Dynamicity of Early and Late Phases of Repolarization in Patients with Remote Anterior Myocardial Infarction: The Interlead Differences

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Background: Repolarization dynamicity (QT/RR) is supposed to be a prognostic marker in post-MI patients. However, data on the relationships between early and late phases of QT and RR intervals (QT peak/RR and T peak–T end/RR) are insufficient, and which ECG lead should be used for the analysis is unclear. We analyzed repolarization dynamicity in patients after anterior MI with and without VT/VF history using two leads of Holter recordings- modified V_5 and V_3. The daytime and nighttime periods were also analyzed.

Methods: Cohort of 88 patients after anterior MI (>6 months) consisted of 43 patients without VT/VF (33 males; 59 ± 12 years; LVEF: 41 ± 7%; NoVT/VF), and 45 patients with VT/VF history- ICD implanted as secondary prevention (40 males; 64 ± 10 years; LVEF: 32 ± 8%; VT/VF). QT/RR, QT peak/RR and T peak–T end/RR were calculated from 24-hour ECG for the entire recording, daytime and nighttime periods, from V_5 and V_3 leads, respectively.

Results: VT/VF patients had lower LVEF ($P = 0.001$). There were no differences in age and gender. VT/VF group had steeper QT/RR, QT peak/RR, and T peak–T end/RR in V_5: 0.233 ± 0.04 versus 0.150 ± 0.05, $P = 0.0001$, 0.181 ± 0.04 versus 0.120 ± 0.04, $P = 0.0001$, 0.052 ± 0.02 versus 0.030 ± 0.02, $P = 0.0001$, and in V_3: 0.201 ± 0.04 versus 0.149 ± 0.05, $P = 0.0001$, 0.159 ± 0.03 versus 0.118 ± 0.04, $P = 0.0001$, and 0.042 ± 0.02 versus 0.031 ± 0.02, $P = 0.004$; respectively. VT/VF patients had higher indices in V_5 than in V_3 lead ($P = 0.001$). QT/RR and QT peak/RR were steeper at daytime period in both leads. It was not found for T peak–T end/RR.

Conclusions: Patients with VT/VF history are characterized by steeper relationships between repolarization duration and RR intervals. These findings are more evident in modified V_5 lead.

Ann Noninvasive Electrocardiol 2012;17(2):101–107

QT dynamicity; QT peak; T peak–T end; myocardial infarction; ventricular tachycardia; ventricular fibrillation

Identification of post–myocardial infarction patients (post-MI) being at higher risk of cardiac death or sudden cardiac death (SCD) is still a primary goal of many studies and trials.[1] Dynamicity of the ventricular repolarization measured as a relationship between QT interval and preceding RR cycle duration was found to be simple method, which may be assessed noninvasively from Holter recordings. The steepness of QT/RR slope indicates heart-rate dependency of repolarization duration, what reflects magnitude of the repolarization prolongation at longer RR cycles and shortening of

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Conflict of interest: none declared

QT at lower RR cycles. Steeper slopes were found in healthy subjects during daytime period and in women, but day-to-night differences decreased with age.[2,3] The interindividual and intraindividual differences were also found, which seems to be genetically and physiologically determined. In post-MI patients, it is supposed that nonadequate prolongation of repolarization duration during lower heart rates, and/or excessive shortening of repolarization at higher rates may contribute to malignant ventricular arrhythmias occurrence (VT/VF).[4] However, there is still small number of articles that contain data on QT dynamicity behaviour in post-MI patients. Chevalier[5] for the first time showed the relationship between QT/RR slope and risk of death and SCD in post-MI patients. Similar results were given from MADIT II subanalysis,[6,7] and by Jensen et al.[8] Cygankiewicz and Zareba found repolarization dynamicity as independent risk factor of total mortality and SCD in patients with heart failure due to ischemic and nonischemic left ventricle (LV) impairment.[9,10] This study has also reported steeper QT/RR slopes and significant reduction of day-to-night differences in VT/VF patients—ICD recipients.[11] However, further studies are still recommended to prove the clinical utility of QT dynamicity indices in risk stratification.[12]

As it is well known, the repolarization process consists of two phases—early repolarization (QT peak: time from the onset of QRS complex to the peak of T wave) and late phase (T peak–T end: time from the peak to the end of T wave). QT peak was found to be strongly related to autonomic nervous system influences, T peak–T end is regarded as a repolarization phase independent of sympathovagal modulation and related to instrinsic myocardial attributes, which, in post-MI patients, may be a consequence of changes in myocardial wall structure or/and persistent local ischaemia.[13] Long-term, beat-to-beat analysis of the QT interval with the use of Holter recordings seems to be helpful method in assessment of repolarization duration and QT dynamicity. However, up to day, there is still no consensus which lead should be used for the most accurate analysis of repolarization indices.

The purpose of the study was to analyze dynamicity of early and late phases of repolarization in patients with remote anterior MI with and without history of VT/VF, with the use of two basic lead configurations of Holter recordings—modified lead V_5 and V_3.

METHODS

Study Population

The cohort of 124 patients with remote anterior MI (>6 months from the episode) was examined retrospectively. All clinical data were collected including the history of arterial hypertension (HA), diabetes mellitus (DM), previous CABG (patients who underwent CABG procedure <6 months before hospitalization were excluded), treatment with beta-blockers and angiotensin converting enzyme inhibitors (ACEI). Sixteen patients were excluded from analysis due to the treatment with amiodarone or high doses of sotalol (>240 mg/day), and in 20 cases Holter recordings did not meet criteria of accurate analysis of repolarization given below. Study population consisted of 88 subjects and was, then, divided into two groups: 43 patients without history of VT/VF episodes (33 males; 59 ± 12 years; LVEF: 41 ± 7%; NoVT/VF group) and 45 patients with hemodynamically unstable VT or VT/VF history, all subjects had cardioverter-defibrillator (ICD) implanted as secondary prevention of SCD (40 males; 64 ± 10 years; LVEF: 32 ± 8%; VT/VF).

Echocardiography was performed with commercial system Vivid 7 (GE, Vingmed, Horten, Norway) and LVEF was assessed using Simpson's method. Holter recordings were performed in VT/VF subjects before ICD implantation at least 10 days after VT/VF episode(s). Patients with episodes of atrial tachycardia, atrial flutter/fibrillation, and numerous atrial (PAC) and/or ventricular (PVC) ectopic captures (>1/min) during recording were not included. All patients were fully mobile with functional class NYHA I or II.

QT/RR, QT peak/RR, and T peak–T end/RR were calculated from 24-hour Holter ECG during the entire recording (E), daytime (D), and nighttime (N) periods, from both modified V_5 and V_3 leads, simultaneously.

Measurement of QT Dynamicity

Repolarization indices (QT, QT peak, and T peak–T end) were analyzed on a Pathfinder 700 (Reynolds Medical, Hertford, UK) from the 3-lead Holter recordings (Lifecard CF, Reynolds Medical). All Holter recordings met the following criteria: sinus rhythm, minimum 18 hours of recording and minimum of 90% of successive QT interval suitable for analysis. Amplitude of T waves was >0.25

Table 1. Study Population Characteristics—Average ± SD.

Variables	NoVT/VF (n = 43)	VT/VF (n = 45)	P value
Men	33 (77%)	40 (89%)	0.16
Age (years)	59 ± 12	64 ± 10	0.06
Hypertension	26 (61%)	26 (58%)	0.006
Diabetes mellitus	13 (31%)	10 (22%)	0.46
Previous CABG	3 (7%)	12 (27%)	0.022
LVEF (%)	41 ± 7%	32 ± 8%	0.005
beta-blockers	40 (93%)	40 (89%)	0.20
ACEI	34 (79%)	35 (78%)	0.55
Average HR (bpm)	65 ± 9	66 ± 8	0.38
Minimum HR (bpm)	53 ± 8	54 ± 7	0.24
PAC (median, 25–95 percentile)	7 (1–12)	32 (2–88)	0.01
PVC (median (25–95 percentile)	264 (10–681)	517 (264–1202)	0.001

ACEI-angiotensin converting enzyme inhibitors; CABG = coronary artery bypass grafting; HR = heart rate; LVEF = left ventricle ejection fraction; PAC = premature atrial contraction; PVC = premature ventricular contraction

mV, the polarity of T waves was positive or negative, all recordings with biphasic T waves were not included. QT interval was measured automatically from CS2 channel, which is closest to anteroseptal V_3 lead[14] and CM5 channel, which corresponds to V_5 lead from the standard 12-lead ECG. Files of QT and RR intervals generated with commercial QT/RR Research Tools Package Reynolds Medical v. 1.0 were then analyzed on a personal computer with commercially available package Statistica v. 7.1 (StatSoft Inc., Tulsa, OK, USA). QT/RR, QT peak/RR, and T peak–T end/RR slopes as linear regression functions between repolarization indices and preceding RR cycles were computed from the entire recording (E) and from daytime (D) (2 p.m.–10 p.m.) and nighttime (N) (10 p.m.–6 a.m.) periods.

Statistical Analysis

All continuous variables are presented as means ± SD and categorical variables as absolute numbers and proportions. Continuous data were compared with the Student's *t*-test, Mann–Whitney *U*-test, ANOVA, and ANOVA Friedmann tests, categorical variables with the chi-square test or Fisher's exact test, where appropriate.

In order to analyze the relationships between QT dynamicity indices differences the log-linear regression analysis with covariates, Pearson's correlation coefficients, MANOVA and MANCOVA tests were used. These were done with regard to the categorical as well continuous variables. The best combinations of sensitivity and specificity were taken from the receiver-operating characteristics analysis (ROC). P value of <0.05 was considered as significant. Statistical analysis was performed with Statistica 7.1 (StatSoft Inc., Tulsa, OK, USA).

The study protocol was approved by the Local Ethical Committee.

RESULTS

Patient Clinical Characteristics

The clinical data of NoVT/VF and VT/VF subjects were summarized in Table 1. Study groups did not differ in age, gender, the presence of diabetes, and treatment (beta-blockers, ACE inhibitors). Previous CABG was more frequent in VT/VF patients (only three out of NoVT/VF patients have had CABG procedure). This group had also lower LVEF (32 ± 8 vs. 41 ± 7%, P = 0.005), and more frequent both PAC and PVC. Study groups did not differ in average and minimum heart rates.

Analysis of QT Dynamicity Indices

The relationships between the study parameters and continuous variables such as LVEF, age, HR avg, HR min, PAC, and PVC number were found to be weak or moderate (with r <0.50) (Table 2-results given for LVEF, age, and HR avg).

Univariate analysis performed for all study parameters (QT/RR, QT peak/RR, and T peak–T end/RR obtained in modified V_5 and V_3 leads) revealed that all indices were higher in V_5 lead in VT/VF subjects, but not in NoVT/VF patients (Table 3). Similar differences were found for daytime and nighttime periods, all slopes were significantly steeper in V_5 than V_3, in VT/VF subjects,

Table 2. Relationships between Study Indices (Entire Recording) and Basic Continuous Covariates

Variables	R Spearman	P value
LVEF and QT/RR (V_5)	−0,50	0.001
LVEF and QT peak/RR (V_5)	−0,46	0.001
LVEF and T peak–T end/RR (V_5)	−0.32	0.002
LVEF and QT/RR (V_3)	−0.42	0.001
LVEF and QT peak/RR (V_3)	−0.34	0.002
LVEF and T peak–T end/RR (V_3)	−0.33	0.002
Age and QT/RR (V_5)	0.11	0.31
Age and QT peak/RR (V_5)	0.04	0.71
Age and T peak–T end/RR (V_5)	0.11	0.31
Age and QT/RR (V_3)	0.08	0.47
Age and QT peak/RR (V_3)	0.12	0.26
Age and T peak–T end/RR (V_3)	0.02	0.84
HR avg and QT/RR (V_5)	0.37	0.001
HR avg and QT peak/RR (V_5)	0.41	0.001
HR avg and T peak–T end (V_5)	0.25	0.02
HR avg and QT/RR (V_3)	0.34	0.002
HR avg and QT peak/RR (V_3)	0.28	0.01
HR avg and T peak–T end/RR (V_3)	0.18	0.09

but not in NoVT/VF patients (Table 4). We did not find the significant influence of the gender on the differences between study groups. There were no remarkable influences of the age, number of PAC and PVC, on the differences between study groups in multivariate analyses. The basic model finally included the age, LVEF, and HR avg. As the result it was found that only QT peak/RR and T peak–T end/RR at nighttime period had $P > 0.05$ for NoVT/VF versus VT/VF (Table 3 and 4).

The day-to-night differences occurred in both groups for QT/RR and QT peak/RR, but not for T peak–T end/RR. All indices were found higher during daytime period.

Sensitivity and Specificity of Repolarization Dynamicity Indices

According to ROC curves the cutoff value with the highest test accuracy was taken for each study parameter (data for entire period are presented in Table 5). The odds ratios were higher for all indices computed from V_5 lead.

DISSCUSION

This study showed that patients with remote anterior MI and history of malignant ventricular arrhythmias had increased repolarization dynamicity expressed as slope of linear regression between QT, QT peak or T peak–T end, and preceding RR intervals. It was observed both during daytime and nighttime period, independently. The results obtained for VT/VF subjects showed the presence of significant differences between repolarization dynamicity parameters measured at two basic channels of Holter recording with higher values in lead configuration corresponding to V_5 in standard 12-lead ECG. Diagnostic values of the all study indices were also higher when data from modified V_5 were analyzed.

Studies on healthy subjects revealed the presence of sex-dependent differences in QT/RR relationship which was steeper in women.[2] In this study the gender related influence on the repolarization dynamicity indices has not been found. It is in concordance with results presented by Bonnemeier et al.,[15] the possible effect of gender on QT dynamics had also not been presented in other articles.[5,8,10] Moreover, it is meaningful to mark that adjustment of QT dynamicity to other categorical and continuous variables showed influence not remarkably significant on differences between study groups.

Table 3. QT Dynamicity Indices in Study Groups—Entire Recording (Mean ± SD)

	NoVT/VF	VT/VF	P
QT/RR (V_5)	0.150 ± 0.048	0.233 ± 0.043	0.0001 (0.0001)
QT/RR (V_3)	0.149 ± 0.051	0.201 ± 0.040	0.0001 (0.0001)
	0.694	0.0001	
QT peak/RR (V_5)	0.120 ± 0.041	0.181 ± 0.043	0.0001 (0.0001)
QT peak/RR (V_3)	0.118 ± 0.044	0.159 ± 0.033	0.0001 (0.001)
	0.201	0.015	
T peak–T end/RR (V_5)	0.030 ± 0.020	0.052 ± 0.018	0.0001 (0.001)
T peak–T end/RR (V_3)	0.032 ± 0.021	0.042 ± 0.017	0.005 (0.01)
	0.245	0.002	

P given in parenthesis, after adjustment for age, LVEF, and HR avg.

Table 4. QT Dynamicity Indices in Study Groups—Daytime and Nighttime Periods (Mean ± SD)

	NoVT/VF	VT/VF	P
QT/RR (V_5) daytime	0.139 ± 0.058	0.218 ± 0.061	0.0001 (0.0001)
QT/RR (V_3) daytime	0.139 ± 0.059	0.203 ± 0.054	0.0001 (0.001)
QT/RR V_5 versus V_3 daytime (P)	*0.526*	*0.002*	
QT peak/RR (V_5) daytime	0.109 ± 0.0453	0.159 ± 0.050	0.0001 (0.0001)
QT peak/RR (V_3) daytime	0.106 ± 0.057	0.142 ± 0.047	0.001 (0.004)
QT peak/RR V_5 versus V_3 daytime (P)	*0.168*	*0.009*	
T peak–T end/RR (V_5) daytime	0.030 ± 0.021	0.059 ± 0.018	0.0001 (0.0001)
T peak–T end/RR (V_3) daytime	0.032 ± 0.022	0.051 ± 0.024	0.001 (0.002)
T peak–T end/RR V_5 versus V_3 daytime (P)	*0.216*	*0.01*	
QT/RR (V_5) nighttime	0.117 ± 0.051	0.190 ± 0.059	0.0001 (0.003)
QT/RR (V_3) nighttime	0.120 ± 0.046	0.157 ± 0.067	0.007 (0.03)
QT/RR V_5 versus V_3 nighttime	*0.957*	*0.001*	
QT peak/RR (V_5) nighttime	0.095 ± 0.046	0.139 ± 0.055	0.0001 (0.002)
QT peak/RR (V_3) nighttime	0.094 ± 0.042	0.122 ± 0.053	0.02 (0.069)
QT peak/RR V_5 versus V_3 nighttime (P)	*0.94*	*0.016*	
T peak–T end/RR (V_5) nighttime	0.025 ± 0.014	0.053 ± 0.027	0.0001 (0.001)
T peak–T end/RR (V_3) nighttime	0.028 ± 0.015	0.036 ± 0.024	0.081 (0.232)
T peak–T end/RR V_5 versus V_3 nighttime (P)	*0.645*	*0.001*	

P given in parenthesis, after adjustment for age, LVEF and HR avg

Table 5. Odds Ratio, Sensitivity, and Specificity of Indices of Repolarization Dynamicity in Study Population

	Cutoff Value	Sensitivity	Specificity	Test Accuracy	OR (95%CI)	P
QT/RR						
Lead V_5	0.198	82%	81%	82%	9.1 (3.4–28.9)	0.0001
Lead V_3	0.181	56%	76%	66%	4.1 (1.64–10.4)	0.003
QT peak/RR						
Lead V_5	0.167	51%	89%	70%	7.95 (2.6–23.9)	0.0001
Lead V_3	0.156	44%	86%	65%	4.9 (1.74–14.0)	0.003
T peak–T end/RR						
Lead V_5	0.047	55%	83%	69%	6.4 (2.4–17.5)	0.0002
Lead V_3	0.040	51%	71%	61%	2.7 (1.1–6.55)	0.03

There were no patients on amiodarone or other true antiarrhythmics in our study. However, it was reported that beta-blockers had remarkable influence on QT/RR relationship. Bonnemeier et al.[16] found that treatment with carvedilol, and in less extent with metoprolol, improved QT dynamicity in patients after PCI for acute MI. It was also reported by Furukawa et al.[17] in post-MI patients who were treated with metoprolol, bisoprolol, or carvedilol. Our study groups were very similar with respect to the treatment with beta-blockers, and what should be underscore >90% of patients were treated mostly with metoprolol, rarely bisoprolol or carvedilol. Therefore, the effect of beta-blockade on the results, in our opinion, might be omitted.

Diurnal differences in QT dynamics were reported in healthy subjects. Sredniawa et al.[2] and Jensen et al.[18] reported that QT/RR slope was steeper at daytime period and less steep at night. Faber et al.[19] in patients with severe heart failure revealed a complete loss of day-to-night differences. A significant decrease in day-to-night pattern in post-MI patients, especially those who experienced VT/VF, was presented in our previous study.[11] In recent article, it was not the purpose of the study and, therefore, we did not discuss this problem.

Prognostic value of QT/RR and QT peak/RR slopes was evaluated in few studied. Chevalier et al.,[5] in prospective multicenter GREPI trial, analyzed the group of 265 patients with acute MI and

found QT/RR >0.18 as a strong predictor of SCD in this population, but only when assessed from daytime period. Jensen et al. found QT/RR slope measured in acute phase of MI to be significantly higher in patients who died during 3-years follow-up. Cygankiewicz et al. analyzed group of 542 patients with congestive heart failure, in 49% of ischemic origin. They found significantly higher QT/RR and QT peak/RR slopes in nonsurvivors, both at daytime and nighttime periods. They concluded that QT/RR >0.22 and QT peak/RR >0.20 during the daytime were associated with an increased risk of total mortality but not a SCD risk. In this article, we did not analyze a predictive value of repolarization dynamicity indices because of retrospective protocol of the study. However, VT/VF patients, similarly to nonsurvivors in articles cited above, were characterized by a steeper QT/RR and QT peak/RR slopes during both daytime and nighttime periods. In our study, the best cutoff points for QT/RR and QT peak/RR were very close to those presented by Cygankiewicz or Chevalier. Sensitivity, specificity, and odds ratios calculated for these cut-off points, in our opinion, were satisfactory for the use in diagnostic evaluation of post-MI patients, especially for QT/RR measured from entire recording in V_5 lead, which has the highest operating room and test accuracy.

Interestingly, in recently published article, Jarvenpaa et al.[20] found steeper QT/RR slopes in post-MI patients without history of VF, than in those who had been resuscitated from VF. It was observed during both daytime and nighttime. It should be underscored, that authors analyzed patients who suffered from ventricular fibrillation, with no history of VT, what may, also in our opinion, influence these results. It seems that further studies regarding the relationship between the type of ventricular arrhythmias and the repolarization dynamicity are necessary.

In this study we reported, that T peak–T end/RR slopes were also steeper in VT/VF patients. Nakagawa et al. demonstrated in the group of healthy volunteers, that T peak–T end/RR slopes were significantly greater in women than men with values of 0.025 ± 0.009 and 0.011 ± 0.012, respectively. Results of T peak–T end/RR obtained in our study population were 2- to 3-fold higher. According to our knowledge, there are no articles regarding the T peak–T end/RR relationship in post-MI patients. However, it may be speculated that stronger relationship between T peak–T end and preceding RR cycle might be related to changes in myocardial attributes caused by myocardial infarction scar and surrounding ischemic tissue. The explanation of this phenomenon and its clinical utility needs further analysis.

One of the findings presented in this article is the presence of differences in repolarization dynamicity indices measured in different leads of Holter recording. This problem was previously mentioned by Yeragani et al.[21] who found significant differences between QT variability parameters obtained from continuous ECG recordings with channels corresponding to leads V_5, V_1, and V_3. Hiromoto et al.[22] reported presence of strong relationships between echocardiographic LV function indices and QT variability parameters, but only when measured from leads corresponding to the myocardial infarction site. In our study all dynamicity indices were less steep in V_3 lead, with lower sensitivity, specificity, and odds ratio. These interlead differences might be related to inhomogeneity of repolarization process in subsequent layers of myocardium, as well as differences in the proportions between ischemic and necrotic myocardium as the consequence of prior anterior infarction. However, both modified leads used in this study, correspond to the anterior site of myocardial infarction and patterns of repolarization dynamicity which might be found in other, not related to MI location ECG leads are unknown. It may be regarded as the limitation of our study, but, on the other hand, it was also its advantage. These results suggest the presence of the spatial dispersion of repolarization dynamicity, which may contribute to the VT/VF generation mechanisms.

These results may have important implication for the further studies. In our opinion, the same lead should be used in analysis of repolarization indices and repolarization dynamicity in all examined subjects. On the other hand, it might be that higher value of repolarization dynamicity should be used when two or even more measures in study patient are possible. However, the issue of relationship between site of MI and optimal lead configuration should be further explored.

Study Limitations

The study had a retrospective protocol, but in our opinion, the comparison of two so different groups of patients may add important information on diagnostic power of repolarization dynamicity. The

clinical value of repolarization dynamicity is still under intensive exploration. Therefore, we think that any information on repolarization dynamics, especially taken from VT/VF survivors, may be important in preparing further large clinical studies. However, it is meaningful to mark that our findings need to be considered with a caution and the confirmation of our observations in prospective studies is absolutely necessary.

Another limitation might be related to different LVEF in study groups. The significant relationships between LVEF and repolarization indices were found and some interactions on the dynamicity steepness could not be omitted.

CONCLUSIONS

Patients with malignant ventricular arrhythmias are characterized by steeper relationships between repolarization duration (entire, early, and late phase) and RR intervals. These findings were more evident in modified V_5 than V_3 lead, indicating on the spatial dispersion of repolarization dynamicity.

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