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Comparison between Ventricular Gradient and a New Descriptor of the Wavefront Direction of Ventricular Activation and Recovery

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Summary

Background: Total R T cosine (TCRT) is a new descriptor of repolarization heterogeneity that quantifies the deviation between the directions of ventricular depolarization and repolarization. It revives the old concept of ventricular gradient (VG).

Hypothesis: Our goal was to examine whether TCRT and VG contain nonredundant information by comparing their reaction to autonomic tests, namely, postural changes and Valsalva maneuver.

Methods: Digital 12-lead electrocardiograms were recorded in 16 patients with cardiovascular syndrome X (SX, chest pain, exercise-induced ST-depression, normal coronary arteries, 3 men, age 60 ± 9 years) and 40 healthy volunteers (31 men, age 33 ± 7 years) during postural changes and Valsalva maneuver. The angle (VG_A) [°] and magnitude (VG_M) [ms.mV] of VG in reconstructed XYZ leads and TCRT (average cosine of the angles between the QRS and T vectors in mathematically reconstructed three-dimensional space) were calculated.

Results: (mean ± standard of the mean): In healthy subjects, VGM and TCRT decreased, whereas VGA increased in the sitting and standing compared with supine position (TCRT: 0.61 ± 0.05, 0.47 ± 0.06, 0.29 ± 0.08, supine, sitting, and standing, $p < 0.05$) and during phase II Valsalva (TCRT: 0.47 ± 0.06 vs. 0.61 ± 0.05, $p < 0.01$ in supine, 0.24 ± 0.08 vs. 0.37 ± 0.07, $p < 0.01$ in standing). In patients with SX, VG_M decreased in the standing position, VG_A did not change significantly, while TCRT decreased only in patients without T-wave abnormalities ($n = 9$) (TCRT in standing and supine: 0.55 ± 0.09 vs. 0.68 ± 0.08, $p < 0.05$). VG_M increased during Valsalva in patients with SX. Total R T cosine correlated strongly with VG_A ($r = -0.84$, $p < 0.00001$) and, unlike VG_M, did not correlate with heart rate.

Conclusions: Ventricular gradient and TCRT contain nonredundant information. In healthy subjects, they react sensitively to autonomic provocation. In patients with SX, their reaction is attenuated, which suggests disturbance of the autonomic control of repolarization.

Key words: repolarization, ventricular gradient, total R T cosine, postural changes, Valsalva

Introduction

The reliable assessment of ventricular repolarization heterogeneity from the standard 12-lead electrocardiogram (ECG) is still an unresolved problem. Simple indices based on interlead variability of repolarization intervals or areas, such as QT dispersion, oversimplify reality[1,2] and have limited practical value. More advanced methods for quantitative repolarization assessment have been proposed,[3] but their clinical utility is still unclear.

Recently, a new descriptor of ventricular repolarization was proposed.[4] It quantifies the difference between the global direction of depolarization and repolarization, expressed as an average cosine of the angles between the QRS and T vectors in a mathematically derived three-dimensional (3-D) space (total R to T cosine, TCRT). It has been demonstrated that TCRT was more reproducible and better separated normal

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from abnormal ECGs than conventional repolarization parameters, such as QT dispersion and the corrected QT interval.[4] Two subsequent studies on prospectively collected databases showed that TCRT predicted independently adverse outcome in patients post myocardial infarction.[5, 6] Although these results need to be confirmed in truly prospective studies, it seems that TCRT has a significant potential for clinical assessment of repolarization and risk stratification of cardiac patients.

However, TCRT revives the old concept of ventricular gradient (VG),[7, 8] albeit that its calculation is based on a different principle. It is known that VG reflects the local variations in action potential duration and thus provides a global estimate of spatial heterogeneity of ventricular repolarization.[9, 10] Nevertheless, the link between VG and the risk of ventricular arrhythmia occurrence has never been studied systematically, and in the era of cardiac risk stratification the concept fell into oblivion.

The aim of this study was to compare VG and TCRT to determine whether they contain nonredundant information. For this purpose, we examined their reaction to basic autonomic tests, namely, postural changes and Valsalva maneuver. We studied a group of patients with cardiovascular syndrome X (SX), since autonomic disturbances have long been implicated in the genesis of this syndrome.[11–15] The results were compared with those obtained in healthy subjects.[16, 17]

Materials and Methods

Study Population

We investigated 16 patients (3 men, age 60.4 ± 9.1 years, range 44–79 years) with cardiovascular SX, diagnosed on the basis of typical chest pain, ST-segment depression during exercise, and no valvular, myocardial, or coronary artery disease.[18–20] None of the subjects had a history of myocardial infarction or coronary spasm. Drug treatment included diltiazem (n = 2), verapamil (n = 1), aminophylline (n = 2), long-lasting nitrate (n = 1), potassium-channel activator (nicorandil) (n = 1), and hormone replacement therapy (n = 2). Nine patients had normal baseline 12-lead ECGs, while 7 of 16 (45%) presented with repolarization abnormalities consisting of nonspecific ST-T wave changes or low-voltage T waves.

The control group included 40 subjects (31 men, mean age 33.1 ± 7.3 years, range 18–56 years) with no history of cardiovascular disease and normal resting 12-lead ECGs.[16, 17] None of them was taking medications with known or suspected autonomic or cardiovascular effect. The local Ethics Committee approved the study and all participants provided written informed consent.

Study Protocol

All participants performed postural changes (resting supine position for 10 min, followed by sitting, unsupported standing, supine, and standing position, 4 min in each position) and Valsalva maneuver (continuous expiration against 40 mmHg pressure for 30 s in controls and 20 s in patients with SX.[21] Healthy subjects performed Valsalva maneuver three times in the supine and three times in the standing position, with 4 min of rest before each maneuver. Patients with SX performed Valsalva maneuver twice in the sitting position, with 4 min of rest before each maneuver.

Twelve-lead digital ECGs (250 Hz, 12 bit A/D conversion, SEER MC ambulatory recorder, GE Marquette, Milwaukee, Wisc., USA) with Mason-Likar electrode configuration[22] were recorded continuously during the tests. The so-called "median beats" were constructed from each 10-s ECG sample of each lead[23] (QT Guard software package, GE Marquette) and subsequently were used for calculation of VG and TCRT.

Ventricular Gradient

The QRS- and T-wave areas of each beat in each lead were calculated automatically (ECG Research Workstation package, GE Marquette). The QRS- and T-wave areas in orthogonal XYZ leads were derived from the 12-lead QRS- and T-wave areas using validated transfer coefficients.[24] The magnitude of the spatial VG (VG_M) [ms.mV] was calculated as:

$$VG_m = \sqrt{(QRS_X + T_X)^2 + (QRS_Y + T_Y)^2 + (QRS_Z + T_Z)^2}$$

where QRS_W and T_W are the areas of the QRS complex and of the T wave in the orthogonal lead W, respectively. The angle of the spatial VG (VG_A) [degrees (°)], was calculated as the angle between vectors originating in the center of 3-D coordinates with final points of [QRS_X, QRS_Y, QRS_Z] and [T_X, T_Y, T_Z], respectively.

Calculation of Total R T Cosine

The calculation of TCRT is described in detail elsewhere.[4] In brief, the eight independent leads of the 12-lead ECG were subjected to singular value decomposition[25] using custom-written software. The method finds a system of eight independent leads (S_1...S_8), in which S_1 contains most of the ECG energy, that is, it corresponds to the direction in which the ECG signal varies most. S_2 contains most of the remaining ECG energy, and so forth. It has been shown that the first three leads $S_1S_2S_3$ contain 99% of the whole ECG energy.[25] The TCRT is defined as the average of the cosines of the angles between the QRS and T vectors in leads $S_1S_2S_3$. In effect, TCRT measures the difference between the directions of propagation of the wavefronts of depolarization and repolarization. Lower (and negative) values correspond to greater deviation between the two wavefronts.

Statistical Analysis

Baseline values for each parameter in each subject were calculated from the last 8 min of the baseline 10-min supine recording. Spearman rank correlation coefficients between

the parameters and between parameters and heart rate were estimated from the baseline values. The mean values of each parameter from all recordings in each position were used for comparison. The average values of each Valsalva maneuver were compared with the average value of the preceding 4-min rest. Mann-Whitney test, Wilcoxon paired test, and one-way within subject analysis of variance (ANOVA) were used for comparison of groups, as appropriate. All values were expressed as mean ± standard error of the mean (SEM). Statistical significance was defined as $p < 0.05$.

Results

Body Position (Table I)

The VG_M in all positions and TCRT in the standing position differed significantly between controls and patients (TCRT: 0.29 ± 0.08 vs. 0.55 ± 0.08, $p < 0.05$); VG_A was not significantly different between patients and controls.

Generally, TCRT changed in the same direction as VG_M and opposite to VG_A direction. In controls, VG_M and TCRT significantly decreased, while VG_A significantly increased in the sitting and further in standing compared with supine position. (Table I, Figure 1A). After assuming a new position, most of the changes of VG and TCRT were accomplished within 20 to 30 s (Fig. 2).

In the patient group, VG_M was significantly reduced in the sitting and standing compared with supine position, while VG_A and TCRT were not significantly changed (Table I). When patients with normal T waves were analyzed separately, TCRT was significantly reduced in the standing (0.55 ± 0.08) compared with the supine (0.68 ± 0.008) and sitting position (0.66 ± 0.07, $p = 0.03$) (Table I, Fig. 1C).

Valsalva Maneuver (Table II)

In controls, VGA significantly increased while VG_M and TCRT significantly decreased during phase II Valsalva (Table II) compared with the preceding rest. In patients with SX, VG_M significantly increased during phase II Valsalva, while VG_A significantly decreased only in patients without T-wave abnormalities (46.1 ± 4.3° vs. 50.0 ± 5.2°, $p = 0.02$) (Table II). The TCRT was not significantly affected by Valsalva maneuver in patients with SX.

Correlation between the Descriptors (Table III)

In steady-state supine condition, TCRT correlated strongly with VG_A in controls ($R = -0.84$, $p < 0.00001$), while in patients the correlation was moderate and of borderline statistical significance ($R = -0.46$, $p = 0.074$) (Table III). There was no significant correlation between TCRT and VG_M. Of all parameters, only VG_M in controls correlated significantly with the heart period ($R = 0.45$, $p = 0.01$, Table III).

TABLE I Effect of posture on ventricular gradient and total RT cosine (mean ± standard error of the mean)

	Supine	Sitting	Standing	p Value [c]
Normal subjects (n = 40)				
RR (ms)	1001 ± 24	876 ± 20	789 ± 19	< 0.01
VG_A (°)	44.9 ± 3.4	48.0 ± 3.7	58.4 ± 4.2	< 0.01 [d]
VG_M (mV.ms)	51.5 ± 3.8	48.7 ± 3.8	43.9 ± 3.4	< 0.01
TCRT	0.61 ± 0.05	0.47 ± 0.06	0.29 ± 0.08	< 0.01
SX patients (n = 16)				
RR (ms)	962 ± 43	890 ± 42	834 ± 46	< 0.01
VG_A (°)	54.8 ± 6.5	52.4 ± 7.0	59.6 ± 7.4	NS
VG_M (mV.ms)	31.0 ± 3.7 [b]	27.2 ± 3.6 [b]	25.7 ± 3.9 [b]	< 0.01 [e]
TCRT	0.66 ± 0.07	0.55 ± 0.11	0.58 ± 0.08 [a]	NS
SX patients with no T-wave abnormalities (n = 9)				
VG_A (°)	46.1 ± 5.7	46.3 ± 5.0	50.7 ± 4.0	NS
VG_M (mV.ms)	40.6 ± 3.3	36.1 ± 4.2	35.5 ± 4.7	< 0.05 [a]
TCRT	0.68 ± 0.08	0.66 ± 0.07 [g]	0.55 ± 0.09 [g]	0.03 [g]

The values for each position are averaged from all recordings in that position.
[a] $p < 0.05$ vs. normal subjects.
[b] $p < 0.01$ vs. normal subjects.
[c] For comparison between the three positions.
[d] Except for $p < 0.05$ between supine and sitting.
[e] Except for p = NS between sitting and standing.
[f] Except for p = NS between supine and sitting position.
[g] Of borderline statistical significance ($0.05 < p < 0.06$) vs. normal subjects.
Abbreviations: RR = RR interval, VG_A = angle of ventricular gradient, VG_M magnitude of ventricular gradient, TCRT = total R T cosine, SX = syndrome X, NS = not significant.

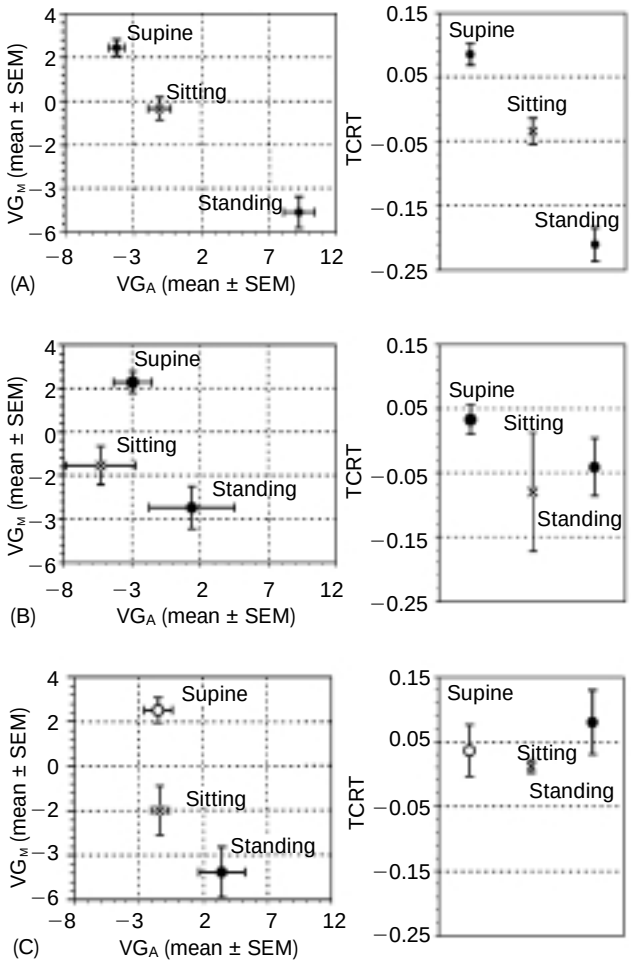

FIG. 1 Effect of posture on VG and TCRT in healthy subjects (n = 16) (A), patients with SX (n = 16) (B), and patients with SX with normal T waves (n = 9) (C). Data are presented in normalized values (e.g., deviations from the mean value). VG_A = angle of ventricular gradient [°], VG_M = magnitude of ventricular gradient [ms.mV], TCRT = total R T cosine, SX = syndrome X, SEM = standard error of the mean.

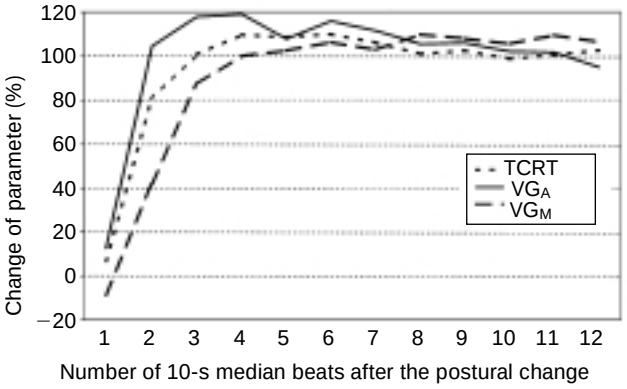

FIG. 2 Change of VG and TCRT as a function of the number of electrocardiograms during the first 2 min of a postural change in healthy subjects. Data are presented as normalized values. Ventricular gradient and TCRT during the first 2 min in a new position are compared with the mean value of the last 2 min in the previous position. The average change for the whole 4-min period in the new position is expressed as 100%. The results of the four postural transitions (i.e., supine→sitting→standing→supine→standing) are averaged. After each postural change, the average value of VG or TCRT for the new position is already reached in the second or third recording. Abbreviations as in Figure 1.

Discussion

The main finding of the study can be summarized as follows:

1. The TCRT paralleled closely the reaction of VG to postural changes and Valsalva maneuver. Nevertheless, TCRT and VG correlated only partially in steady-state supine position.
2. In healthy subjects, VG and TCRT reacted sensitively and rapidly to postural changes and Valsalva maneuver. In patients with SX, reactions were significantly attenuated.

TABLE II Effect of Valsalva maneuver on ventricular gradient and total RT cosine (mean ± standard error mean)

	Normal subjects (n = 40)				Syndrome X patients (n = 16)	
	Supine rest	Valsalva supine	Standing rest	Valsalva standing	Sitting rest	Valsalva sitting
RR (ms)	965 ± 24	891 ± 24 [b]	817 ± 22	749 ± 23 [b]	912 ± 43	840 ± 39 [b]
VG_A (°)	40.2 ± 3.01	43.7 ± 3.24 [a]	53.7 ± 4.08	58.8 ± 4.15 [a]	58.3 ± 8.11	58.7 ± 7.36
VG_M (m.Vms)	56.7 ± 4.00	52.0 ± 3.80 [b]	49.1 ± 3.93	42.6 ± 3.34 [b]	25.6 ± 3.53	28.4 ± 3.89 [a]
TCRT	0.61 ± 0.05	0.47 ± 0.06 [b]	0.37 ± 0.07	0.24 ± 0.08 [b]	0.52 ± 0.10	0.46 ± 0.13

Effect of phase II Valsalva maneuver on the descriptors (average values of all Valsalva maneuvres and all preceding 4-min resting periods).

[a] $p < 0.05$ vs. rest.

[b] $p < 0.01$ vs. rest.

TABLE III Correlation between the descriptors

		RR	VG_A	VG_M
VG_A	Healthy subjects	−0.29		
	SX patients	0.01		
VG_M	Healthy subjects	0.45 (0.01)	−0.36 (0.04)	
	SX patients	0.35	−0.40	
TCRT	Healthy subjects	0.10	−0.84 (0.000)	0.02
	SX patients	−0.23	−0.46 (0.074)	−0.26

Spearman correlation coefficients (R) between the descriptors. P values, if they are less than or close to 0.05, are given in parentheses. Abbreviations as in Table I.

The Concept of Ventricular Gradient

Both TCRT and VG_A quantify the angle between the vectors of depolarization and repolarization, and therefore they changed in opposite directions. The lack of significant correlation between TCRT and VG_A in patients with SX ($R = -0.46$, $p = 0.074$) could be explained by the different methods of their calculation. Ventricular gradient is calculated in standard orthogonal XYZ leads, whose orientation in space is subject independent and is defined purely anatomically. Leads $S_1S_2S_3$ can be regarded as XYZ leads that are spatially reoriented in each individual in such a way as to capture most of the ECG energy (for details see Appendix to Ref. No. 26). Thus, leads $S_1S_2S_3$ can be regarded as "individually optimized" XYZ leads, and TCRT as an "optimized" VG_A.

The interest in VG has been related mainly to its (relative) independence of the sequence of ventricular activation and, consequently, to its ability to distinguish primary from secondary ST-T changes. Although it was known that VG resulted from (and therefore provided a global measure of) the spatial variation of action potential duration,[9, 10] its relation to ventricular arrhythmogenesis and the risk of sudden death has never been tested prospectively. The TCRT has the same physiologic background, and this probably explains its predictive power for adverse outcome in patients post myocardial infarction.[5, 6] Kors *et al.* also demonstrated that T-axis deviation was predictive of cardiac mortality.[27] The VGA and TCRT can be regarded as "relative T axis" and "optimized relative T axis," respectively.

The moderate correlation between VG_A and VG_M and the lack of correlation between VG_M and TCRT can be explained by the fact that VG_M depends not only on the angle but also on the magnitudes of the QRS and T vectors. To our knowledge, no studies have compared the clinical significance of the angle and the magnitude of VG.

The rapid reactions of VG and TCRT to postural changes and Valsalva maneuver in healthy subjects (Figs. 2 and 3) sug-

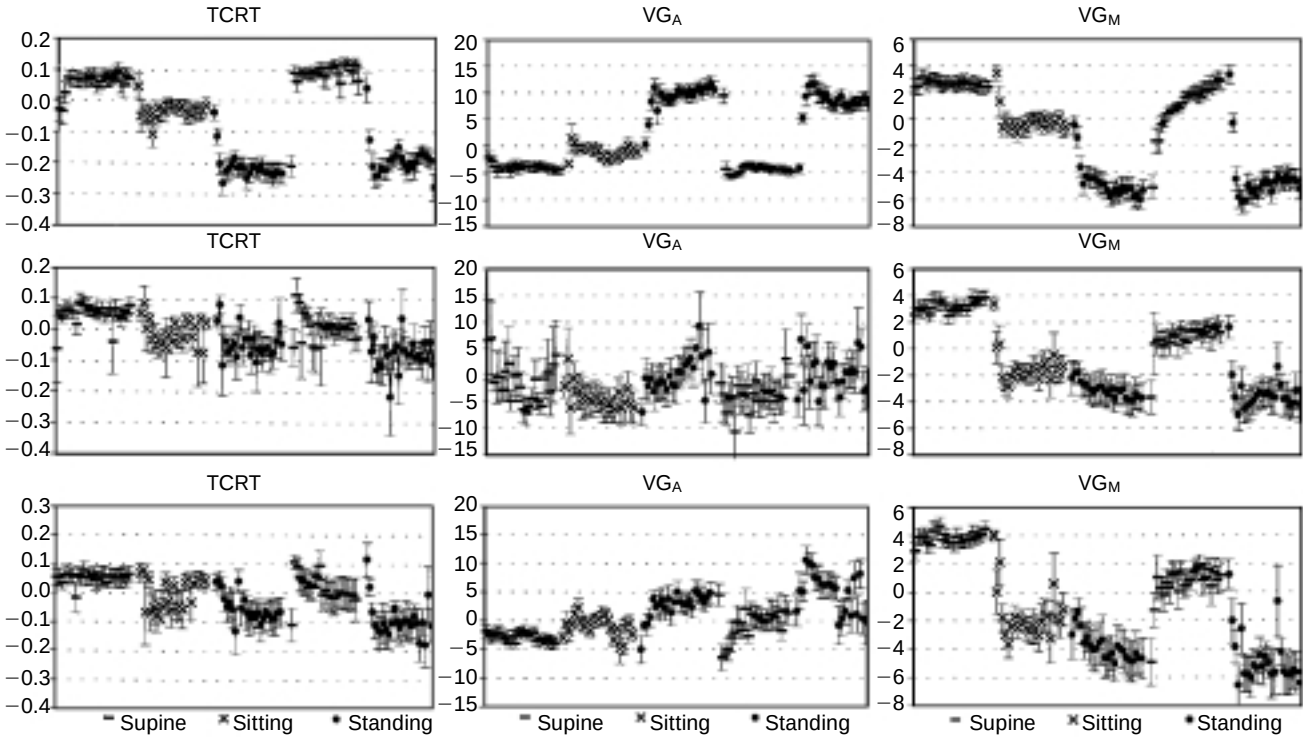

FIG. 3 Effect of body position on VG and TCRT in healthy subjects (A), patients with SX (B), and patients with SX with normal T waves (C). Each bar represents the value of the respective descriptor from one median electrocardiogram (ECG). Data are presented as normalized values; that is, deviation of the value of each median ECG beat from the mean value of all recordings in all positions. The gaps between the recordings in the separate positions are introduced only for clarity. Abbreviations as in Figure 1.

gest that they could be used to detect autonomic effects on ventricular repolarization. Reduction of the magnitude of VG in standing position compared with supine and during the strain phase of Valsalva maneuver has been described previously.[28] Although in healthy subjects TCRT and the heart period followed the same trend during postural changes (Fig. 3) and Valsalva maneuver, they did not correlate in steady state supine position. This suggests that rather than TCRT being driven by the heart rate, both TCRT and the heart rate are under autonomic control. Previous studies have found significant correlation between VG and heart rate,[28, 29] and on this basis a parameter similar to VG found limited use as a sensor for rate-adaptive pacing.[29–32]

Comparison between Healthy Subjects and Patients with Syndrome X

The attenuated response of VG and TCRT to postural changes and Valsalva maneuver, which was independent of the presence of baseline T-wave abnormalities, suggests the presence of abnormal autonomic control of ventricular repolarization in patients with SX. Shift of autonomic control toward sympathetic predominance in patients with SX has been reported previously.[11–15] Although several of these patients were taking cardioactive medications such as diltiazem, verapamil, aminophylline, and long-lasting nitrate, these drugs were more likely to influence heart rate than ventricular repolarization. Still, the RR interval did not differ significantly between patients and controls, and the effect of postural changes and Valsalva maneuver on heart rate was preserved. Hence, the response of VG and TCRT to autonomic provocation could hardly be attributed to drug effects on cardiac autonomic tone.

Other authors have also reported repolarization abnormalities in patients with SX. Lee *et al.*[33] found a higher increase in the "corrected" QT dispersion during transition from supine to standing in 26 patients with SX, compared with age- and gender-matched healthy controls and patients with coronary artery disease. Leonardo *et al.*[34] studied 16 patients with SX very similar in age and gender to those in our study. The QT dispersion was 75 ± 100 ms in patients and 30 ± 10 ms in controls (although described as "not significantly different"). Atenolol reduced QT dispersion in patients (to 17 ± 10 ms, $p < 0.05$), but not in controls (26 ± 10 ms, NS). In our study, QT dispersion was not significantly different between patients and controls in the supine position, but increased significantly during Valsalva in patients (20.3 ± 2.5 vs. 38.6 ± 5.4 $p = 0.001$), but not in controls (supine: 28.3 ± 2.4 vs. 29.4 ± 1.7, standing: 24.1 ± 1.9 vs. 24.5 ± 1.4, p = NS). However, in all these studies the differences in QT dispersion between patients and controls were within the error of both automatic and manual measurement of QT dispersion,[35–39] and the latter could hardly be regarded as a reliable parameter for quantification of repolarization abnormalities.

Limitations of the Study

Patients and controls differed significantly in age and gender, which may have influenced VG;[40] however, TCRT and VG did not differ significantly between patients and healthy subjects in supine position. Patients and controls performed Valsalva maneuver differently, since for many cardiac patients it would be difficult to maintain pressure for 30 s in the supine or standing position. However, the first 10 healthy subjects also performed Valsalva maneuver in the sitting in addition to the supine and standing position. The TCRT and VG_M significantly decreased during phase II Valsalva in the sitting position (TCRT: 0.49 ± 0.11 vs. 0.56 ± 0.09, $p = 0.034$; VG_M: 39.4 ± 3.1 vs. 42.3 ± 3.3, $p = 0.045$), while VG_A was not changed significantly. This suggests Valsalva maneuver affected repolarization independently of the body position.

The exact speed of reaction of TCRT and VG to autonomic effects cannot be estimated from 10-s median ECG beats. Still, it seems that VG and TCRT respond to autonomic provocation as fast as the heart rate (Fig. 3) and faster than other repolarization parameters, such as QT interval, QT dispersion, T-area dispersion, and indices from principal component analysis of the T wave.[12] The precise estimation of the electrophysiologic effects of all four phases of Valsalva maneuver requires analysis of beat-to-beat data, rather than 10-s median beats.

For accurate assessment of the autonomic effects on ventricular repolarization, a study under more strictly controlled conditions, for example, complete pharmacologic autonomic blockade with propranolol and atropine, is needed. To assess the effect of heart rate, postural changes, and autonomic influences, VG and TCRT should be measured during fixed-rate atrial pacing and/or graded physical exercise in the supine and standing position. However, our (main) goal was to compare VG and TCRT, using their reaction to autonomic tests rather than to study the autonomic influence on ventricular repolarization.

Conclusions

Ventricular gradient and TCRT provide clinically applicable methods for quantification of ventricular repolarization abnormalities. They contain nonredundant information. It is likely that VG and/or TCRT may find application for detection of autonomic effects on ventricular level, for example, in implantable antiarrhythmic devices or systems for in-hospital ECG monitoring.

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