Postextrasystolic Repolarization Abnormalities in ST-U Segment in Patients with Ventricular Arrhythmias

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Background: Changes in U-wave amplitude after premature ventricular contractions (PVC) are known as prognostic markers in the long QT syndrome dependent on bradycardia. The purpose of the study was to find correlation between postextrasystolic ST-U segment changes and a history of sustained ventricular tachycardia or ventricular fibrillation (VT/VF).

Methods: The ST-U segment configurations were taken from the 24-hour ambulatory ECG. The comparison of the morphology of these segments was performed between sinus beats preceding PVC's and first postextrasystolic beats.

Population: Two groups of patients were evaluated: 1) 32 patients with VT/VF history (VT/VF group), and 2) 36 patients with potentially malignant arrhythmia (structural heart disease with frequent PVCs and/or nonsustained VT- nsVT) (non-VT/VF group).

Results: We found T-wave changes in 8 patients (25%) from the VT/VF group and in 12 patients (33.3%) from the nonVT/VF group ($P = \text{NS}$) and U-wave changes in 13 patients (40.6%) and 3 patients (8.3%), respectively ($P < 0.05$). Other ECG indexes related to PVC's were also considered: RR interval, coupling interval (CI), prematurity index (PI), and postextrasystolic pause (PP). The analysis of these ECG indices revealed, when compared with patients without T-U-wave changes, that the occurrence of U-wave changes was significantly related to longer RR interval of the sinus rhythm preceding PVC: 1025 ± 211 vs 918 ± 200 ms ($P < 0.05$). The prematurity index was lowest in patients with U-wave changes: 0.54 ± 0.12 vs 0.65 ± 0.16 ($P < 0.01$) while postextrasystolic pauses leading to the postextrasystolic U-wave changes were significantly longer: 1383 ± 223 vs 1130 ± 247 ms ($P < 0.001$). CI did not differentiate patients: 556 ± 108 vs 584 ± 117 ms ($P = \text{NS}$).

Conclusions: Postextrasystolic changes in ST-U segment configuration are dependent on bradycardia, low prematurity index of the PVC, and the lengthening of the postextrasystolic pause. U-wave changes more frequently appeared in patients with malignant arrhythmias. Follow-up study is needed to assess if they might be predictive for the occurrence or reoccurrence of arrhythmic episodes.

A.N.E. 2002;7(1):17-21

ventricular arrhythmia; ventricular repolarization; ambulatory ECG

There are many studies about factors that can be useful in stratifying patients with higher risk of occurrence or reoccurrence of malignant ventricular arrhythmias. Some of them, such as frequent premature ventricular contractions (PVC), low values of heart rate variability, the occurrence of ven-

tricular late potentials, duration of the ST segment depression, dispersion of QT interval, and the prolongation of QT, are taken or calculated from ambulatory ECG recordings. Some of these parameters are related to the repolarization phase of ventricular electrical activity¹ and when taken

Table 1. Study Population

	VT/VF Group	NonVT/VF Group	P
Gender	7 females, 25 males	5 females, 31 males	NS
Age (years)	52 ± 12	54 ± 16	NS
CHD	23	31	NS
Congestive CMP	0	3	NS
Hypertrophic CMP	3	2	NS
RVAC	2	0	NS
Idiopathic arrhythmia	6	0	<0.05
LVEF (%)	40 ± 15	43 ± 14	NS

VT/VF group = patients with malignant ventricular arrhythmias (VT and/or VT/VF); NonVT/VF group = patients with PVC (> 10/hour and/or nsVT) and structural heart disease; CHD = coronary heart disease; CMP = cardiomyopathy; LVEF = left ventricle ejection fraction; RVAC = right ventricle arrhythmogenic cardiomyopathy.

from the surface ECG (like QT/QU intervals) represent its transmural process.

The prognostic value of the T and/or U wave abnormalities observed in surface ECG has been discussed in many studies. Malfatto et al. found that notched or biphasic T waves were more frequent in patients with long QT syndrome and with a history of cardiac arrest.² An increase in T-wave amplitude, observed before the onset of spontaneous ventricular tachycardia (VT) or ventricular fibrillation (VF), can also be triggered by shortening of RR intervals due to augmentation of sympathetic activity.³ The beat-to-beat changes in amplitude, phase, and shape which can be found in surface ECG or ambulatory Holter recordings, known as T-wave alternans, are frequently recorded in patients with coronary heart disease, long QT syndrome, Prinzmetal's angina, and with VT/VF episodes.⁴

Several studies have also shown that the refractory period is dependent on the length of the preceding R-R cycle and the sequence of the cardiac cycle changes: from short to long or from long to short. A short-long-short sequence is relatively common in patients with episodes of VT/VF.⁵ Recently a correlation between the postextrasystolic U-wave augmentation and the history of ventricular tachyarrhythmias has been suggested. This fact has been observed both in patients with long QT interval and without prolongation of QT, and it can indicate that U wave reflects early afterdepolarizations which play an important role in the initiation of tachyarrhythmias.^{6,7}

In this study we evaluated postextrasystolic repolarization abnormalities in the ST-U segment in patients without prolongation of QT interval with ventricular arrhythmias, both with and without

history of episodes of ventricular tachyarrhythmias-VT/VF. The aim of the study was to determine if the configuration of the ST-U segment of postextrasystolic beats compared to the ST-U morphology during sinus rhythm can be useful in differentiation of those patients.

METHODS

Study Population

The data were obtained in 68 consecutive patients with a history of ventricular arrhythmias, 56 males, age: 53 ± 13 years. The population was divided into two groups according to the type of arrhythmias. Group I (VT/VF group) consisted of 32 patients with malignant ventricular arrhythmias in history (sustained VT or VF), 29 of them underwent cardioverter-defibrillator implantation (ICD). Group II (non-VT/VF group) was composed of 36 patients with potentially malignant ventricular arrhythmia defined as frequent (> 10/hour) PVCs and/or nonsustained VT, and presence of organic heart disease (Table 1). All patients underwent 24-hour ECG recording performed with Oxford FD3 three-channel digital recorders. Clinical data and results of echocardiographic examinations were also collected. Patients with prolonged QT interval in standard 12-lead surface ECG were not included in the study.

Analysis of ST-U Segment

Three-channel ECG recordings (25 mm/s, 10 mm/1mV) taken from different periods of day and night (at least five different episodes of PVC) were used. The configuration of the ST-U segment of the sinus beat before and immediately after a PVC was

Table 2. Presence of Postextrasystolic ST-U Segment Changes in Study Population

	VT/VF Group	NonVT/VF Group	P
T-wave changes	8 (25%)	12 (33.3%)	NS
U-wave changes	13 (40.6%)	3 (8.3%)	<0.05
T- and/or U-wave changes taken together	21 (65.6%)	15 (41.6%)	<0.05

analyzed. The ST-U segment of the postextrasystolic sinus beat was classified as follows: no changes, T-wave changes, or U-wave changes. A no changes classification was made if both T and U waves were identical. T-wave changes were recognized if a ≥ 0.1 mV increase or decrease in T-wave amplitude and/or postextrasystolic inversion of T wave was observed. U-wave changes were defined as the appearance of a new U wave, an increase or decrease in U-wave amplitude of ≥ 0.1 mV or the appearance of a new positive deflection on the descending part of the T wave.

The following intervals for each episode of changes in ST-U segment were also calculated manually from three-channel recordings: RR interval in the two sinus beats preceding PVC (RR), coupling interval (CI)- RR interval between a PVC and preceding sinus QRS complex, prematurity index (PI)- CI divided by the RR, and postextrasystolic pause (PP).

Statistical Analysis

All data were analyzed with chi-square test, unpaired Student's *t*-test, and Friedman's ANOVA when appropriate. Basic probability data were calculated using: true positive (TP)- when U-wave changes had been present in VT/VF group, true negative (TN)- when no U-wave changes had been found in non-VT/VF group, false positive (FP)- when U-wave changes had been present in non VT/VF group, and false negative (FN)- when no U-wave changes had been found in VT/VF group. Next basic features of the test were also calculated: Sensitivity = $TP/(TP+FN)$, specificity = $TN/(TN+FP)$, positive predictive value (ppv) of the test = $TP/(TP+FP)$ and negative predictive value (npv) of the test = $TN/(TN+FN)$.

RESULTS

Patients did not differ in age and gender (Table 1). Coronary heart disease (CHD) was the most common (80%) structural heart disease in the study

population. Left ventricle ejection fraction (LVEF) was higher in the nonVT/VF group: $40 \pm 15\%$ vs $43 \pm 14\%$, but this difference was not statistically significant.

No changes in ST-U segment when comparing postextrasystolic beat with sinus beat preceding PVC were found in 11 patients (34.4%) in the VT/VF group and in 21 patients (58.4%) in the nonVT/VF group with no statistical significance (Table 2). T-wave changes were observed in 8 patients (25%) in the VT/VF group, and in 12 patients (33.3%) in the nonVT/VF group—the difference was also not significant. The occurrence of U-wave changes was significantly higher ($P < 0.05$) in the VT/VF group (40.6%) than in the nonVT/VF group (8.3%). Both T-wave and/or U-wave changes were significantly more common in the VT/VF group ($P = 0.04$).

The analysis of the ECG indices related to PVC revealed that the occurrence of U-wave changes was significantly related to longer RR interval of the sinus rhythm preceding PVC ($P < 0.05$) (Table 3). The prematurity index was lowest in patients with U-wave changes ($P < 0.01$) while postextrasystolic pauses leading to the postextrasystolic U-wave changes were significantly longer ($P < 0.001$). Patients with presence of the postextrasystolic T-wave changes were also characterized by lower PI (0.57 ± 0.14) and longer PP (1261 ± 227 ms) than patients with no ST-U segment changes.

The basic sinus rhythm leading to ST-U segment changes was lower in the VT/VF group than in the nonVT/VF group (1005 ± 130 ms vs 934 ± 207 ms). The prematurity index was also lower (0.52 ± 0.09 vs 0.58 ± 0.15) while the postextrasystolic pause was longer (1410 ± 170 ms vs 1290 ± 314 ms). All these differences were not statistically significant but this observation can be important because of the frequency of the occurrence of ST-U segment changes is different in patients with and without VT/VF in their history. Indices related to PVC did not differentiate patients when no ST-U segment changes were found.

Table 3. Indices of ECG in Study Population and in the VT/VF and NonVT/VF Groups

	RR (ms)	CI (ms)	PI	PP (ms)
No changes	918 ± 200	584 ± 117	0.65 ± 0.16	1130 ± 247
T-wave changes	896 ± 115	505 ± 98**	0.57 ± 0.14*	1261 ± 227*
U-wave changes	1025 ± 211*	556 ± 108	0.54 ± 0.12**	1383 ± 223***
T-/U-waves changes	978 ± 165	529 ± 108*	0.55 ± 0.12**	1363 ± 240***
VT/VF Group				
No changes	945 ± 181	568 ± 114	0.61 ± 0.13	1195 ± 226
T-/U-waves changes	1005 ± 130	529 ± 115	0.52 ± 0.09	1410 ± 170
NonVT/VF Group				
No changes	898 ± 211	588 ± 119	0.67 ± 0.16	1101 ± 252
T-/U-waves changes	934 ± 207	530 ± 98	0.58 ± 0.15	1290 ± 314

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ for T and/or U wave changes versus no changes; CI = coupling interval; PI = prematurity index; PP = postextrasystolic pause; RR = R-R interval calculated from the sinus rhythm preceding PVC; T/U = all patients with either T wave or U wave changes.

The presence of changes of U wave in ECG had relatively low sensitivity (41%), but specificity, ppv and npv had rather high values, respectively, 92, 81, and 79% (Table 4).

DISCUSSION

In recent years increasing interest has been focused on noninvasive assessment of patients at risk of ventricular tachyarrhythmias and sudden cardiac death. Prolongation of ventricular repolarization and markers of its inhomogeneity such as QT dispersion of sinus beats, premature ventricular beats, and T-wave alternans are frequently observed in patients prone to ventricular tachyarrhythmias.^{4,8} It has also been suggested that postextrasystolic T-U segment changes, especially postextrasystolic U-wave augmentation, may be a new marker of increased arrhythmic risk.⁷ Viskin et al. reported that low ejection fraction and postextrasystolic U-wave augmentation were independently associated with history of malignant ventricular arrhythmia. Our study confirms that postextrasystolic U-wave changes are common (40.6%) in patients at risk of ventricular tachyarrhythmias.

T-wave changes were less specific and were observed both in patients with malignant and potentially malignant arrhythmia.

Postextrasystolic U-wave changes were related to longer basic cycle length, shorter prematurity index, and longer postextrasystolic pause. A similar relationship has also been observed in other studies.⁷ The genesis of the U wave has long been unclear. The origin of U wave can be due to delayed repolarization of the His-Purkinje fibers, but recent studies suggest that it may be a result of the activity of a special population of myocardial cells, M cells, which have been found in dogs and humans.^{6,9} Human M cells occupy a substantial volume (about 30%) of the ventricular wall, are located in the deep subepicardial layers, and have specific electrophysiologic properties as a prolongation of their action potential in response to rapid changes in the heart rate. Antzelevitch and Sicouri⁶ have suggested that M cells could play a pathophysiologic role in arrhythmia generation, especially in long QT syndromes. It has been shown that M cells develop early afterdepolarizations and triggered activity, and because of their longer action potential may also create reentrant arrhythmias. Our study confirms this observation. The postextrasystolic changes were observed in our study in patients with longer RR interval during sinus rhythm, shorter coupling interval, and longer postextrasystolic pause. It suggests rate dependence of U-wave occurrence which can be explained by M cell activity.

Table 4. Prognostic Significance of U-Wave Changes in Study Population

Sensitivity	Specificity	PPV	NPV
41%	92%	81%	79%

Successful risk stratification for arrhythmic events or sudden death would allow judicious prophylactic implantation of ICD or use of antiarrhythmic agents. The prediction of sudden cardiac death after myocardial infarction using a single risk parameter, such as low left ventricular function (< 35%–40%), frequent PVCs (> 10/hour), presence of late potentials, decreased heart rate variability (SDNN < 70 ms), or baroreflex sensitivity (< 3.0 ms/mm Hg) is controversial and has still limited prognostic value. This problem was assessed by several studies indicating that the sensitivity and specificity were 40%–93% and 40%–82%, respectively.^{10–14} The absence of late potentials in postmyocardial infarction patients has highest negative predictive value (98%), but the usefulness of all of these markers is limited by its low positive predictive value (11%–38%). Our study has shown that such simple methods as the observation of the occurrence of new U wave or changes of its amplitude after PVC has had relatively high specificity and positive and negative predictive values, which are comparable with methods mentioned above. These results suggest that analysis of postextrasystolic U-wave might add some prognostic information.

The available data suggest that the combination of variables provides the stronger risk prediction, especially when variables reflecting different aspects, such as substrate, trigger, and modulator are used.^{14,15} It appears that an assessment of the ventricular function combined with parameters from Holter monitoring (PVCs, heart rate variability [HRV], heart rate turbulence, and repolarization abnormalities) should provide effective approach for risk stratification. Therefore, follow-up study in our population is needed to assess prognostic value of postextrasystolic ST-U segment changes and to compare it with mentioned conventional risk markers.

CONCLUSIONS

Postextrasystolic changes in ST-U configuration are dependent on slower basic rhythm, shorter prematurity index of the PVC, and lengthening of the postextrasystolic pause. These changes more frequently appear in patients with malignant ventricular arrhythmias. Follow-up study is needed to assess if they might be predictive for the occurrence and reoccurrence of arrhythmic episodes.

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