T-Wave Variability for the Prediction of Fast Ventricular Arrhythmias
– Prospective, Observer-Blind Study –

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Background: The clinical value of T-wave variability (T-var) for ventricular arrhythmia (VA) risk prediction was evaluated.

Methods and Results: Three 20-min Holter-ECG-based T-var measurements (I1 at baseline, I2 after 6.5±1.6 months and I3 after 13.1±2.0 months) were done in 121 patients. T-var was defined as the amplitude variability of the T-wave with the maximum of T-wave oscillation. The endpoint was a fast, potentially fatal VA (>240 beats/min). During follow-up (20±4 months) 20/121 patients (55% ischemic heart disease, 15% preserved left ventricular ejection fraction [LVEF]) had fast VA terminated by ICD or external shock. Although T-var did not differ between patients with vs. without fast VA at baseline (I1: 10.7±7.3 µV vs. 7.8±4.1 µV, P=0.170), patients with fast VA had higher T-var compared to those without fast VA at 2 subsequent measurements (I2: 14.0±6.5 µV vs. 8.2±3.6 µV, P=0.030; I3: 17.0±5.4 µV vs. 8.8±4.6 µV, P=0.004). The increase in T-var between I1 and I2 was higher in patients with fast VA (ΔT-var= 7.0±3.9 µV), as compared to patients without (ΔT-var=0.4±4.3 µV). After adjustment for LVEF in a multiple logistic regression model, the odds ratio for developing fast VA was 1.1 (P=0.056) for each 1-µV increment in T-var at I1.

Conclusions: T-var is elevated in patients with fast VA, and both elevation of T-var and increase in T-var may complement LVEF in VA risk stratification. (Circ J 2015; 79: 318–324)

Key Words: Risk stratification; T-wave variability; Ventricular arrhythmia

Identifying which patients might benefit the most from implantable cardioverter defibrillator (ICD) therapy remains challenging. Left ventricular ejection fraction (LVEF), with its limitations, was used as the main risk stratification tool in landmark trials. Presently, no marker exists in terms of risk stratification that qualifies itself as a gold standard. Much attention has been paid to exercise T-wave alternans, a tool for ventricular arrhythmia (VA) risk stratification providing high negative predictive value. However, because of the need to elevate heart rate to 105–110 beats/min, this approach has limited applicability. A conceptually related measure, T-wave variability (T-var), has been investigated as a quantitative approach to assess repolarization abnormalities. T-wave alternans is a special form of T-var characterized by a 2:1 pattern (+− or −+−) of beat-to-beat polarity changes in repolarization, whereas T-var encompasses beat-to-beat changes in repolarization in the shape, amplitude and polarity of the T-wave. T-var is elevated more than twice as much in patients with fast VA as compared to those without (T-var=0.4±4.3 µV vs. T-var=7.0±3.9 µV). The increase in T-var between measurements I2 and I3 was higher in patients with fast VA (ΔT-var= 3.6±4.7 µV) than in patients without (ΔT-var=0.4±4.3 µV). After adjustment for LVEF in a multiple logistic regression model, the odds ratio for developing fast VA was 1.1 (P=0.056) for each 1-µV increment in T-var at I1.

Conclusions: T-var is elevated in patients with fast VA, and both elevation of T-var and increase in T-var may complement LVEF in VA risk stratification.

Key Words: Risk stratification; T-wave variability; Ventricular arrhythmia
T-Wave Variability for VA Prediction

Methods

We conducted a prospective observational, single (assessor)-blind study at the Medical University of Vienna, Austria from 2011 to 2013. The local ethics committee approved this study. All subjects gave written consent for study participation. Test results were not disclosed to participants or their attending physicians. Patients were investigated on 20-min ECG for T-var calculation at 3 time points: first measurement, baseline; second measurement and first follow-up with device interrogation, at 6 months; third measurement and second follow-up with device interrogation, at 12 months; third follow-up with device interrogation, at 18 months. Subsequently, final follow-up endpoints were connected with T-var results.

Patients
All 121 consecutive patients already had implanted devices capable of VA storage. Patients were eligible to participate if they were at least 18 years old and were implanted with an ICD for primary prevention, a pacemaker or a loop recorder. Exclusion criteria were dependency on ventricular pacing, QRS width >180 ms, permanent atrial fibrillation (AF), and adverse reactions to skin electrodes.

Cardiac Pump Function
Echocardiography following a local standard protocol was conducted in sinus rhythm using a Vivid 7 ultrasound machine (GE Healthcare, Milwaukee, WI, USA) or an ACUSON Sequia C256® (Acuson, Mountain View, CA, USA).

ECG Measurement and Definitions
T-var was assessed at rest, in the morning using a digital Holter recorder (SpiderView®; ELA Medical, Sorin Group, Paris, France). Seven electrodes were placed in pseudo-orthogonal Frank (XYZ) configuration and a 20-min recording was conducted in the supine position. High sampling rates (1,000 Hz) with a resolution of 2.5 \( \mu \)V were used. The vector magnitude (VM) was calculated from leads X, Y and Z for further processing: \( VM = \sqrt{X^2 + Y^2 + Z^2} \).

A previously reported analysis of T-var reported on T-wave amplitude variability (TAV) only. In the underlying study T-var is calculated for the segment with the highest OWF (T-var=TA×OWF). The oscillation pattern of T-wave amplitudes is derived from 4 consecutive beats (2:1 oscillation pattern of type + – + –). The sum of the occurrences of this oscillation pattern is divided by the number of total possible occurrences within the cluster (reproduced with the permission of Ela Medical, Sorin Group, Paris, France).
ning of repolarization was delayed in 20-ms increments with an upper limit of 200 ms for further processing. Thus, 180 ms was the maximum allowed QRS width for analysis. The end of the repolarization was defined as 50% of the RR-interval.\cite{5,14} T-var was calculated from T-wave segments with the highest OWF. T-var was computed from all valid clusters. Non-valid clusters were excluded from analysis, such as non-sinus beats and/or unstable heart rates (RR change >20% above or below the mean cluster RR interval), QRS >180 ms, and/or noise level >10 μV.

### Endpoints and Classification of Events

The primary endpoint of this study was the occurrence of a potentially fatal, fast VA. Independent, experienced cardiologists reviewed device-stored data. Fast, potentially fatal VA was defined as ventricular tachycardia (VT) >240 beats/min or ventricular fibrillation (VF). All other ICD treatment due to VT <240 beats/min (which was not considered fast, potentially fatal VA), was not included in analysis. Inappropriate ICD treatment leading to VA with ICD treatment, or ICD treatment accelerating slow VT to fast VT, was also not included in analysis. All ICD were programmed to allow maximum possible detection duration.

### Statistical Analysis

Mean T-var was calculated for every patient and every follow-up point among all available valid clusters. Student’s t-test was used to test for the difference in mean T-var between groups (significance level 0.05). The Bonferroni-Holm correction for multiple testing was applied. The ratio of patients with fast VA vs. patients without events was 1:5. With 120 included patients in total, and SD=7.5 μV and 5 μV in the group with and without VA, respectively, a mean difference of 5 μV in T-var between the 2 groups could be detected with a power of 0.85 at an adjusted level of 0.05/3. ANOVA was used to compare continuous variables between groups, or, if the assumptions were not met, the Kruskal-Wallis test was used. Nominal variables were compared using contingency tables in combination with chi-squared test or Fisher’s exact test. Logistic regression models were calculated to analyze the effect of T-var on the occurrence of a VA event during follow-up. The sensitivity and specificity of mean T-var to predict the occurrence of VA was analyzed using receiver operating characteristic (ROC) curve. The best cut-off point was estimated as the T-var with the highest sum of sensitivity and specificity. Statistical analysis was done using SPSS 21.0 for Windows, SAS 9.3 or R 2.14.

### Table. Patient Characteristics

|                          | All patients (n=121) | Fast VA (n=20) | No event (n=101) | P-value |
|--------------------------|----------------------|---------------|------------------|---------|
| Age (years)              | 61±15                | 59±21         | 62±14            | 0.65    |
| Male                     | 83 (68.6)            | 16 (80)       | 67 (66.3)        | 0.297   |
| Obesity                  | 57 (47.1)            | 4 (20)        | 53 (52.5)        | 0.01    |
| Current smoker           | 68 (56.2)            | 10 (50)       | 58 (57.4)        | 0.62    |
| Diabetes mellitus        | 23 (19)              | 4 (20)        | 19 (18.8)        | 1       |
| Hypertension             | 78 (64.5)            | 13 (65)       | 65 (64.3)        | 0.96    |
| NYHA class               |                      |               |                  | 0.299   |
| I                        | 75 (62)              | 10 (50)       | 65 (64.4)        |         |
| II                       | 42 (34.7)            | 10 (50)       | 32 (31.7)        |         |
| III                      | 4 (3.3)              | 0 (0)         | 4 (4)            |         |
| No CM                    | 22 (18.2)            | 1 (5)         | 21 (20.8)        | 0.24    |
| Dilative CM              | 26 (21.5)            | 7 (35)        | 19 (18.8)        |         |
| Ischemic CM              | 54 (44.6)            | 11 (55)       | 43 (42.6)        |         |
| Hypertrophic CM          | 8 (6.6)              | 1 (5)         | 7 (7.4)          |         |
| Channelopathy            | 11 (9)               | 0 (0)         | 11 (10.9)        |         |
| LVEF >55%                | 56 (46.3)            | 3 (15)        | 53 (52.5)        | 0.03    |
| 46–55%                   | 21 (17.4)            | 3 (15)        | 18 (17.8)        |         |
| 35–45%                   | 18 (14.9)            | 5 (25)        | 13 (12.9)        |         |
| <35%                     | 26 (21.5)            | 9 (45)        | 17 (16.8)        |         |
| Device implanted         |                      |               |                  | 0.08    |
| ICD                      | 90 (74.4)            | 19 (95)       | 71 (70.3)        |         |
| Pacemaker                | 10 (8.3)             | 0 (0)         | 10 (9.9)         |         |
| Loop-recorder            | 21 (17.4)            | 1 (5)         | 20 (19.8)        |         |
| Medication               |                      |               |                  |         |
| Class I AAD              | 1 (0.8)              | 0 (0)         | 1 (1.1)          | 1       |
| Class II AAD             | 98 (81)              | 19 (95)       | 79 (78.2)        | 0.12    |
| Class III AAD            | 23 (19)              | 7 (35)        | 16 (15.8)        | 0.06    |
| Class IV AAD             | 17 (14)              | 1 (5)         | 16 (15.8)        | 0.3     |
| Digitalis                | 6 (5)                | 1 (5)         | 5 (4.9)          | 1       |
| Antidepressants          | 23 (19)              | 4 (20)        | 19 (18.8)        | 1       |

Data given as mean±SD or in (%). AAD, anti-arrhythmic drug; CM, cardiomyopathy; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; VA, ventricular arrhythmia.
Results

Patient Characteristics
All 121 patients (male, 69%; median age, 63 years; range, 21–88 years) either had ICD (n=90), pacemakers with VA storage capability (n=10) or loop recorders (n=21). Main characteristics are summarized in Table. The most frequent morbidity was ischemic cardiomyopathy (45%) followed by dilated cardiomyopathy (22%). Only 22% of patients had <35% LVEF, and 74% had ICD.

T-Var Assessment and Events
First T-var measurement (I1) was performed in all patients, second (I2) and third (I3) T-var measurements were performed 6.5±1.6 and 13.1±2.0 months after I1 in 79 and 90 patients, respectively. Starting from I1, the follow-up time was between 3 and 27 months, but for most patients close to 2 years, with 25%, 50% and 75% quartiles at 20, 22 and 24 months, respectively. Follow-up was complete in 103 patients (85%; Figure 2). Fifteen percent of patients were not further eligible after I1 due to refusal to participate (n=12), converting to persistent AF (n=3), widening of QRS >180 ms (n=2), or dependency on pacing (n=1; Figure 2). T-var analysis was possible in 75.2% of all measurements (I1: n=95, 78.5%; I2: n=60, 75.9%; I3: n=61, 67.8%). In the remaining 24.8% of patients T-var could not be calculated due to frequent non-sinus beats, unstable heart rate or elevated noise level. During a mean follow-up of 20±4 months, 20/103 patients (19%) experienced fast VA: fast VT in 14 patients (14%), which was terminated with anti-tachycardia pacing in 7 cases, terminated with ICD shock in 6 cases, and terminated by external cardioversion in 1 patient with an implanted loop recorder. Another 6 patients (5%) experienced VF, which was ICD shock-terminated. In 5 patients VT with heart rate <240 beats/min without syncope was recorded and not considered as an event. In addition, 1 patient experienced asystole and 1 patient died due to heart failure. There were no significant differences with regard to age, sex, New York Heart Association class or anti-arrhythmic drugs in patients with or without fast VA. Patients with fast VA were more likely to have reduced LVEF (P=0.03) and were less likely to be obese (P=0.01; Table).

Course of T-Var
Figure 3 shows mean T-var at time points I1, I2 and I3 in the group with fast VA (upper line) and without an event (lower line). The first measurement of T-var (I1) did not differ between the 2 groups (10.7±7.3 vs. 7.8±4.1 µV, P=0.170). The second (I2) and third (I3) measurements showed significantly higher mean T-var in patients with fast VA, as compared with patients without events. (I2: 14.0±6.5 vs. 8.2±3.6 µV, P=0.03; I3: 17.0±5.4 vs. 8.8±4.6 µV, P=0.004, respectively, adjusted P-values). On ROC analysis the best cut-off was T-var>8.54 µV at I1 with 77% sensitivity and 71% specificity (area under the curve [AUC]=0.606; Figure 4A) to predict fast VA. At I2, T-var>10.06 µV was found to be the best cut-off for fast VA after I2 with 89% sensitivity and 73% specificity (AUC=0.828; Figure 4B).

Change in T-Var and Prediction of Fast VA
Fifty-eight patients with in total 11 VA events after I2 were analyzed for ΔT-var (ΔT-var=T-var at I2 minus T-var at I1). The increase in T-var between I1 and I2 was higher in patients with fast VA (ΔT-var=7.0±9.3 µV), as compared with patients without events (ΔT-var=0.4±4.3 µV). The latter had stable T-var over time. In the present model, the best cut-off was ΔT-var >6.91 µV with 78% sensitivity and 97% specificity for the occurrence of fast VA (AUC=0.841; Figure 4C).

T-Var and LVEF as Independent Predictors
Patients stratified according to the degree of LV function had similar T-var, suggesting that LVEF had no impact on T-var. Patients were dichotomized into 2 groups, LVEF >55% and LVEF ≤55%: I1: 8.1±5.4 µV vs. 8.4±5.2 µV (P=0.795); I2: 9.2±4.3 µV vs. 9.3±5.4 µV (P=0.928); and I3: 8.5±3.0 µV vs. 11.8±7.2 µV (P=0.090), respectively. After adjustment for LVEF on multiple logistic regression, the odds for developing VA were estimated to increase by a factor of 1.1 (P=0.056) for each 1-µV increment in T-var at I1, and by 1.4 (P=0.009) for each 1-µV increment in T-var at I2. The odds ratio for AT-var was 1.3 (P=0.006) when adjusted for LVEF. None of the patients with LVEF>55% and T-var below the cut-off had VA during follow-up (Figure 5).

Discussion
The main finding of the present study was that patients with subsequent fast, potentially fatal VA had higher T-var on short-term ECG compared with those without.

The present findings are clinically important, because we found that (1) T-var is significantly higher in patients before the occurrence of fast VA; and (2) both high T-var and an increase in T-var predicted fast VA independently of LV function, with high sensitivity and specificity.

To the best of our knowledge, this is the first study using...
both OWF and TAV to calculate T-var. Previous studies used TAV only. In the present study we calculated T-var for the segment with a maximum of oscillation (OWF), taking all aspects of repolarization into account. These differences in methodology might explain differences in absolute values and estimated cut-offs. We found that mean T-var was significantly elevated in patients with fast VA during 2 years of follow-up. Furthermore, T-var remained a significant predictor for these events after adjustment for LVEF, and appears to provide additional information, independent of LVEF, in arrhythmia risk stratification. T-var >8.5–10 µV was found to be a good cut-off range for predicting fast VA. In addition, we showed, for the first time, by performing serial measurements, that T-var increases in patients developing fast VA. In the present patients, an increase in T-var > 6.91 µV within 6 months predicted the occurrence of VA with 78% sensitivity and 97% specificity. Furthermore, T-var was stable in patients without VA during 2 years of follow-up. This suggests that the cut-offs for T-var obtained from short-term ECG-recording could be used at any time during individual follow-up.

Analysis of baseline clinical and ECG parameters is crucial for patient counseling and device reimbursement by healthcare providers. TAV was predictive for VA in MADIT II patients, namely in patients with a history of myocardial infarction and reduced LVEF. In particular, Couderc et al found that TAV >59 µV was predictive of arrhythmic events. Sobue et al showed that patients with recurrence of VA had a trend towards higher maximum TAV as compared with patients without recurrent VA (56 µV vs. 36 µV). Ribeiro et al noted that an increase >30 µV² TAV or a square-root equal to 5.5 µV was independently related to all-cause mortality. TAV was also associated with the occurrence of VA in patients with dilated cardiomyopathy. Previous studies noted a lower maximum TAV in patients who survived a cardiac arrest and a decrease of TAV in patients with LV reverse remodeling after CRT implantation. To date, only 1 study reported on ICD patients with increased T-wave alternans and TAV shortly before the onset of spontaneous VA. In contrast, Levitt et al found no differences in TAV between high-risk patients and healthy controls, although TAV was reproducible in patients with ventricular dysfunction. These conflicting results suggest that T-var calculation based solely on TAV may not be a reliable tool for VA prediction in patients with electrical conduction problems or ventricular dysfunction. The present study proposes a refined methodology for T-var calculation, namely T-var, taking T-wave oscillations into account. For example, if the T-wave amplitude is noisy and not organized as an oscillation pattern, OWF will be 0 or close to 0. T-var will be close to 0, even though TAV might be high. This illustrates the potential value of OWF in T-var measurement. The use of OWF might be important because patients with a history of VA or congenital long QT syndrome, or competitive athletes, have an elevated TAV, as compared to age- and sex-matched controls.

Interestingly, TAV had no day/night periodicity and was constantly higher in patients with Brugada syndrome with VA (46.6 µV) as compared with asymptomatic patients and healthy controls (35.5 µV). Conversely, TAV was increased during the day only in patients with long QT syndrome (34 µV² vs. 25 µV² in controls). In order to exclude day/night periodicity effects we propose to record individual ECG at the same point in daytime.
present findings may have overestimated the predictive value of T-var. Second, as reported by others,\textsuperscript{17} in up to 32\% of cases, assessment of T-var was not possible, which qualifies this method as add-on tool only. Finally, it should be emphasized that this methodology in calculating T-var is new, and has not been verified by others. Therefore, the T-var and an estimated cut-off range between 8.54 and 10.06 µV represent pilot study data.

Perspectives
In contrast to the proven value and recommendations regarding quantitative T-wave alternans assessment,\textsuperscript{20} evidence regarding T-var is very limited. There is still a need to define parameters for T-var measurement: in the present study, we used five 100-ms T-wave windows, whereas others have used 50-ms windows.\textsuperscript{8,12,14,18} To the best of our knowledge there are no studies available on the advantages of the different settings. The possible hypothesis that T-var increase is caused by the recurrence of fast VA needs to be confirmed in future studies.

Conclusions
Considering the high impact of impaired repolarization on the occurrence of life-threatening VA, assessment of T-var is warranted. In the present study T-var measurements were found to be highly predictive for the occurrence of potentially fatal, fast VA, irrespective of the degree of LV function. Cut-off values for the prediction of fast VA were either an increase >6.91 µV and/or absolute T-var ranging between 8.54 µV and 10.06 µV. In clinical practice assessment of T-var may complement LVEF in arrhythmia risk prediction.

Disclosures
Conflict of Interest: None declared.

Study Limitations
The present study had limitations. First, it cannot be ruled out that all VT episodes would have led to death. Therefore, the

Figure 4. Receiver operating characteristic (ROC) curve of mean T-wave variability (T-var) for the prediction of fast ventricular arrhythmia (VA): (A) T-var at I1; (B) T-var at I2; and (C) T-var at I2 minus T-var at I1 (ΔT-var). Area under the ROC curve (AUC) was 0.606, 0.828, and 0.841 for the prediction of fast VA, respectively. •, observed values with the highest sum of sensitivity and specificity.

Figure 5. Independence of T-wave variability (T-var) and left ventricular ejection fraction (LVEF). Lower left quadrant, low-risk patients with normal LVEF and T-var below the calculated cut-off (T-var at I2=10.06 µV); upper right quadrant, high-risk patients with LVEF ≤55% and T-var above the calculated cut-off (>10.06 µV). Red, patients who experienced fast ventricular arrhythmia during follow-up. The dots are slightly staggered in the vertical direction to avoid overlap of identical observations.
Author Contributions
Concept/design: Pezawas; data analysis/interpretation: all; drafting article: Pezawas, Stojkovic; critical revision: all; statistics: Ristl; approval: all.

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