Utility of Short-Term Variability of Repolarization as a Marker for Monitoring a Safe Exercise Training Program in Patients With Cardiac Diseases

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SUMMARY

In order to begin searching for new markers for safe exercise training in patients with cardiac diseases, we tested the sensitivity and reliability of the short-term variability of repolarization (STV_{QT}) in comparison with QT interval, QTc, and T_{peak}-T_{end} interval (T_{p-e}) in patients with cardiac diseases.

Nine patients (8 men, 1 woman; 58 ± 10 years) were enrolled. The cardiac rehabilitation (CR) program consisted of walking, bicycling on an ergometer, and calisthenics for 30-50 minutes/session and 3-5 sessions/week for 3 months. ECGs of 31 consecutive sinus beats were obtained before and after the CR program. RR and QT intervals were measured in the aV_L lead. The mean orthogonal distance from the diagonal to the points of the Poincaré plots was determined using the following equation; STV_{QT} [$= \Sigma |QT_{n+1}$-$QT_n/(30 \times 2^{1/2})$], as a marker of temporal dispersion of repolarization. Also, T_{p-e} of 5 consecutive beats was measured as a marker of spatial dispersion.

No fatal arrhythmias were observed in the CR. No significant difference was observed in the RR or QT interval between at baseline and at the end of the CR program. Meanwhile, QTc, STV_{QT} and T_{p-e} decreased significantly from 429 ± 27 to 400 ± 17 ($P < 0.01$), from 6.8 ± 1.3 to 4.7 ± 1.4 msec ($P < 0.001$), and from 74.8 (61.2/79.1) to 64.8 (51.4/70.7) msec (median (25th/75th percentile), $P < 0.01$), respectively.

STV_{QT} together with T_{p-e} and QTc may reflect the time-courses of safe exercise training. (Int Heart J 2011; 52: 304-307)

Key words: Beat to beat variability of repolarization, Temporal dispersion, Spatial dispersion, Repolarization reserve, Cardiac rehabilitation

While the incidence of cardiac arrest has been reported to be low during supervised sessions of cardiac rehabilitation (CR),[1)] its fatality rate is high once it has happened. Recently, CR has been indicated for patients with moderate heart failure who would have higher risk of arrhythmic events than those with mild heart failure, increasing the need for sensitive and reliable markers for predicting the onset of lethal arrhythmias in CR. Electrophysiological testing, including ambulatory Holter monitoring, signal-averaged electrocardiography, autonomic dysfunction and heart rate variability tests, QT interval prolongation and spatial dispersion analysis, and programmed ventricular stimulation have been used to identify patients at high risk for sudden cardiac death,[2-5)] which can be time-consuming, less sensitive, and possess a lack of versatility.

Temporal dispersion of ventricular repolarization; namely, beat-to-beat variability of repolarization calculated as short-term variability of QT intervals (STV_{QT}), has been developed for a canine sudden cardiac death model.[6)] Recently, the STV_{QT} has been applied to clinical research, showing that patients with drug-induced and congenital long-QT syndrome have greater values of QTc and STV_{QT} compared with asymptomatic patients.[7,8)] Furthermore, its clinical usefulness was also confirmed in patients with nonischemic heart failure.[9)] In the present study, we tested the sensitivity and reliability of STV_{QT} in patients with cardiac diseases who were successfully discharged after the 3-month CR program.

METHODS

In the present study, 9 patients (8 men, 1 woman; 58 ± 10 years) were enrolled, and all were successfully discharged after the 3-month CR program. Patient profiles are summarized in Table I. Indications for CR were postcardiac surgery [coronary bypass, (cases 1, 3, 7, and 8); valvular surgery, (case 6)]; recent percutaneous coronary intervention (cases 2, 4, and 9); and noncoronary heart disease (case 5). Inclusion criteria were at

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Received for publication April 27, 2011.
Accepted May 23, 2011.

Table I. Patient Profile

	Age (year)	Gender	Underlying heart disease	Intervention	LVEF (%)	eGFR (mL/minute/1.73m^2)
Case 1	40	Male	Ischemic heart disease	Coronary artery bypass graft surgery	35	67.3
Case 2	50	Male	Acute myocardial infarction	Percutaneous coronary intervention	60	76.4
Case 3	70	Male	Effort angina pectoris	Coronary artery bypass graft surgery	62	53.2
Case 4	54	Male	Acute myocardial infarction	Percutaneous coronary intervention	62	75.7
Case 5	56	Male	Idiopathic dilated cardiomyopathy		41	63.9
Case 6	68	Female	Aortic valve insufficiency	Aortic valve replacement	45	33.5
Case 7	61	Male	Acute coronary syndrome	Coronary artery bypass graft surgery	37	45.1
Case 8	55	Male	Acute myocardial infarction	Coronary artery bypass graft surgery	35	80.6
Case 9	67	Male	Acute myocardial infarction	Percutaneous coronary intervention	64	83.1

LVEF indicates left ventricular ejection fraction and eGFR, estimated glomerular filtration rate.

rest electrocardiographic recording in sinus rhythm that allowed analysis of 31 consecutive beats without premature supraventricular or ventricular complexes before and after the 3-month CR program. At baseline, diuretics were prescribed for 5 patients (cases 1, 5, 6, 7, and 8), angiotensin-converting enzyme inhibitors for 3 (cases 5, 6, and 9), angiotensin II type-1 receptor blocker for 1 (case 2), nitrates for 3 (cases 1, 2, and 7), beta-blockers for 6 (cases 1, 3, 5, 6, 7, and 8), and calcium antagonists for 3 (cases 1, 3, and 7). None of the patients was taking a class I or III antiarrhythmic agent.

CR Program: The CR program consisted of walking, bicycling on an ergometer and calisthenics with duration of 30-50 minutes/session and frequency of 3 to 5 sessions/week for 3 months. Exercise intensity was determined individually at 40-60% of heart rate reserve (Karvonen's equation: k = 0.4-0.6), an anaerobic threshold level obtained in a maximal symptom-limited cardiopulmonary exercise test, or at levels 11-13 ("fairly light" to "somewhat hard") of the 6-20 scale rating of perceived exertion. The exercise program usually began with supervised sessions for 1 week, followed by home exercise combined with once or twice a week supervised sessions for the remaining period of the CR program. Home exercise consisted mainly of brisk walking at a prescribed heart rate for 30-50 minutes, 3 to 5 times a week. All patients provided written informed consent before entering our CR program.

Electrocardiographic recording: At the beginning and the end of the 3-month CR program, 12-lead electrocardiographic recordings over 3 minutes were performed using the Cardio Star FX-7542 ECG recorder (Fukuda Denshi Co., Tokyo) in all subjects in a supine position after 10 minutes at rest. Twelve-lead electrocardiography was calibrated to 50 mm/second and 20 mm/mV. A single observer manually measured the RR and QT intervals of 31 consecutive beats, which were averaged. QT intervals were determined in lead aV_L from the onset of the QRS complex to the end of the T wave employing the method of Lepeschkin and Surawicz.[10] QT intervals were corrected for heart rate (QTc interval) using Bazett's formula.[11]

STV, defined as the mean orthogonal distance from the diagonal to the points of the Poincaré plots, was calculated as [$STV_D = \Sigma|D_{n+1}-D_n|/(30 \times 2^{1/2})$], where D_n represents the RR or QT interval of beat n for each subject. For instance, STV_{QT} [= $\Sigma|QT_{n+1}-QT_n|/(30 \times 2^{1/2})$], is a recently established sensitive marker of temporal dispersion of ventricular repolarization. This analysis acknowledges large beat-to-beat differences in repolarization duration to a higher degree than previously clinically applied algorithms of QT variability, which are based on variance.[12]

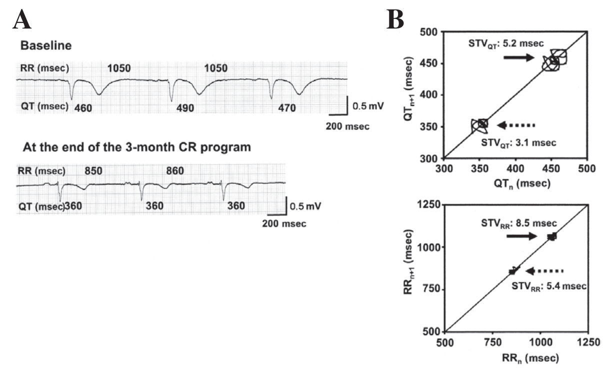

Figure. Representative electrocardiogram and associated Poincaré plots of the QT and RR intervals. **A:** Typical tracings of ECG before and after the 3-month cardiac rehabilitation (CR) program (in case 4). **B:** Typical examples of Poincaré plots of the QT interval and RR interval. Poincaré plots of 31 consecutive QT or RR intervals measured from the same patient (case 4). Solid and dot arrows indicate Poincaré plots at the baseline and the end of the 3-month CR program, respectively.

T_{peak}-T_{end} interval (T_{p-e}) is a well-known sensitive marker of spatial dispersion of ventricular repolarization.[13] A single observer manually measured T_{p-e} of 5 consecutive beats, and the average was calculated.

Clinical data: All 9 patients underwent echocardiography (Aplio XG ultrasonoscope, Toshiba Co., Tokyo) equipped with a 2.5-MHz transducer before starting the CR program. Left ventricular (LV) internal diameters were obtained from the parasternal short-axis view, approximately at the mid-ventricular level, using direct two-dimensional measurements or targeted M-mode echocardiography if the M-mode cursor could be positioned perpendicular to the septum and LV posterior wall. The LV ejection fraction was calculated by the Teichholz method.[14]

The estimated glomerular filtration rate (eGFR) was calculated, where eGFR = 194 × serum creatine$^{-1.094}$ × age in years$^{-0.287}$ for men, whereas that for females was obtained by adjusting for sex; eGFR female = eGFR × 0.739.[15]

Statistical analysis: Data are presented as the mean ± standard

Table II. Electrocardiographic Parameters at Baseline and the Values at the End of the 3-Month CR Program

Subject	Time	RR (msec)	QT (msec)	QTc	STV_{RR} (msec)	STV_{QT} (msec)	T_{p-e} (msec)
Case 1	Baseline	1082	425	409	33.9	6.4	77.2
	End	1064	423	410	18.6	5.9	71.6
Case 2	Baseline	815	416	460	10.4	9.0	74.8
	End	796	377	422	11.6	5.9	71.6
Case 3	Baseline	861	392	422	3.3	8.7	72.8
	End	1009	389	388	5.9	6.6	66.4
Case 4	Baseline	1061	457	443	8.5	5.2	129.6
	End	859	356	384	5.4	3.1	47.2
Case 5	Baseline	864	363	391	6.6	5.9	56.8
	End	986	382	385	8.7	3.8	52.8
Case 6	Baseline	848	393	427	5.9	6.1	62.4
	End	861	392	422	5.4	4.5	56.0
Case 7	Baseline	799	420	470	5.4	6.1	81.2
	End	1176	429	395	13.2	5.7	64.8
Case 8	Baseline	792	395	444	9.4	7.1	78.4
	End	814	375	416	17.4	4.0	70.4
Case 9	Baseline	806	357	398	4.2	6.8	57.6
	End	864	354	381	6.4	2.6	45.6
Baseline		881 ± 111	402 ± 31	429 ± 27	9.7 ± 9.4	6.8 ± 1.3	74.8 (61.2/79.1)
End		937 ± 129	386 ± 26	400 ± 17*	10.3 ± 5.2	4.7 ± 1.4**	64.8 (51.4/70.7)*

CR indicates cardiac rehabilitation; STV_{RR}, short-term variability of RR intervals; STV_{QT}, short-term variability of QT intervals; and T_{p-e}, T_{peak}-T_{end} intervals. Mean ± standard deviation or median (25th/75th percentile). $^{*}P < 0.01$, $^{**}P < 0.001$ compared with baseline.

deviation or the median (25th/75th percentile) when appropriate. Significant differences of paired data within a parameter were determined using the paired *t*-test or Wilcoxon signed rank test. A *P* value < 0.05 was considered statistically significant.

Results

Fatal arrhythmia was not observed in any patient during a supervised session of CR. In 4 out of 9 patients (cases 3, 7, 8, and 9), cardiopulmonary exercise testing was performed before and after the CR program, and their exercise intensity of durability increased after the CR. Typical tracings of ECG before and after the 3-month CR program are depicted in Figure A. Changes in the ECG parameters are summarized in Table II. Corrected QT intervals (QTc) decreased significantly after the end of the 3-month CR program, whereas no significant change was detected in the RR or QT intervals.

Typical examples of Poincaré plots of the QT interval are shown in Figure B, in which the QT interval and STV_{QT} decreased after the CR program. Changes in the temporal and spatial dispersion of ventricular repolarization are also summarized in Table II. STV_{QT} and T_{p-e} decreased significantly after the CR program.

Discussion

Fatal arrhythmia was not detected during supervised sessions of CR in patients, whereas ameliorations of temporal dispersions (ie, STV_{QT}) and spatial dispersion of ventricular repolarization (ie, T_{p-e}) were clearly demonstrated.

STV_{QT} has been shown to be a clinically useful marker for predicting the onset of lethal arrhythmia in patients with congenital as well as acquired heart diseases.[8,9] In our study, STV_{QT} at baseline was 6.8 ± 1.3 msec, which was greater than those reported in asymptomatic patients (5.4 ± 2.2 msec)[8], but was smaller than those in patients with congenital long-QT syndrome (9.2 ± 3.9 msec)[8] and with nonischemic heart failure having a history of ventricular tachycardia (10.1 ± 2 msec).[9] Thus, the extent of risk for lethal arrhythmia in the currently enrolled patients can be estimated to be moderate based on the average values of STV_{QT}. On the other hand, comparative analysis suggests that cases 2 and 3 might have been at risk for lethal arrhythmias since the STV_{QT} was 9.0 and 8.7 msec at baseline, respectively. Our previous animal study has demonstrated that the presence of severe bradycardia and/or sustained volume overload to the heart can increase STV_{QT} in the canine sudden cardiac death model.[16] Since we do not know now why the 2 patients showed higher values of STV_{QT}, further follow-up studies will be needed for these patients to clarify their causal link.

Previous animal studies have shown that a marked increase in STV_{QT} accompanied by QT-interval prolongation can be a sign toward the generation of early afterdepolarization.[16,17] In this study, STV_{QT} as well as T_{p-e} decreased significantly together with shortening of QTc after the 3-month CR program, indicating a reduction of temporal and spatial dispersions of repolarization of the ventricles. Recently, we have demonstrated that the L/N-type Ca^{2+} channel blocker cilnidipine decreased the STV_{QT} and shortened the QT interval by reducing the plasma angiotensin II and aldosterone levels in a canine sudden cardiac death model.[18] Such amelioration of STV_{QT} was not attained after any other pharmacological intervention,[18] indicating that the 3-month CR program may have similar effects on patients with cardiac diseases to those attained by cilnidipine in the canine sudden cardiac death model.

Study limitations: Since the number of patients included in the study was small and there is no control group, the current study can be considered as a pilot study to begin exploring new markers for a safe exercise training program in patients with cardiac diseases. Our findings need to be confirmed in a larger cohort of patients.

Conclusion: STV_{QT} together with T_{p-e} and QTc may reflect the time-courses of safe exercise training.

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