# Repolarization Lability Measured by Spatial TT' Angle

Larisa G Tereshchenko

Oregon Health and Science University, Knight Cardiovascular Institute, Portland, Oregon, USA
Johns Hopkins University School of Medicine, Cardiovascular Division, Baltimore, Maryland, USA

## Abstract

*Aims: Increased T peaks cloud volume is associated with increased risk of ventricular arrhythmias (VA) in cardiomyopathy (CM) patients. T peaks cloud volume is formed, as a result, of (1) the angle between consecutive T-vectors and (2) temporal variability in T-vector amplitude. This study compares association of these two factors with VA.*

*Methods: Baseline orthogonal ECGs were recorded during 5 min at rest in 414 patients with structural heart disease [mean age 59.4±12.0; 68% whites; 73% men; 45% non-ischemic CM] before implantation of implantable cardioverter-defibrillator (ICD) for primary prevention of sudden cardiac death. The spatial TT' angle between consecutive spatial T vectors was calculated using the definition of the inner product.*

*Results: During a median 14 months of follow-up, 61 patients experienced sustained VA with appropriate ICD therapies. In a multivariable Cox regression model after adjustment for age, sex, race, spatial TT' angle was associated with VA (HR 1.03; 95%CI 1.0-1.05; P=0.034). Interaction with CM type was found: TT' angle was strongly associated with polymorphic VT/VF in non-ischemic CM (HR 1.04; 95%CI 1.0-1.05; P=0.033).*

*Conclusion: Increased spatial TT' angle is associated with increased risk of VA.*

## 1. Introduction

Accurate risk stratification of sudden cardiac death (SCD) due to potentially reversible ventricular tachycardia (VF) /ventricular fibrillation (VF) remains an important goal. Increased repolarization lability is mechanistically linked with VT/VF[1-3]. Novel method of dynamic vectorcardiography (VCG) was recently developed [4,5] to assess repolarization lability. Prospective study of patients with structural heart disease, systolic dysfunction, and implantable cardioverter-defibrillator (ICD) implanted for primary prevention of SCD showed that relatively large T-peaks cloud volume is associated with increased risk of VT/VF and appropriate ICD therapies[5].

Two major factors contribute to the T-peaks cloud volume formation: spatial TT' angle between consecutive spatial T vectors, and temporal variability of spatial T vector amplitude. While variability of spatial T-vector amplitude was previously shown associated with VT/VF[6], predictive value of spatial TT' angle has not been previously studied. I hypothesized that increased spatial TT' angle is associated with VT/VF and appropriate ICD therapies in cardiomyopathy (CM).

## 2. Methods

This study analyzed the data of previously published prospective study of the first consecutive 414 participants[5] of the Prospective Observational Study of Implantable Cardioverter-Defibrillators (PROSE-ICD), recruited at the Johns Hopkins Hospital site with at least 6 months of follow-up. PROSE-ICD (NCT 00733590) is an ongoing multicenter prospective observational cohort study of primary prevention ICD patients with structural heart disease[7].

### 2.1. Patient population

The study protocol was approved by the Johns Hopkins IRB, and all patients signed informed consent before entering the study. PROSE-ICD inclusion and exclusion criteria have been previously described[5,7].

High resolution (1000Hz) orthogonal XYZ ECG was recorded by PC ECG machine (Norav Medical Ltd, Thornhill, ON, Canada) before ICD implantation. As previously described[5], this study excluded patients (1) in rhythm other than sinus, (2) with frequent premature ventricular, or atrial contractions (PVCs/PACs) > 15%.

### 2.2. Spatial TT' angle

ECG analysis was performed on 30 consecutive sinus beats by custom software, written in MATLAB (MathWorks,Inc., Natick, MA). Dynamic VCG analysis was performed as previously described[4,5,8,9]. The peak of spatial T-vector was detected automatically on the T-

loop as the furthest point away from the origin point. The spatial TT' angle (Figure 1) between consecutive spatial T-vectors was calculated using the definition of the inner product:

$$TT'angle = \arccos\frac{T*T'}{|T|*|T'|}. \quad (1)$$

Mean TT' angle was averaged over 30 consecutive sinus beats (Figure 1).

Figure 1. Measurement of mean spatial TT' angle

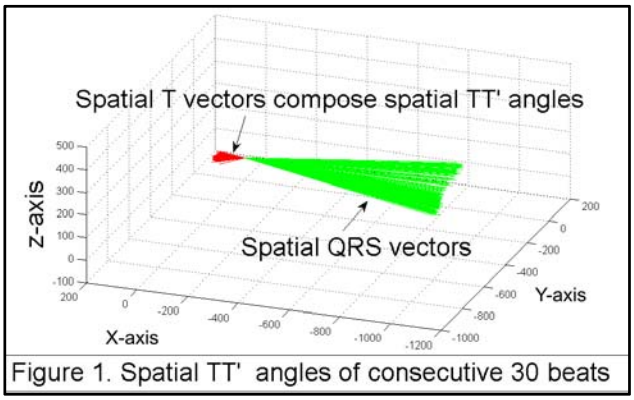


Figure 1. Spatial TT' angles of consecutive 30 beats

## 2.3. Variability of spatial T vector

Normalized variance of spatial T-vector amplitude (TampVN) was calculated according to the equation:

$$TampVN = \log\left[\frac{Variance\ of\ spatial\ T\ vector\ amplitude}{mean\ spatial\ T\ vector\ amplitude^2}\right]$$

In addition, the square root of the mean of the sum of the squares of the successive differences in spatial T vector amplitude between adjacent beats (TamprMSSD) was calculated.

## 2.4. Study outcomes

ICD device was interrogated every 6 months. End-point adjudication committee evaluated ICD therapies as previously described[5]. Appropriate ICD therapies [either shock or antitachycardia pacing] for sustained VT/VF served as the primary outcome in this study. ICD therapies for (1) monomorphic VT (MMVT) and (2) polymorphic VT (PVT)/VF served as two secondary outcomes. Adjudication rules applied were previously described[5].

## 2.5. Statistical analysis

STATA 13 (StataCorp LP, College Station, TX) was used for analysis. Results are presented as mean and standard deviation (SD) for normally distributed variables and as median and interquartile range (IQR) for non-normally distributed variables. As it is known that mechanisms of VT/VF in ischemic cardiomyopathy (ICM) and non-ischemic cardiomyopathy (NICM) are different[10], we stratified our analyses by the type of CM. *T*-test was used to compare normally distributed variables; Wilcoxon rank-sum test was used to compare variables with a skewed distribution. Pearson's chi-squared test was used to compare categorical variables. Survival analysis was performed with tested parameters of repolarization lability (spatial TT' angle, TampVN, TamprMSSD), entered one-by-one as continues variables. Cox regression models were adjusted by demographics (age, sex, race), and stratified by CM type. Association between spatial TT' angle and VT/VF was evaluated through the use of fully adjusted Cox regression model incorporating quadratic splines with 4 knots: at 2.1, 4.7, 8.5, 28.2 degrees for all patients; at 2.3, 4.9, 8.9, 24.4 degrees for ICM group; at 1.9, 4.3, 7.3, 32.4 degrees for NICM group.

# 3. Results

## 3.1. Patient population

Comparison of patient clinical characteristics in ICM vs. NICM is presented in Table 1.

Table 1. Clinical characteristics of patients

| Characteristic | ICM(n=227) | NICM(n=187) | P |
|---|---|---|---|
| Age(SD), y | 63.9(10.3) | 53.9(11.7) | <0.0001 |
| Males, n(%) | 196(86.3) | 104(55.6) | <0.0001 |
| Whites, n(5) | 179(78.9) | 101(54.0) | <0.0001 |
| LVEF(SD), % | 23.8(7.7) | 19.8(9.3) | <0.0001 |
| NYHA≥III class | 119(52.4) | 92(49.2) | 0.514 |
| LVDD(SD), cm | 5.9(0.9) | 6.1(1.0) | 0.235 |
| Smokers, n(%) | 187(85.4) | 101(56.4) | <0.0001 |
| Amiodarone, n(%) | 27(31.8) | 10(17.9) | 0.066 |
| Inducible VT, n(%) | 80(62.0) | 26(36.1) | <0.0001 |
| β-blockers, n(%) | 191(95.5) | 165(95.9) | 0.838 |
| LBBB, n(%) | 43(18.9) | 51(27.3) | 0.051 |
| CRT-D, n(%) | 47(20.7) | 73(39.0) | <0.0001 |
| BMI(SD), kg/m$^2$ | 28.6(5.3) | 29.4(6.6) | 0.196 |

NICM patients had more advanced heart failure, the higher probability of having left bundle branch block (LBBB) and accordingly, implanted cardiac resynchronization therapy defibrillator (CRT-D). Remarkable race-, sex-, and age-differences between two CM types were noted: NICM patients were more likely younger black females.

## 3.2. Repolarization lability in ICM vs. NICM

Heart rate was higher, and spatial T-vector amplitude was larger in NICM (Table 2), as compared to ICM. No statistically significant differences in repolarization lability were observed between two CM types.

Table 2. Repolarization lability in ICM and NICM

| Characteristic | ICM(n=227) | NICM(n=187) | P |
|---|---|---|---|
| Heart rate(SD), bpm | 68.5(12.1) | 74.4(13.7) | <0.0001 |
| TT' angle(SD), deg | 6.6(4.3-11.5) | 5.8(3.5-10.3) | 0.116 |
| T-vector amp, mV | 0.13(0.09-0.21) | 0.15(0.1-0.28) | 0.026 |
| TampVN(SD) | -4.5(1.3) | -4.5(1.6) | 0.902 |
| TamprMSSD, mV | 18(13-28) | 20(14-30) | 0.076 |

## 3.3. VT/VF events with appropriate ICD therapies

During a median 14 months of follow-up, 61 of the 414 patients (9.6% per person-year of follow-up) experienced sustained VT/VF with appropriate ICD therapies. There were no differences in the rate of primary and secondary end-points in ICM and NICM (Table 3). In an age,- sex-, and race- adjusted Cox regression analyses neither left ventricular ejection fraction (LVEF), nor New York Heart Association (NYHA) heart failure (HF) class associated with VT/VF events.

Table 3. Outcomes in ICM and NICM

| End-point | ICM(n=227) | NICM(n=187) | P |
|---|---|---|---|
| All VT/VF, n(%) | 37(16.3) | 24(12.8) | 0.322 |
| MMVT, n(%) | 22(9.7) | 20(10.7) | 0.736 |
| PVT/VF, n(%) | 12(5.3) | 4(2.1) | 0.098 |

## 3.4. Spatial TT' angle

Results of survival analyses are shown in Table 4, and Figures 2-4. One degree increase in TT' angle was associated with 2.5% increase in the risk of VT/VF. Interaction with CM type was found: spatial TT' angle was associated with VT/VF in NICM, but not in ICM.

Table 4. Adjusted by age, sex, and race hazard ratio (95% CI) for VT/VF by 1 degree increase in spatial TT' angle

| | All patients | ICM | NICM |
|---|---|---|---|
| | HR, 95%CI; P | HR, 95%CI; P | HR, 95%CI; P |
| VT/VF | 1.025(1.0-1.048); 0.034 | 0.99(0.93-1.04); 0.624 | 1.034(1.01-1.06); 0.003 |
| MMVT | 1.027(1.0-1.057); 0.055 | 1.01(0.94-1.08); 0.782 | 1.030(1.00-1.059); 0.040 |
| PVT/VF | 1.030(0.993-1.068); 0.104 | 0.98(0.89-1.08); 0.730 | 1.043(1.01-1.084); 0.033 |

Figure 2. Adjusted Hazard Ratio with 95% CI for VT/VF, associated with spatial TT' angle in all patients.

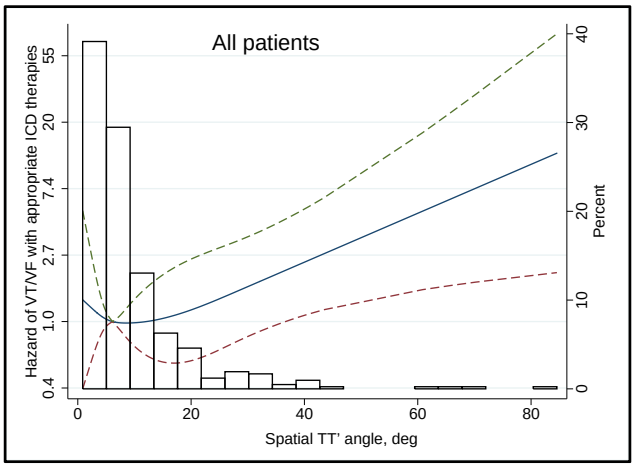



Figure 3. Adjusted Hazard Ratio with 95% CI for VT/VF, associated with spatial TT' angle in ICM.

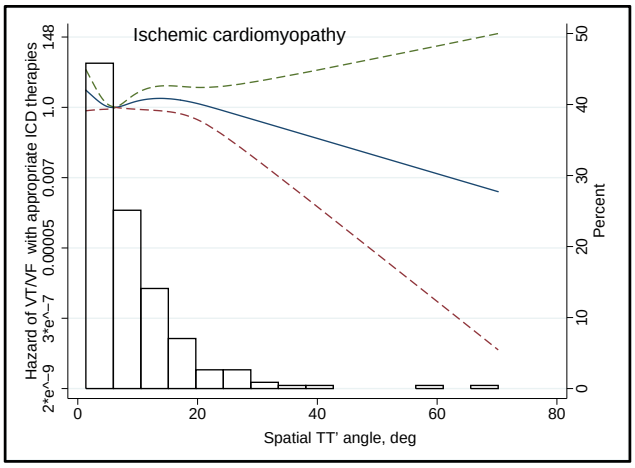
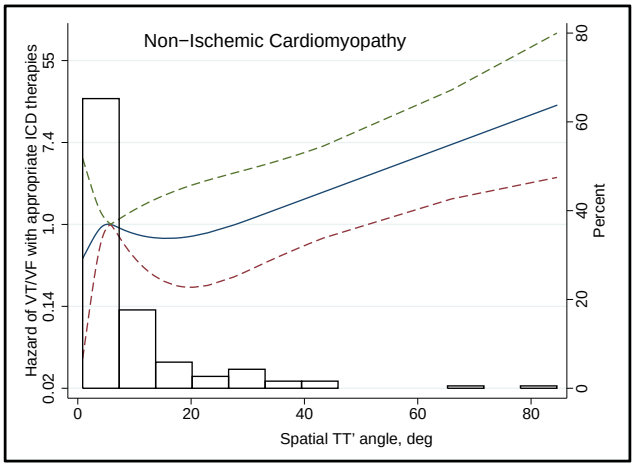



Figure 4. Adjusted Hazard Ratio with 95% CI for VT/VF, associated with spatial TT' angle in NICM.



Strength of association between increasing spatial TT' angle and MMVT, as compared to PVT/VF, was similar.

In this study variability in spatial T-vector amplitude (neither TampVN, nor TamprMSSD) did not associate with VT/VF.

## 4. Discussion

This study showed that spatial TT' angle is associated with sustained ventricular arrhythmias and appropriate ICD therapies in primary prevention ICD patients. Increase in spatial TT' angle by one degree was associated with 2.5% increase in VT/VF risk. Given that TT' angle ranged from 0.9 to 84.6 degrees, associated with TT' angle risk of VT/VF could become substantial in individual patients. In this study spatial TT' angle was associated with both MMVT and PVT/VF. However, importantly, the interaction with CM type was observed: TT' angle was strongly associated with VT/VF in NICM, but not in ICM. In NICM, association of TT' angle with PVT/VF (4.3% risk increase per one degree of TT' angle) was stronger than the association with MMVT (3.0% risk increase per one degree of TT' angle).

Results of this study support theoretical investigations [1-3], indicating importance of repolarization lability for arrhythmogenesis, and further elucidate conditions, which are essential for manifestation of repolarization lability. Pueyo et al[1] demonstrated that stochastic $I_{ks}$ properties do not manifest, unless other pathological conditions (reduced repolarization reserve and/or cell-to-cell uncoupling) are present. Spatial TT' angle reflects beat-to-beat changes in a summed spatial vector of cardiac repolarization, and therefore, reliably[11] quantifies repolarization lability, both temporal and spatial heterogeneity of repolarization.

Mechanisms of VT/VF in NICM and ICM differ.

NICM is characterized by diffuse myocardial disease process, which facilitates manifestation of repolarization lability with proportionally augmented risk of VT/VF.

ICM, in contrast, is characterized by localized scar and dispersion of activation times rather than refractoriness [10]. Degree of diffuse disease in ICM is determined by post-myocardial infarction (MI) remodeling and by factors, which indirectly and in multifactorial fashion relate to the post-MI scar *perse*, and varies from patient to patient, which explains inconsistent association of spatial TT' angle with VT/VF in ICM in this study.

## 5. Conclusions

Spatial TT' angle is associated with sustained ventricular arrhythmias (in particular with PVT/VF) in primary prevention ICD patients (predominantly in NICM). Spatial TT' angle is a measure of repolarization lability, spatial and temporal heterogeneity of repolarization.


## Acknowledgements

Author thanks Lichy Han, BS, for data analysis, as well as PROSE-ICD participants and staff for their important contribution.

This work was supported by the NIH 1R01HL118277.


## References


[1] Pueyo E, Corrias A, Virag L et al. A multiscale investigation of repolarization variability and its role in cardiac arrhythmogenesis. Biophys J 2011;101:2892-2902.

[2] Heijman J, Zaza A, Johnson DM et al. Determinants of beat-to-beat variability of repolarization duration in the canine ventricular myocyte: a computational analysis. PLoS Comput Biol 2013;9:e1003202.

[3] Tanskanen AJ, Greenstein JL, O'Rourke B, Winslow RL. The role of stochastic and modal gating of cardiac L-type Ca2+ channels on early after-depolarizations. Biophys J 2005;88:85-95.

[4] Han L, Tereshchenko LG. Lability of R- and T-wave peaks in three-dimensional electrocardiograms in implantable cardioverter defibrillator patients with ventricular tachyarrhythmia during follow-up. J Electrocardiol 2010;43:577-582.

[5] Tereshchenko LG, Han L, Cheng A et al. Beat-to-beat three-dimensional ECG variability predicts ventricular arrhythmia in ICD recipients. Heart Rhythm 2010;7:1606-1613.

[6] Couderc JP, Zareba W, McNitt S, Maison-Blanche P, Moss AJ. Repolarization variability in the risk stratification of MADIT II patients. Europace 2007;9:717-723.

[7] Cheng A, Dalal D, Butcher B et al. Prospective observational study of implantable cardioverter-defibrillators in primary prevention of sudden cardiac death: study design and cohort description. J Am Heart Assoc 2013;2:e000083.

[8] Han L, Cheng A, Sur S, Tomaselli GF, Berger RD, Tereshchenko LG. Complex assessment of the temporal lability of repolarization. Int J Cardiol 2013;166:543-545.

[9] Sur S, Han L, Tereshchenko LG. Comparison of sum absolute QRST integral, and temporal variability in depolarization and repolarization, measured by dynamic vectorcardiography approach, in healthy men and women. PLoS One 2013;8:e57175.

[10] Vassallo JA, Cassidy DM, Kindwall KE, Marchlinski FE, Josephson ME. Nonuniform recovery of excitability in the left ventricle. Circulation 1988;78:1365-1372.

[11] Feeny A, Han L, Tereshchenko LG. Repolarization lability measured on 10-second ECG by spatial TT' angle: reproducibility and agreement with QT variability. Journal of Electrocardiology 2014.



Address for correspondence: Larisa G. Tereshchenko, MD, PhD, 3181 SW Sam Jackson Park Rd; UHN62; Portland, OR, 97239. E-mail address: tereshch@ohsu.edu