Italy*

Background: The QT variability index, calculated between Q- and the T-wave end ($QT_{end}VI$), is an index of temporal myocardial repolarization lability associated with sudden cardiac death (SCD) in chronic heart failure (CHF). Little is known about temporal variability in the other two temporal myocardial repolarization descriptors obtained from $Q–T_{peak}$ and $T_{peak}–T_{end}$ intervals. We therefore investigated differences between these indexes in patients with CHF who died suddenly and in those who survived with a left ventricular ejection fraction (LVEF) ≤35% or >35%.

Methods and Results: We selected 127 ECG and systolic blood pressure (SPB) recordings from outpatients with CHF all of whom had been followed up for 30 months. We calculated RR and SPB variability by power spectral analysis and $QT_{end}VI$, $QT_{peak}VI$, $T_{peak}T_{end}VI$. We then subdivided data patients into three groups SCD, LVEF ≤ 35%, and LVEF > 35%. The LVEF was higher in the SCD than in the LVEF ≤ 35% group, whereas no difference was found between the SCD and LVEF > 35% groups. $QT_{end}VI$, $QT_{peak}VI$, and $T_{peak}T_{end}VI$ were higher in the SCD and LVEF ≤ 35% groups than in the LVEF > 35% group. Multivariate analysis detected a negative relationship between all repolarization variability indexes, low frequency obtained from RR intervals and LVEF.

Conclusions: Our data show that variability in the first ($QT_{peak}VI$) and second halves of the QT interval ($T_{peak}–T_{end}VI$) significantly contributes to the $QT_{end}VI$ in patients with CHF. Further studies should investigate whether these indexes might help stratify the risk of SCD in patients with a moderately depressed LVEF.

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chronic heart failure; QT variability; heart rate variability; autonomic nervous system; sudden cardiac death
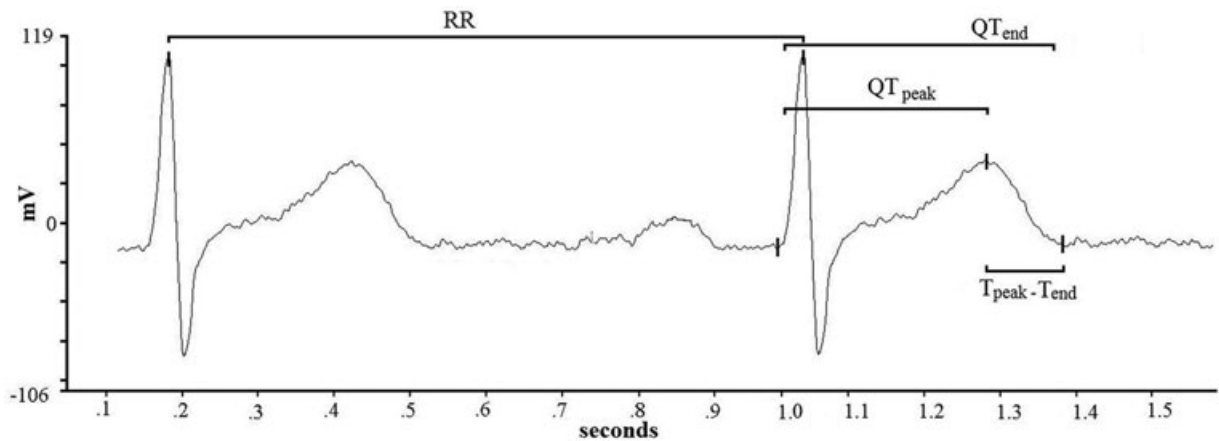
Myocardial repolarization lability may predispose patients with chronic heart failure (CHF) to sudden cardiac death (SCD) from ventricular arrhythmia.[1,2] A marker currently used to assess temporal myocardial repolarization lability is the QT variability index ($QT_{end}VI$).[3–5] In subjects with severe or moderate left ventricular dysfunction, an increased $QT_{end}VI$ is strongly associated with the SCD event.[6–11] Myocardial repolarization is nevertheless a highly complex electrophysiological phenomenon that directly implicates ventricular myocardial ion channel function and, indirectly,

Address for correspondence: Gianfranco Piccirillo, M.D., Ph.D., Dipartimento di Scienze Cardiovascolari, Respiratorie, Nefrologiche e Geriatriche, "Sapienza" University of Rome, Viale del Policlinico 00185 Rome, Italy. Fax: 0039-06-49970118; E-mail: gianfranco.piccirillo@uniroma1.it

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Figure 1. Representative example of RR, Q–T_{end}, Q–T_{peak}, and T_{peak}–T_{end} interval measurements from a single lead ECG.

reflects autonomic nervous system control.[1,2] Thus, spatial[12,13] and temporal[14,15] myocardial repolarization dispersion are both influenced by several structural changes in the ventricular myocardium, as well as by autonomic cardiovascular control and many other factors including age,[15,16] and medications.[17-19] Even in healthy subjects, the duration of myocardial repolarization, is inherently nonhomogeneous given that the action potential has a shorter duration in epicardial than in M-cell layers.[20,21] Some investigators suggest that the Q–T_{peak} interval on the surface electrocardiogram (ECG) (Fig. 1), measured as the distance between the Q-wave and the T-wave peak, mainly reflects the termination of epicardial repolarization, whereas the T_{peak}–T_{end} interval (Fig. 1), calculated from the peak when the T-wave ends, reflects the termination of M-cell layer repolarization and, accordingly, could be a noninvasive marker of transmural repolarization dispersion.[20,21] In patients with CHF, whether these two repolarization variables, whose sum forms the entire Q–T interval duration (QT_{end}) (Fig. 1), exhibit temporal nonhomogeneity as does the classically assessed Q–T_{end} interval, remains unclear.

We therefore designed this retrospective study to investigate whether one of the two temporal myocardial repolarization dispersion descriptors, QT_{peak}VI and $T_{peak}T_{end}$VI, undergoes greater changes in patients with CHF and hence is stronger in predicting SCD than the classic QT_{end}VI. To accomplish this aim, we calculated all these three indexes from a single 5-minute surface ECG recording, and compared the data for subjects with CHF who had died of SCD and outpatients who survived whose systolic function was severely depressed (left ventricular ejection fraction, LVEF, ≤35%) or moderately depressed (LVEF > 35%).

METHODS

Study Subjects

For this study we retrospectively selected 127 short-term (5 minutes) ECG and systolic blood pressure (SBP) recordings from clinically stable outpatients with CHF secondary to dilated postischemic cardiomyopathy, all of whom had been followed up for 30 months. We defined clinically stable patients as those who had not been hospitalized or had their therapy adjusted or had experienced any other acute coronary artery or noncoronary event during the past 3 months. All participants had undergone revascularization either cutaneously or by aorto-coronary artery bypass at least 3 months before the study. None of the patients had malignancy, primary valve disease, atrial fibrillation, extrasystoles (one extrasystole per minute was permitted), or other arrhythmias likely to interfere with heart rate and QT analysis. None of the patients was in New York Heart Association (NYHA) class IV. Before the study none of the subjects had a documented history of cardiac arrest, ventricular tachycardia, or fibrillation. All patients were regularly contacted by phone to acquire information on their clinical conditions. Sudden (presumably arrhythmic) death

was defined as natural death taking place within 1 hour after the onset of acute symptoms or death during sleep. SCD was confirmed in each patient by telephone interview with surviving relatives.

To accomplish the aim of the study, we grouped participants' data into three categories: data from subjects who died of SCD during follow-up, those from survivors with a severely depressed LVEF ($\leq$35%), and those for survivors with a moderately depressed EF (>35%).

Study Protocol and Offline Data Analysis

After a 15-minute rest lying down, each subject underwent a 5-minute, single ECG lead, and a noninvasive beat-to-beat SBP recording during controlled breathing (15 breaths per minute, 0.25 Hz). All digitized signal recordings were analyzed by a single physician (G.P.) blinded to subjects' circumstances.

We measured the following intervals from the respective time series in ECG recordings: RR, $Q-T_{end}$ (from the Q-wave to the T-wave end), $Q-T_{peak}$ (from the Q-wave to the T-wave peak), and $T_{peak}-T_{end}$ (difference between QT_{end} and QT_{peak}) (Fig. 1). We therefore calculated mean and variance values for each of these intervals and then we used the original formula proposed by Berger et al.[3] to calculate three different QT variability indexes:

$$QT_{end}VI = \log_{10}\{[[QT_{end}\text{variance}]/[QT_{end}\text{mean}]^2]/$$
$$[[RR\text{variance}]/[RR\text{mean}]^2]\}$$

$$QT_{peak}VI = \log_{10}\{[[QT_{peak}\text{variance}]/[QT_{peak}\text{mean}]^2]/$$
$$[[RR\text{variance}]/[RR\text{mean}]^2]\}$$

$$T_{peak}T_{end}VI = \log_{10}\{[[T_{peak}T_{end}\text{variance}]/$$
$$[T_{peak}T_{end}\text{mean}]^2]/[[RR\text{variance}]/ [RR\text{mean}]^2]\}$$

From the same 5-minute ECG segments we also determined the total power of RR intervals and SBP (TP_{RR}, TP_{SBP}), and their total spectral density.[22] For RR and SBP we calculated the following spectral components: a high-frequency (HF_{RR}, HF_{SBP}) component (from 0.15 to 0.40 Hz Eq), a low-frequency (LF_{RR}, LF_{SBP}) component (from 0.04 to 0.15 Hz Eq), and a very low-frequency (VLF_{RR}, VLF_{SBP}) component (below 0.04 Hz Eq). We also measured LF and HF central frequencies.

The α index was calculated by dividing the square root of the spectral density for heart rate by the square root of the corresponding spectral density for SPB, as described by Robbe et al.[23] and later by other investigators[24, 25]:

$$\alpha LF = \sqrt{LF} RR/\sqrt{LF} SBP;$$
$$\alpha HF = \sqrt{HF} RR/\sqrt{HF} SBP.$$

The same ECG intervals, together with beat-to-beat SBP recording, were also used to determine power spectral analysis with an autoregressive algorithm also for QT_{end}, QT_{peak}, and $T_{peak}-T_{end}$ intervals (Fig. 2).[22] Cross-spectral analysis was then used to evaluate the reciprocal influence (coherence function) between RR, QT_{end}, QT_{peak}, and $T_{peak}-T_{end}$.[3] Coherence expresses the fraction of power at a given frequency in either time series and provides an index of a linear relationship between the input and output signals. The coherence function $\gamma[f]$ was then computed according to the formula described elsewhere:[3, 14]
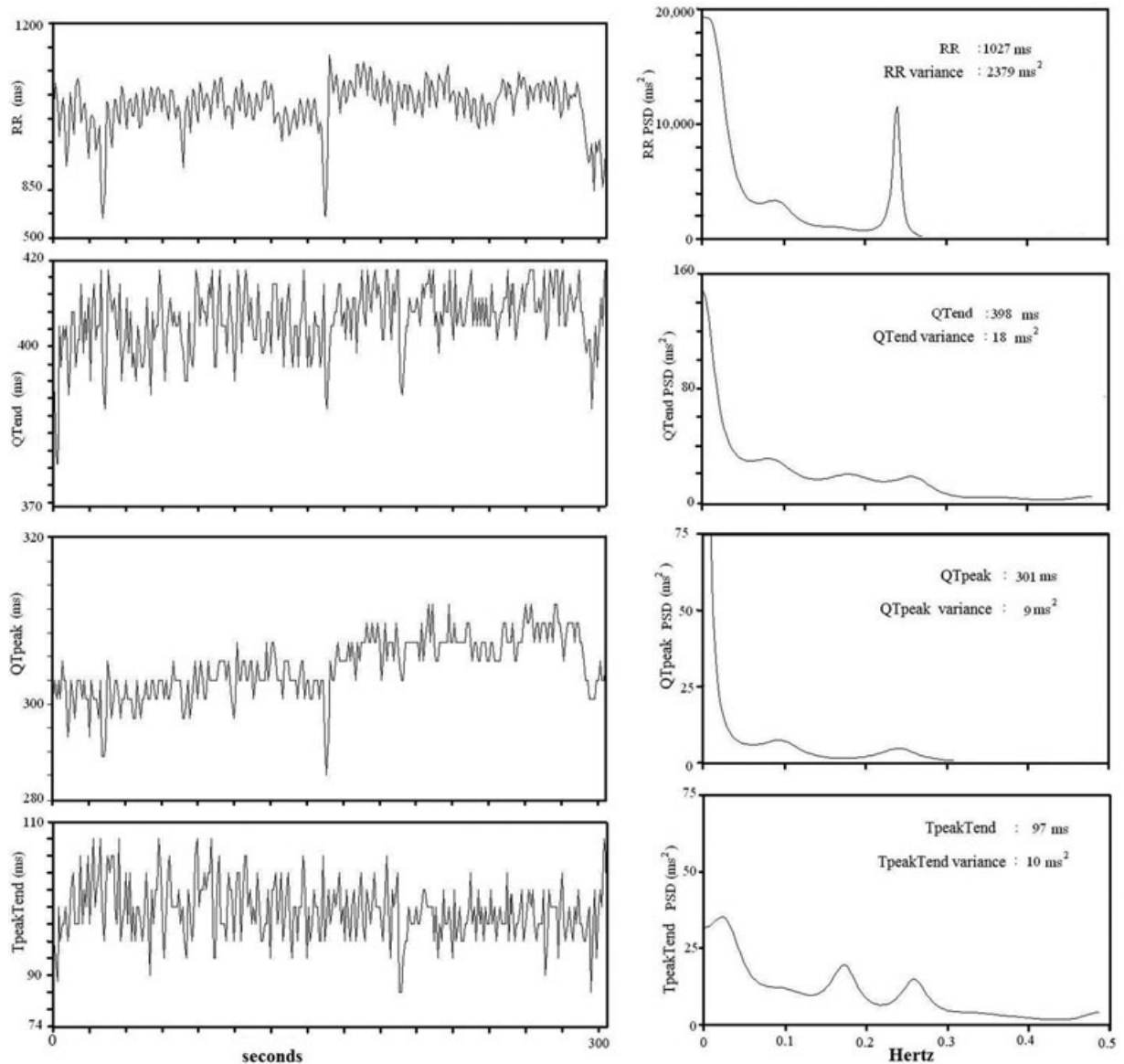
$$\gamma[f] = \frac{|P_{XY}[f]|^2}{Pxx[f]Pyy[f]},$$

where f is frequency, Pxx [f] is the RR interval spectrum, Pyy[f] is the QT interval spectrum, and Pxy[f] is the cross spectrum. The coherence function measures the degree of linear interaction between RR and QT interval oscillations as a function of their frequency. The value of the coherence function ranges between zero and one. Mean coherences were measured by averaging $\gamma[f]$ over the frequency bands: from 0 to 0.50 Hz.

Software for data acquisition and storage and for spectral analysis were designed and produced by our research group and are described in detail elsewhere.[4, 5, 12, 13, 25–27]

Last, from the same 5-minute ECG segment, the corrected $Q-T_{end}$, $Q-T_{peak}$, and $T_{peak}-T_{end}$ intervals were obtained according to the formulas proposed by Bazett ($QT_{end}/RR^{0.5}$; $QT_{peak}/RR^{0.5}$; $T_{peak}-T_{end}/RR^{0.5}$), Friedericia ($QT_{end}/RR^{0.33}$; $QT_{peak}/RR^{0.33}$; $T_{peak}-T_{end}/RR^{0.33}$), Lilly ($QT_{end}/RR^{0.4}$; $QT_{peak}/RR^{0.4}$; $T_{peak}-T_{end}/RR^{0.4}$], and Framingham ($QT_{end} + [0.154 \times \{1000 - RR\}]$; $QT_{peak} + [0.154 \times \{1000 - RR\}]$; $T_{peak} - T_{end} + [0.154 \times \{1000 - RR\}]$]).

Statistical Analysis

Unless otherwise indicated all data are expressed as means $\pm$ SD. Data with skewed distribution are given as median and interquartile range [75th percentile – 25th percentile]. Categorical

Figure 2. Representative example of a 5-minute ECG recording (left panels) and related power spectral analysis (right panels) RR, Q–T_{end}, Q–T_{peak}, T_{peak}–T_{end} intervals in a subject with a left ventricular ejection fraction >35%.

variables were analyzed with the chi-square test. One-way analysis of variance (ANOVA) and1 Bonferroni test were used to compare data for the normally distributed variables. Kruskal-Wallis and Mann-Whitney test were used to compare nonnormally distributed variables (as evaluated by Kolgomorov-Smirnov test). Stepwise multiple regression analysis was used to determine possible relationships between the three indexes ($QT_{end}VI$, $QT_{peak}VI$, and $T_{peak}T_{end}VI$) and the other clinical and spectral data. P values less than or equal to

0.05 were considered statistically significant. All data were evaluated with the database SPSS-PC+ (SPSS-PC+ Inc, Chicago, IL, USA).

RESULTS

Of the 127 participants with CHF initially enrolled, 43 subjects were excluded for various reasons and a total 84 subjects therefore completed the study. Of the 43 subjects who were excluded, 11 died of causes other than SCD, and 23

Table 1. General Characteristics in the Three Study Groups, Patients with Chronic Heart Failure (CHF) Who Died of Sudden Cardiac Death (SCD) during Follow-Up, and Survivors Who Had a Left Ventricular Ejection Fraction (LVEF) ≤35% or >35%

Variables	SCD Group N = 12 Subjects	LVEF ≤ 35% Group N = 41 Subjects	LVEF > 35% Group N = 31 Subjects	P-Values [ANOVA]
Age (years)	67 ± 11	62 ± 12	59 ± 10	NS
M/F	10/2	36/5	29/3	NS
BMI (kg/m^2)	25 ± 5	27 ± 4	27 ± 4	NS
HR (beats/min)	72 ± 11	68 ± 9	64 ± 10	NS
SBP (mm Hg)	122 ± 27	114 ± 21	118 ± 22	NS
DBP (mm Hg)	65 ± 14	61 ± 14	64 ± 11	NS
QT$_{end\ Bazett}$ (ms)	401 ± 75[c]	390 ± 44	371 ± 30	0.007
QT$_{end\ Fridericia}$ (ms)	413 ± 73[c]	382 ± 46	368 ± 33	0.021
QT$_{end\ Lilly}$ (ms)	416 ± 74[c]	385 ± 45	369 ± 31	0.013
QT$_{end\ Framingham}$ (ms)	412 ± 74[c]	384 ± 45	369 ± 31	0.023
Q$_{peak\ Bazett}$ (ms)	305 ± 28	311 ± 42	291 ± 27	NS
QT$_{peak\ Fridericia}$ (ms)	300 ± 28	305 ±43	289 ± 28	NS
QT$_{peak\ Lilly}$ (ms)	302 ± 28	308 ± 43	290 ± 27	NS
QT$_{peak\ Framingham}$ (ms)	302 ± 28	310 ± 41	291 ± 26	NS
T$_{peak}$ -T$_{end\ Bazett}$ (ms)	116 ± 63[a,c]	78 ± 30	79 ± 17	0.002
T$_{peak}$ -T$_{end\ Fridericia}$ (ms)	113 ± 62[a,c]	76 ± 30	79 ± 17	0.003
T$_{peak}$ -T$_{end\ Lilly}$ (ms)	114 ± 62[a,c]	77 ± 30	79 ± 17	0.003
T$_{peak}$-T$_{end\ Framingham}$ (ms)	121 ± 70[a,c]	89 ± 34	83 ± 23	0.015
Coronary disease				
1 Vessel	2	1	2	NS
2 Vessels	4	17	14	NS
3 Vessels	6	23	15	NS
LVEF (%)	42 ± 8[b]	30 ± 5[d]	45 ± 7	0.0001
NYHA class (I/II/III)	1/8/3	3/19/19	6/19/7	NS
Serum K$^+$	4.1 ± 0.1	4.1 ± 0.2	4.2 ± 0.3	NS
β-blockers	8	31	24	NS
Furosemide	4	26	8	NS
ACEi/Sartans	9	29	30	NS
Spironolactone	3	16	8	NS
Digoxin	2	10[e]	0	0.033
Amiodarone	2	2	1	NS

Data are expressed as mean ± SD.
[a]P < 0.05 SCD vs LVEF ≤ 35% group.
[b]P < 0.001 SCD vs LVEF ≤ 35% group.
[c]P < 0.05 SCD vs LVEF > 35% group.
[d]P < 0.001 LVEF ≤ 35% vs LVEF > 35% group.
[e]P < 0.05 LVEF ≤ 35% vs LVEF > 35% group.
M/F = male/female; BMI = body mass index; HR = heart rate; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

subjects refused to collaborate. No patient had an implantable cardioverter defibrillator placed for primary SCD prophylaxis either because they underwent assessment before the Multicenter Automatic Defibrillator Trial (MADIT II) was published or because they voluntarily refused ICD implantation.

Neither age, body mass index (BMI), gender distribution, heart rate, systemic arterial pressures, NYHA class, coronary disease, or drug therapy differed significantly between the three study groups, whereas the ECG recording showed a significantly longer corrected Q–T$_{end}$ and T$_{peak}$–T$_{end}$ intervals in the SCD group than in the LVEF >35% group. The group with an LVEF ≤35% had a lower LVEF than the other two groups and used digoxin more frequently (Table 1).

The temporal repolarization dispersion index QT$_{end}$VI was significantly higher in the LVEF ≤35% than in the LVEF >35% group. Conversely, QT$_{peak}$VI was significantly higher in the LVEF ≤35% and SCD groups than in the LVEF

Table 2. QT Data Obtained in the Three Study Groups, Patients with Chronic Heart Failure (CHF) Who Died of Sudden Cardiac Death (SCD) during Follow-Up, and Survivors Who Had a Left Ventricular Ejection Fraction (LVEF) $\leq 35\%$ or $> 35\%$

Variables	SCD Group N = 12 Subjects	LVEF $\leq 35\%$ Group N = 41 Subjects	LVEF $> 35\%$ Group N = 31 Subjects	P-Values [ANOVA]
QT_{end} (ms)	401 ± 80	368 ± 53	364 ± 44	NS
QT_{end}variance (ms^2)	66[192]	52[60]	20[39]	NS
RR (ms)	926 ± 221	895 ± 128	966 ± 31	NS
RR variance	324[1177]	669[1078]	805[1399]	NS
QT_{end}VI	−0.28[1.29]	−0.22[0.83][d]	−0.72[0.56]	0.004
RR→QT_{end}, coherence	0.265 ± 0.093	0.243 ± 0.061	0.263 ± 0.060	NS
QT_{peak} (ms)	291 ± 39	294 ± 49	285 ± 35	NS
QT_{peak}variance (ms^2)	27[66]	19[20][d]	8[15]	0.044
QT_{peak}VI	−0.36[1.54][b]	−0.54[0.87][c]	−0.98[0.57]	0.001
RR→QT_{apex}, coherence	0.277 ± 0.075	0.271 ± 0.068	0.301 ± 0.098	NS
$T_{peak} - T_{end}$ (ms)	109 ± 63[a,b]	73 ± 29	78 ± 18	0.004
$T_{peak} - T_{end}$variance (ms)	100[195][b]	46[74][d]	22[33]	0.044
$T_{peak} - T_{end}$VI	1.26[1.48][b]	1.15[1.20][d]	0.47[0.93]	0.001
RR→$T_{peak} - T_{end}$, coherence	0.217 ± 0.045	0.220 ± 0.056	0.241 ± 0.058	NS

Values are expressed as mean $\pm$ SD or median [interquartile range 75th percentile–25th percentile].
[a]$P < 0.05$ SCD vs LVEF $\leq 35\%$ group.
[b]$P < 0.05$ SCD vs LVEF $> 35\%$ group.
[c]$P < 0.001$ LVEF $\leq 35\%$ vs LVEF $> 35\%$ group.
[d]$P < 0.05$ LVEF $\leq 35\%$ vs LVEF $> 35\%$ group.

$>35\%$ group (Table 2). Similarly, $T_{peak}T_{end}$VI were significantly higher in the LVEF $\leq 35\%$ and SCD groups than in the LVEF $>35\%$ group (Table 2).

No significant differences were found in power spectral analysis of RR intervals, SBP and the α index in the three groups, except for TP, VLF, and LF obtained from RR variability. Specifically, TP_{RR} and VLF_{RR} were significantly lower in the SCD and LVEF $\leq 35\%$ groups than in LVEF $>35\%$ group (Table 3). LF_{RR} had significantly lower values in the LVEF $\leq 35\%$ than in the LVEF $>35\%$ group (Table 3).

The stepwise multiple regression analysis testing QT_{end}VI as dependent variables detected significant negative relationships with LF_{RR} ($\beta = -0.37$; standard error = 0.04; P = 0.0001), LVEF ($\beta = -0.33$; standard error = 0.00; P = 0.0001), and BMI ($\beta = -0.26$; standard error = 0.02; P = 0.008) (Table 4, Fig. 3). Conversely, the multiple regression analysis testing QT_{peak}VI as dependent variables, disclosed a significant relationship with LF_{RR} ($\beta = -0.59$; standard error = 0.04; P = 0.0001) and LVEF ($\beta = -0.28$; standard error = 0.00; P = 0.0001) but not with BMI (Table 4, Fig. 3). The regression analysis run with $T_{peak} - T_{end}$VI as dependent variable yielded similar results (LF_{RR}:

$\beta = -0.42$; standard error = 0.07; P = 0.0001; LVEF: $\beta = -0.26$; standard error = 0.01; P = 0.014) (Table 4).

DISCUSSION

The major original finding in this retrospective study is that patients who died of SCD during follow-up, notwithstanding an only moderately depressed LVEF, showed a larger QT_{peak}VI and $T_{peak}T_{end}$VI than patients with CHF who survived. Accordingly, these two temporal myocardial repolarization dispersion indexes seem able to predict subjects at risk of SCD among patients who the current ACC-AHA-ESC guidelines consider ineligible for ICD implantation for primary SCD prophylaxis. Our second finding is that the three temporal myocardial repolarization dispersion indexes we investigated, namely QT_{end}VI, QT_{peak}VI, and the $T_{peak}T_{end}$VI, correlate inversely with LF_{RR}. This somewhat expected finding is of clinical interest because LF_{RR} is depressed in patients with CHF who died suddenly,[28–30] improves along with the clinical and hemodynamic improvement induced by β-blocker therapy[26] or biventricular stimulation[30] and is thought to mirror sinus

Table 3. RR and SPB Short-Term Power Spectral Data Obtained in the Three Groups, Patients with Chronic Heart Failure (CHF) Who Died of Sudden Cardiac Death (SCD) during Follow-Up, and Survivors Who Had a Left Ventricular Ejection Fraction (LVEF) ≤35% or >35%

Variables	SCD Group N = 12 Subjects	LVEF ≤ 35% Group N = 41 Subjects	LVEF > 35% Group N = 31 Subjects	P-Values [ANOVA]
TP_{RR} (ms^2)	323 [1175][a]	667 [1012][b]	910 [1348]	0.043
VLF_{RR} (ms^2)	139 [721][a]	304 [792][b]	552 [825]	0.040
LF_{RR} (ms^2)	62 [274]	62 [237][b]	180 [247]	0.049
HF_{RR} (ms^2)	28 [196]	49 [96]	96 [125]	NS
LF/HF	1.4 [1.9]	1.6 [1.9]	1.8 [2.3]	NS
TP_{SBP} (mm Hg^2)	26 [50]	20 [20]	22 [20]	NS
VLF_{SBP} (mm Hg^2)	18 [43]	12 [14]	18 [19]	NS
LF_{SBP} (mm Hg^2)	4 [3]	2 [3]	3 [3]	NS
HF_{SBP} (mm Hg^2)	2 [5]	2 [3]	1 [2]	NS
αLF (ms/mm Hg)	6 [8]	6 [4]	8 [5]	NS
αHF (ms/mm Hg)	7 [9]	7 [8]	8 [13]	NS

Values are expressed as median [interquartile range 75th percentile–25th percentile].
[a]P < 0.05 SCD vs LVEF > 35% group.
[b]P < 0.05, patients with LVEF ≤ 35% vs LVEF > 35% group.
TP = total power; VLF = very low frequency; LF = low frequency; HF = high frequency; RR = RR interval; SBP = systolic blood pressure.

Table 4. Stepwise Multiple Regression Analysis between $QT_{end}VI$, or $QT_{peak}VI$, or $T_{peak}T_{end}$ (Dependent Variables) and other Clinical and Spectral Data (Independent Variables)

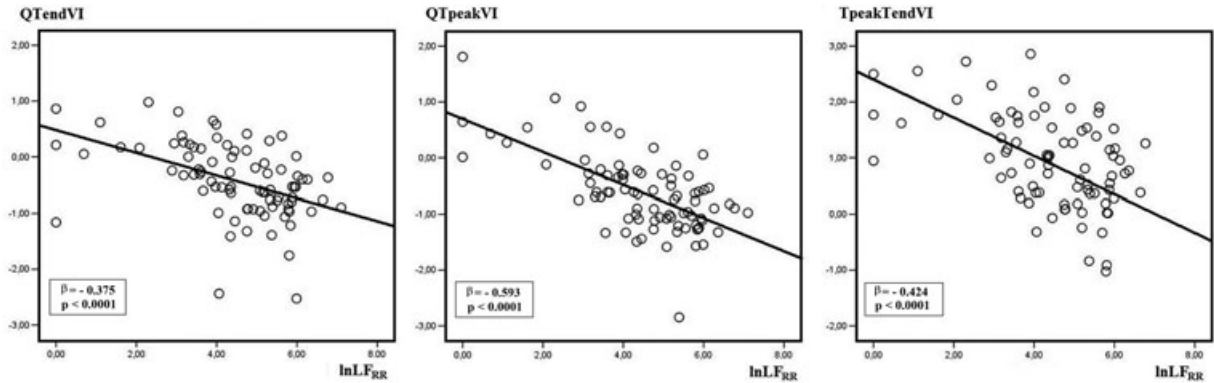|	Ln LF_{RR}			LVEF			BMI				
	β	SE	P	β	SE	P	β	SE	P	R^2	P
$QT_{end}VI$	−0.37	0.04	0.0001	−0.33	0.00	0.001	−0.26	0.02	0.008	0.366	0.0001
$QT_{peak}VI$	−0.59	0.04	0.0001	−0.28	0.00	0.0001	–	–	NS	0.492	0.0001
$T_{peak}T_{end}VI$	−0.42	0.07	0.0001	−0.26	0.01	0.014	–	–	NS	0.284	0.0001

R^2 value (a goodness-of-fit index) with its related P value refers to the fraction of variance explained by each multivariate model (last two columns).
β = standardized regression coefficient value; SE = standard error value.

dysfunction or low baroreceptor sensitivity or both in patients with CHF.[31]

The three ECG intervals we measured, Q–T$_{end}$, Q–T$_{peak}$, and the T$_{peak}$–T$_{end}$ intervals, differ in electrophysiological meaning. Despite remaining controversial,[32–34] some investigators consider that the Q–T$_{peak}$ interval depends on the action potential duration only in the epicardial layer.[20, 21] Conversely, the T$_{peak}$–T$_{end}$ interval predominantly measures myocardial repolarization in the M-cell layer and also in the layers in which depolarization lasts longer. For this reason the T$_{peak}$–T$_{end}$ interval probably reflects the maximum difference in repolarization between the myocardial layers and hence may be a noninvasive marker of transmural dispersion repolarization, reported to be increased in subjects at high risk for SCD.[20, 21] Hence the derived T$_{peak}$–T$_{end}$VI, being influenced mainly by the terminal part of the action potential, namely from the rapidly (I$_{Kr}$) and slowly activating (I$_{Ks}$) components from the delayed rectifier current and the inward rectifier current (I$_{K1}$), could be an exact marker of temporal myocardial repolarization dispersion. Conversely the QT$_{peak}$VI could reasonably depend mainly on oscillations in the first part of action potential (phase 0, 1, and 2) and therefore on inward Na (I$_{Na}$) and Ca (I$_{Ca L}$) currents and on transient K outward currents (I$_{to}$). Given that CHF induces profound changes in the entire repolarization phase and does so by downregulating K currents, increasing late I$_{Na}$ currents and deregulating intracellular Ca,[35] the combined change in QT$_{peak}$VI and T$_{peak}$T$_{end}$VI we observed, rather than being an unexpected

Figure 3. Linear regression analysis between $QT_{end}VI$, $QT_{peak}VI$, and $T_{peak}-T_{end}VI$, natural logarithm of low frequency obtained from RR interval power spectral analysis ($lnLF_{RR}$).

finding, strengthens the hypothesis that several mechanisms concur in causing the arrhythmogenesis in these patients. Most important, temporal variability in $Q-T_{peak}$ and $T_{peak}-T_{end}$ intervals could result in delayed after depolarizations (DADs) or early after depolarizations (EADs) and might indicate the presence of tissue areas containing nonhomogeneous refractory periods that, under favorable circumstances (i.e., ischemia, neurohumoral activation), could set up re-entry circuits thereby triggering malignant ventricular arrhythmias.[20, 21]

Last, the inverse correlation we found between all the QT variability indexes and LF_{RR} and the LVEF indicates how closely these variables are interconnected in neurohumoral activation and repolarization.[36] Even though its precise pathophysiological meaning during CHF remains controversial, the LF_{RR} diminishes during CHF,[22, 31] correlates with SCD risk[28, 29] and increases as treatment induces hemodynamic improvement.[26, 30] Of the three multiple regression analyses we ran in this study, the one achieving major significance was that between $QT_{peak}VI$, LVEF, and LF_{RR}. Current knowledge leaves unanswered the question whether this index correlates with LF_{RR} because both variables are negatively influenced by the LVEF or whether an unknown shared factor causes these two variables to change according to LVEF. This possibility notwithstanding, given that both are risk factors for SCD, we conjecture that both are linked by a single causal factor. Another possible arithmetical explanation might be found in the QTVI formula itself, given that LF_{RR} accounts for RR variance.[22, 37] Nevertheless LF_{RR} component represents just one of the spectral components of heart rate variability and no significant relationship was found between QT variability indexes and HF_{RR} and VLF_{RR}.

This study also helps to reinforce other findings of clinical importance already reported in earlier studies. For example, power spectral analysis investigating RR intervals of heart rate variability but not of SBP or baroreceptor sensitivity, seems able to select persons at high risk of SCD. In our study, TP_{RR} and VLF_{RR}, were strongly depressed in subjects who died of SCD. This finding is of clinical importance even though some investigators doubt whether VLF_{RR} values assessed from short-term (5 minutes) rather than from 24-hour recordings provide reliable results.[22, 38] Last, our study failed to document the previously reported reduced LF_{RR} associated with SCD,[38] probably because we had too few subjects in the SCD group.

LIMITATIONS

Although the small study sample analyzed, particularly in the SCD group, as well as our patients' the single ischemic etiology provide homogenous data for, we acknowledged them also as limitations because they prevent us from extrapolating our findings to other patients with CHF.

CONCLUSIONS

This study provides further evidence supporting greater temporal repolarization lability and lower heart rate variability in subjects with CHF who

died of SCD than in those who survived. Even though our data show that $QT_{peak}VI$ and $T_{peak}-T_{end}VI$ both contribute significantly to $QT_{end}VI$ in patients with CHF, further studies need to investigate their possible role in identifying patients with a moderately depressed LVEF who are at substantial risk of SCD though not yet considered eligible for ICD implantation.

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