Impact of Left Ventricular Remodeling on Ventricular Repolarization and Heart Rate Variability in Patients after Myocardial Infarction Treated with Primary PCI: Prospective 6 Months Follow-up

Krzysztof Szydio, M.D., Ph.D., Krystian Wita, M.D., Ph.D.,
Maria Trusz-Gluza, M.D., Ph.D., Dagmara Urbanczyk, M.D., Ph.D.,
Artur Filipiecki, M.D., Ph.D., Witold Orszulak, M.D. Ph.D., Zbigniew Tabor, M.D.,
Jolanta Krauze, M.D., Ph.D., Wojciech Kwasniewski, M.D., Ph.D.,
Jarosław Myszor, M.D., Ph.D., Maciej Turski, M.D., Jarosław Kolasa, M.D.,
and Jan Szczogiel, M.D.

From the I Department of Cardiology, Silesian Medical University, Katowice, Poland

Background: The relation between postinfarction left ventricle remodeling (LVR), autonomic nervous system and repolarization process is unclear. Purpose of the study was to assess the influence of LVR on the early (QTpeak) and late (TpeakTend) repolarization periods in patients after myocardial infarction (MI) treated with primary PCI. The day-to-night differences of repolarization parameters and the relation between QT and heart rate variability (HRV) indices, as well left ventricle function were also assessed.

Methods: The study cohort of 104 pts was examined 6 months after acute MI. HRV and QT indices (corrected to the heart rate) were obtained from the entire 24-hour Holter recording, daytime and nighttime periods.

Results: LVR was found in 33 patients (31.7%). The study groups (LVR+ vs LVR-) did not differ in age, the extent of coronary artery lesions and treatment. Left ventricle ejection fraction (LVEF) was lower ($38\% \pm 11\%$ vs $55\% \pm 11\%$, $P < 0.001$), both QTc (443 ± 26 ms vs 420 ± 20 ms, $P < 0.001$) and TpeakTendc (98 ± 11 ms vs 84 ± 12 ms, $P < 0.005$) were longer in LVR+ patients, with no differences for QTpeakc. Trends toward lower values of time-domain (SDRR, rMSSD) HRV parameters were found in LVR+ pts. Day-to-night difference was observed only for SDRR, more marked in LVR-group. Remarkable relations between delta LVEF (6 months minus baseline), delta LVEDV and TpeakTendc were found, with no such relationships for QTpeakc.

Conclusions: The patients with LVR have longer repolarization time, especially the late phase-TpeakTend, which represents transmural dispersion of repolarization. Its prolongation seems to be related to local attributes of myocardium and global function of the left ventricle but unrelated to the autonomic nervous influences. Remodeling with moderate LV systolic dysfunction is associated with insignificant decrease in HRV indices and preserved circadian variability. **A.N.E. 2008;13(1):8-13**

QT interval; myocardial infarction; repolarization; dispersion of repolarization heart rate variability; left ventricular remodeling

Left ventricular remodeling (LVR) is characterized by progressive LV dilatation, rearrangement of the wall structure, myocyte hypertrophy, and increase of muscle mass without an increase in wall thickness. LVR may occur despite the persistent pa-

tency of the infarct related artery among patients with acute myocardial infarction (MI) successfully treated with primary percutaneous coronary intervention (PCI).^{1,2} Moreover, it does not correlate strongly with left ventricle ejection fraction

Address for reprints: Dr n.med. Krzysztof Szydio. I Klinika Kardiologii, Śląska Akademia Medyczna, Samodzielny Publiczny Szpital Kliniczny, ul. Ziołowa 47, 40-635 Katowice, Poland. Fax: +48 32 252 36 58; E-mail: krzysztofszydio@onet.eu

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(LVEF).^{3,4} It was also found that LVR influences the prognosis in patients after MI and therefore is a subject of intensive investigation. Little is known about the association between the LVR, autonomic nervous system function, and ventricular repolarization process, which may be prolonged or non-uniform in overloaded left ventricle.^{5,6} Additionally, sympathetic denervation was also found to prolong repolarization time.⁷

New methods facilitate the automatic measurement of the QT interval what provide information about dynamicity and heart rate dependency, and day-to-night differences of repolarization. Furthermore, these methods enable accurate measurement of early (QTpeak) and late (TpeakTend) repolarization. Recently, Antzelevitch et al.^{8,9} demonstrated that differences in the action potential duration between M cells and epicardial or endocardial layers create a transmural dispersion of repolarization which can be measured as the T-wave peak-to-end interval. The relationship between transmural dispersion and occurrence of ventricular tachyarrhythmias was assessed mainly in experimental models and in few studies regarding congenital and acquired long QT syndromes. It may be supposed that this index may be abnormal in patients with LVR.

PURPOSE

The purpose of the study was to assess the influence of LV remodeling on early (QTpeak) and late (TpeakTend) repolarization parameters in patients after MI treated with primary PCI. The day-to-night differences of repolarization parameters and the relation between QT and heart rate variability (HRV) indices, as well left ventricle function were also estimated.

METHODS

Study Population

We prospectively studied 104 patients (75 males and 29 females; mean age 57 ± 10 years) who underwent the first anterior MI treated successfully with primary PCI in the left anterior descending coronary artery (TIMI flow grade 3) within 12 hours from the infarction symptoms onset. Follow-up examinations were performed after 6 months. The study protocol was approved by the Local Ethical Committee.

Echocardiography

Two-dimensional echocardiography was performed twice in each patient: at the second day of acute MI and 6 months later with commercial system Vivid 7 (GE). Left ventricular end-diastolic (LVEDV), end-systolic (LVESV) volume, and left ventricular ejection fraction (LVEF) using Simpson method were assessed. LVR was defined as >20% increase in the LVEDV at 6 months in comparison with the baseline study. According to the presence or absence of remodeling the patients were divided into LVR (+) and LVR (−) groups, respectively. Delta LVEF and delta LVEDV defined as differences between results obtained 6 months after PCI and at baseline (the second day after PCI: LVEF₀ and LVEDV₀, respectively) were also calculated.

Coronary Angiography

A repeated coronary angiography was performed after 6 months after the primary PCI in all patients. Restenosis was defined as >50% diameter stenosis of the culprit lesion on follow-up examination.

24-hour Holter ECG Recording

Holter recordings were performed 6 months after acute MI using three channel Lifecard DelMar Reynolds recorders with the sampling rate of 128 Hz and analyzed with Pathfinder 700 system. Recordings with less than 18 hour of data or frequent premature atrial or ventricular beats (>10 hour), episodes of atrial flutter or fibrillation, were not included. All subjects were in sinus rhythm and did not have bundle-branch block or QRS complex duration >120 ms.

Measurements

Repolarization Parameters

QT time from the beginning of the QRS complex to the end of the T wave, QTpeak time from the beginning of the QRS complex to the peak of the T wave and TpeakTend time from the peak to the end of T wave were used. All these intervals were corrected according to Bazett's formula using preceding RR interval—QTc, QTpeakc, TpeakTendc. QT intervals were measured automatically from CS2 channel, which is closest to anteroseptal V₂ or V₃ leads of standard surface 12-lead ECG recording.¹⁰

The accuracy of automatic measurement was verified manually at 20–30 minutes intervals.

Heart Rate Variability (HRV)

Two most common time domain parameters were used: standard deviation of all RR intervals (SDRR) and root mean square of successive differences of RR intervals (rMSSD).

Both HRV and QT parameters were obtained from the entire recording (E), daytime (D) (2 pm to 10 pm and 6 am to 9 am) and nighttime (N) (10 pm to 6 am) periods.

Statistical Analysis

All variables are given as mean $\pm$ one standard deviation. Data were compared with Student's *t*-test and ANOVA or Mann-Whitney U test, ANOVA Friedman and chi-square test where appropriated. Correlations between variables were determined by Spearman test. Statistical analyses were performed with Statistica 7.1 PL software.

RESULTS

Patient Clinical Characteristics

Left ventricle remodeling was found in 33 (31.7%) patients. The clinical characteristics of LVR (+) and LVR (–) subjects are summarized in Table 1. There was no significant difference in age between the two groups but the proportion of females was higher in LVR (–). They did not differ in treatment (beta-blockers, ACE-I, statins), rate of restenosis, average heart rate, and number of atrial and ventricular premature contractions. Left ventricular end-diastolic volume was higher while ejection fraction was lower in LVR (+) group.

QT Intervals

The results of QT intervals analysis in both study groups are summarized in Table 2. The QTc and TpeakTendc intervals obtained from the entire recording, daytime and nighttime periods in LVR (+) group were significantly longer than those obtained in LVR (–) group. There was trend to higher values of QTpeakc in patients with LV remodeling, but not significant. All repolarization indices

Table 1. Study Population Characteristics

Parameter	LVR (–)	LVR (+)	P<
Gender	46 males/ 25 females	29 male/ 4 females	0.02
Age (years)	57 $\pm$ 9	58 $\pm$ 11	NS
LVEF ₀ (baseline) (%)	43 $\pm$ 7	37 $\pm$ 7	0.001
LVEF (6 months) (%)	55 $\pm$ 11	38 $\pm$ 11	0.001
Diabetes mellitus	7 pts (9.8%)	6 pts (18%)	NS
s/m vessel disease	20/51 pts	10/23 pts	NS
LAD restenosis	36.5%	35.3%	NS
LVEDV ₀ (baseline) (ml)	101 $\pm$ 32	112 $\pm$ 29	= 0.08
LVEDV (6 months) (ml)	104 $\pm$ 45	141 $\pm$ 42	< 0.001
Beta-blockers	98.7%	100%	NS
ACEI	96%	100%	NS
Statins	98.7%	100%	NS
PAC/recording	53 $\pm$ 90	25 $\pm$ 49	NS
PVC/recording	71 $\pm$ 82	67 $\pm$ 97	NS
HR avg (E)	63 $\pm$ 10	64 $\pm$ 10	NS
HR avg (N)	59 $\pm$ 10	60 $\pm$ 8	NS
HR avg (D)	67 $\pm$ 11	68 $\pm$ 10	NS

ACEI = angiotensin convertase inhibitors; HR avg (D) = average heart rate from the daytime period; HR avg (H) = average heart rate from the whole recording; HR avg (N) = average heart rate from the nighttime period; LAD = left anterior descending coronary artery; LVEDV = left ventricle end-diastolic volume; LVEF = left ventricle ejection fraction; PAC = premature atrial contraction; PVC = premature ventricular contraction; s/m = vessel disease- single or multivessel disease.

Table 2. Repolarization and HRV Parameters in Study Groups (Values Given in MS)

Parameter	LVR (–)	LVR (+)	P
QTc (E)	420 ± 20	443 ± 26	<0.001
QTc (N)	420 ± 21	447 ± 24	<0.001
QTc (D)	419 ± 19	441 ± 24	<0.001
QTpeakc (E)	336 ± 21	345 ± 27	NS
QTpeakc (N)	340 ± 36	347 ± 36	NS
QTpeakc (D)	335 ± 21	344 ± 25	NS
TpeakTendc (E)	84 ± 12	98 ± 12	<0.005
TpeakTendc (N)	83 ± 12	96 ± 11	<0.001
TpeakTendc (D)	85 ± 12	97 ± 12	<0.005
SDRR(E)	124 ± 31	119 ± 32	NS
SDRR(N)	96 ± 32	95 ± 19	NS
SDRR(D)	114 ± 31*	104 ± 27**	NS
rMSSD(E)	33 ± 15	28 ± 11	NS
rMSSD(N)	32 ± 13	30 ± 13	NS
rMSSD(D)	29 ± 12	26 ± 11	NS

* P < 0.005 for D versus N in LVR (–).

** P < 0.01 for D versus N in LVR (+).

did not show any day-to-night differences in both study groups. QTc > 440 ms was noted in 8 LVR (–) pts compared with 16 pts from LVR (+) group, P < 0.001.

Heart Rate Variability

We did not find any significant differences between both study groups in analyzed time-domain parameters (Table 2). However, there was a slight tendency to lower values in LVR (+) patients. There were 8 pts (11%) with SDRR < 70 ms in LVR (–) group and 9 pts (27%) in LVR (+), P = 0.04.

The day-to-night difference of SDRR was higher in LVR (–) group (D 114 ± 31 ms vs N 96 ± 32 ms, P < 0.005) than in LVR (+) group (D 104 ± 27

ms vs N 95 ± 19 ms, P < 0.01). We did not find any remarkable differences between D versus N for rMSSD (Table 2).

Correlation coefficients between HRV parameters and repolarization indices were computed and results are shown in Table 3. Relations between HRV and repolarization parameters were assessed using the uncorrected to the heart rate QT values. QT and, especially QTpeak, intervals correlated with both SDRR and rMSSD values independently of the analyzed period of time, while for TpeakTend intervals the correlations were insignificant.

There were significant associations between TpeakTendc intervals and both delta LVEF and delta LVEDV (Table 4) (Fig. 1), which were found in all analyzed periods. In contrast, no significant relations between QTpeakc and both delta LVEF and delta LVEDV were obtained.

DISCUSSION

In the present study, we demonstrated that patients with post MI LVR had longer QTc due to prolongation of TpeakTendc interval. Additionally, we also found a strong correlation between HRV parameters and QTpeak but not TpeakTend intervals which were highly related to 6 months changes in left ventricle ejection fraction and end-diastolic volume.

To minimize factors, such as previous MI, the site of the MI and patency of the infarct related artery, that can affect repolarization parameters and as well HRV, we only examined patients after first anterior MI who had successful primary PCI. The study population was homogenous in age and treatment. The higher number of males in LVR+

Table 3. Correlation Coefficients between HRV Parameters and Repolarization Indices

	QT	QTpeak	TpeakTend
Entire period			
SDRR	0.38*	0.41*	–0.04
rMSSD	0.39*	0.41*	–0.01
Daytime period			
SDRR	0.31**	0.35*	0.02
rMSSD	0.35*	0.39*	–0.10
Nighttime period			
SDRR	0.38*	0.38*	0.02
rMSSD	0.31**	0.35*	–0.02

*P < 0.001 **P < 0.005.

Table 4. Correlation Coefficients between, delta of LVEF, delta of LVEDV, and QT Indices

Parameter	QTc (ms)	QTpeakc (ms)	TpeakTendc (ms)
Entire recording			
Delta LVEF (%)	–0.32*	–0.01	–0.55*
Delta LVEDV (%)	0.37*	0.11	0.46*
Daytime period			
Delta LVEF	–0.32*	–0.06	–0.47*
Delta LVEDV	0.37*	0.12	0.47*
Nighttime period			
Delta LVEF	–0.31**	–0.05	–0.50*
Delta LVEDV	0.35*	0.11	0.49*

*P < 0.001 **P < 0.005.

Figure 1. Scatter plots of correlations between differences (delta) of LVEF and LVEDV obtained 6 months after PCI versus baseline, and repolarization indices: QTc and TpeakTendc calculated from the entire recording.

group, in our opinion, did not affect results remarkably. The occurrence of LVR 6 months after acute MI (31.7%) was very similar to that observed by Bolognese.³ Our LVR+ patients had LV dysfunction, which was moderate (LVEF $38\% \pm 11\%$).

A significant correlation between progressive left ventricle dilatation and QTc prolongation have been shown by Gaudron et al.¹¹ in 134 patients after MI. Similar relation was found in our study, which additionally showed significant prolongation of terminal part of the QT interval—the TpeakTendc (98 ± 12 ms vs. 84 ± 12). To our knowledge, our study is the first one indicating such relation. Recent studies suggest that the peak-to-end interval of the T wave represents the transmural dispersion of the repolarization.^{9,12,13,14} It may be the arrhythmogenic substrate and, therefore, may also be a useful index to predict ventricular tachyarrhythmias. Davey¹⁵ showed that healthy subjects had very similar values of TpeakTendc and QTc (82 ± 5 ms and 421 ± 6 ms) to our LVR (–) patients. Heart failure patients in his study had higher values of both indices (110 ± 7 ms and 461 ± 9 ms) than our LVR (+) subjects.

Circadian variation of QTc was investigated in several studies suggesting that the ventricular repolarization duration is influenced by autonomic nervous system but the results were inconsistent.

Zareba and coworkers¹⁶ did not find day-to-night differences in transmural dispersion duration in healthy group and postinfarction patients with significant LV dysfunction (LVEF $< 35\%$). In our post MI patients with and without LV remodeling all assessed repolarization parameters did not differ between daytime and nighttime periods.

Analysis of HRV revealed only the trend toward lower values of SDRR in LVR (+) patients. The day-to-night difference was also preserved both in LVR(+) and (–) subjects. HRV is affected by many factors, such as age, sex, disease status, and medications. Most cardiovascular drugs, such as beta-blockers, ACE-inhibitors, and statins, widely used in our patients, increase HRV. Moreover, 6 months after acute MI successfully treated with primary PCI, a considerable recovery of HRV should be expected. In our opinion, significant relations between SDRR and both QT and QTpeak in our study may confirm the presence of incomplete vagal withdrawal, even in LVR (+) patients.

We also found the remarkable relations between TpeakTendc and both delta LVEF and delta LVEDV, suggesting strong influence of the left ventricle function and volume changes during post MI remodelling on the terminal part of repolarization.

We think, that these correlations indicate the presence of remarkable relations between

autonomic nervous system activity, left ventricle function, myocardial attributes and the repolarization process. The significance and explanation of these relations needs further studies.

Study Limitations

The sampling rate of 128 Hz (7.8 ms) may be criticized due to limited precision to analyze Tpeak-Tend interval ranging from 70 to 125 ms. It seems that the error, which may occur during analysis is diminished by automatic, beat-to-beat repeated error. Moreover, QT interval analysis and correction were performed by one observer. The second limitation is the presence of patients with one-vessel and multivessel coronary heart disease. Despite the number of patients with different extent of coronary artery lesions was comparable in both groups, the influence of ischemia could be different.

CONCLUSIONS

Patients with LVR are characterized by longer repolarization, especially the late phase TpeakTend, which represents transmural dispersion of repolarization. Its prolongation seems to be related to local attributes of myocardium and global function of the left ventricle but unrelated to the autonomic nervous influences. Remodeling with moderate LV systolic dysfunction is associated with a slight, insignificant decrease in HRV indices and preserved circadian variability.

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