Published in final edited form as:

Heart Rhythm. 2007 August ; 4(8): 1114–1119.

Does Tpeak-Tend Provide an Index of Transmural Dispersion of Repolarization?

Charles Antzelevitch, PhD, FHRS¹, Sami Viskin, MD², Wataru Shimizu, MD, PhD³, Gan-Xin Yan, MD, PhD⁴, Peter Kowey, MD⁴, Li Zhang, MD⁵, Serge Sicouri, MD¹, José M. Di Diego, MD¹, and Alexander Burashnikov, PhD¹

¹Masonic Medical Research Laboratory, Utica, NY

²Department of Cardiology, Tel-Aviv Sourasky Medical Center, and Sackler School of Medicine, Tel-Aviv University, Israel

³Division of Cardiology, Department of Internal Medicine, National Cardiovascular Center, Suita, Osaka, Japan

⁴Main Line Health Heart Center, Wynnwood, PA and Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA

⁵Department of Cardiology LDS Hospital, Intermountain Healthcare, University of Utah School of Medicine, Salt Lake City, UT

Differences in the time course of repolarization of the three predominant myocardial cell types have been shown to contribute to the inscription of the T wave of the electrocardiogram (ECG). Voltage gradients developing as a result of the different time course of repolarization of phases 2 and 3 in the three cell types give rise to opposing voltage gradients on either side of the M region, which are in part responsible for the inscription of the T wave.¹ In the case of an upright T wave, the epicardial response is the earliest to repolarize and the M cell action potential is the latest. In the coronary-perfused wedge preparation, repolarization of the epicardial action potential coincides with the peak of the T wave and repolarization of the M cells is coincident with the end of the T wave, so that the interval from the peak to the end of the T wave provides a measure of transmural dispersion of repolarization (TDR).

Based on these early studies, the Tpeak-Tend interval in precordial ECG leads was suggested to provide an index of transmural dispersion of repolarization.² More recent studies have also provided guidelines for the estimation of transmural dispersion of repolarization in the case of more complex T waves, including negative, biphasic and triphasic T waves.³ In such cases, the interval from the nadir of the first component of the T wave to the end of the T wave was shown to provide an electrocardiographic approximation of TDR.

While these relationships are relatively straight forward in the coronary-perfused wedge preparation, extrapolation to the surface ECG recorded *in vivo* must be approached with great caution and will require careful validation. The Tpeak-Tend interval is unlikely to provide an absolute measure of transmural dispersion *in vivo*, as elegantly demonstrated by Xia and coworkers⁴. However, changes in this parameter are thought to be capable of reflecting changes in spatial dispersion of repolarization, particularly TDR, and thus may be prognostic of arrhythmic risk under a variety of conditions.⁵⁻¹⁰ Takenaka et al. recently demonstrated exercise-induced accentuation of the Tpeak-Tend interval in LQT1 patients, but not LQT2.⁹

Address for correspondence: Dr. Charles Antzelevitch, Gordon K. Moe Scholar, Masonic Medical Research Laboratory, 2150 Bleecker Street, Utica, NY 13501-1787, Phone: 315-735-2217, Fax: 315-735-5648, E-mail: ca@mmrl.edu

There are no conflicts of interest.

These observations coupled with those of Schwartz et al.¹¹, demonstrating an association between exercise and risk for TdP in LQT1, but not LQT2, patients, point to the potential value of Tpeak-Tend in forecasting risk for the development of Torsade de Pointes (TdP). Direct evidence in support of Tpeak-Tend as an index to predict TdP in patients with long QT syndrome (LQTS) was provided by Yamaguchi and co-workers.¹² These authors concluded that Tpeak-Tend is more valuable than QTc and QT dispersion as a predictor of TdP in patients with acquired LQTS. Shimizu et al. demonstrated that Tpeak-Tend, but not QTc, predicted sudden cardiac death in patients with hypertrophic cardiomyopathy.⁸ In a case-controlled study comparing 30 cases of acquired bradyarrhythmias complicated by TdP and 113 cases with uncomplicated bradyarrhythmias, Topilski et al found that QT, QTc and Tpeak-Tend intervals were strong predictors of TdP, with the best single discriminator being a prolonged Tpeak-Tend.¹³ Watanabe et al. demonstrated that prolonged Tpeak-Tend is associated with inducibility as well as spontaneous development of ventricular tachycardia (VT) in high risk patients with organic heart disease.¹⁰

These interesting studies demonstrating an association between an increase in Tpeak-Tend and arrhythmic risk notwithstanding, direct validation of Tpeak-Tend measured at the body surface as an index of TDR is still lacking. Guidelines for such validation have been suggested repeatedly.^{1, 3, 14} Because the precordial leads view the electrical field across the ventricular wall, Tpeak-Tend would be expected to be most representative of TDR in these leads. The precordial leads are unipolar leads placed on the chest that are referenced to Wilson central terminal. The direction of these leads is radially outward from the “center” of the heart, the center of the Einthoven triangle. Unlike the precordial leads, the bipolar limb leads, including leads I, II, and III, do not look across the ventricular wall. While Tpeak-Tend intervals measured in these limb leads may provide an index of TDR, they are more likely to reflect global dispersion, including apico-basal and interventricular dispersion of repolarization.^{4, 15}

A large increase in TDR is likely to be arrhythmogenic because the dispersion of repolarization and refractoriness occurs over a very short distance (the width of the ventricular wall), creating a steep repolarization gradient.^{16, 17} It is the steepness of the repolarization gradient rather than the total magnitude of dispersion that determines its arrhythmogenic potential. Apico-basal or interventricular dispersion of repolarization is less informative because it may or may not be associated with a steep repolarization gradient and thus may or may not be associated with arrhythmic risk.

The other critical point to consider is that TDR can be highly variable in different regions of the ventricular myocardium, particularly under pathophysiologic conditions. Consequently, it is important to measure Tpeak-Tend independently in each of the precordial leads and it is inadvisable to average Tpeak-Tend among several leads.⁴ Because LQTS is principally a left ventricular disorder, TDR is likely to be greatest in the left ventricular wall or septum and thus to be best reflected in left precordial leads or V3, respectively. Yamaguchi et al. in their study of acquired LQTS targeted lead V5.¹² In contrast, because Brugada syndrome is a right ventricular disorder, TDR is greatest in the right ventricular free wall and thus is best reflected in the right precordial leads. For this reason, Castro et al. targeted lead V2 in their study.¹⁸ The criteria for validation of Tpeak-Tend as an index of TDR are therefore fairly simple, requiring 1) that individual precordial leads, and not bipolar limb leads, be evaluated and 2) that TDR be present at baseline and significantly augmented as a result of an intervention.

In a recent paper published in *Heart Rhythm*, Opthof and co-workers¹⁵ set out to test the hypothesis Tpeak-Tend interval reflects transmural dispersion. Plunge electrodes were used to quantitate transmural and global dispersion of repolarization and Tpeak-Tend (Tp-e) was measured only in a single limb lead, lead II, under conditions in which TDR was essentially non-existent: 2.7-14.5 ms. The use of two anesthetics, propofol and isoflurane, known to

suppress sodium channel currents in a variety of cells including M cells, together with the use of a pacing rate of 130 bpm, resulted in essentially no TDR. The recording of precordial ECGs was not possible in this open chest dog model. Thus the two fundamental criteria for validation were not met and the study as designed, for reasons discussed above, could come to no other conclusion than that reached, which is that “Tp-e does not correlate with transmural dispersion of repolarization, but is an index of total dispersion of repolarization”.

Thus, the quest for direct validation or invalidation of Tpeak-Tend measured at the body surface as an index of TDR remains unfulfilled. Although most studies to date concur that Tpeak-Tend provides a measure of spatial dispersion of repolarization, the extent to which an augmented Tpeak-Tend interval is prognostic of arrhythmic risk depends on the proximity of the regions displaying disparate repolarization times (i.e., repolarization gradient). Consequently, it would be helpful to know to what extent Tpeak-Tend provides an index of TDR, in which case the differences in refractoriness are ensured to be within close proximity. To this end, it is noteworthy that an ideal model in which to test the hypothesis is in the chronic atrioventricular (AV) block dog treated with I_{Kr} blockers, since changes in Tpeak-Tend could be accurately correlated with TDR in a model that displays prominent TDR, and additionally correlated with the risk for development of TdP.

Acknowledgements

Supported by grant HL47678 from NHLBI and grants from the American Heart Association and NYS and Florida Grand Lodges F. & A.M.

References

1. Yan GX, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long QT syndrome. *Circulation* 1998;98:1928–36. [PubMed: 9799215]
2. Antzelevitch C, Shimizu W, Yan GX, Sicouri S, Weissenburger J, Nesterenko VV, Burashnikov A, Di Diego JM, Saffitz J, Thomas GP. The M cell: its contribution to the ECG and to normal and abnormal electrical function of the heart. *J Cardiovasc Electrophysiol* 1999;10:1124–52. [PubMed: 10466495]
3. Emori T, Antzelevitch C. Cellular basis for complex T waves and arrhythmic activity following combined $I(Kr)$ and $I(Ks)$ block. *J Cardiovasc Electrophysiol* 2001;12:1369–78. [PubMed: 11797994]
4. Xia Y, Liang Y, Kongstad O, Liao Q, Holm M, Olsson B, Yuan S. In vivo validation of the coincidence of the peak and end of the T wave with full repolarization of the epicardium and endocardium in swine. *Heart Rhythm* 2005;2:162–9. [PubMed: 15851290]
5. Wolk R, Stec S, Kulakowski P. Extrasystolic beats affect transmural electrical dispersion during programmed electrical stimulation. *Eur J Clinical Invest* 2001;31:293–301. [PubMed: 11298775]
6. Tanabe Y, Inagaki M, Kurita T, Nagaya N, Taguchi A, Suyama K, Aihara N, Kamakura S, Sunagawa K, Nakamura K, Ohe T, Towbin JA, Priori SG, Shimizu W. Sympathetic stimulation produces a greater increase in both transmural and spatial dispersion of repolarization in LQT1 than LQT2 forms of congenital long QT syndrome. *J Am Coll Cardiol* 2001;37:911–9. [PubMed: 11693770]
7. Frederiks J, Swenne CA, Kors JA, van Herpen G, Maan AC, Levert JV, Schaliij MJ, Bruschke AV. Within-subject electrocardiographic differences at equal heart rates: role of the autonomic nervous system. *Pflugers Arch* 2001;441:717–24. [PubMed: 11294255]
8. Shimizu M, Ino H, Okeie K, Yamaguchi M, Nagata M, Hayashi K, Itoh H, Iwaki T, Oe K, Konno T, Mabuchi H. T-peak to T-end interval may be a better predictor of high-risk patients with hypertrophic cardiomyopathy associated with a cardiac troponin I mutation than QT dispersion. *Clin Cardiol* 2002;25:335–9. [PubMed: 12109867]
9. Takenaka K, Ai T, Shimizu W, Kobori A, Ninomiya T, Otani H, Kubota T, Takaki H, Kamakura S, Horie M. Exercise stress test amplifies genotype-phenotype correlation in the LQT1 and LQT2 forms of the long-QT syndrome. *Circulation* 2003;107:838–44. [PubMed: 12591753]
10. Watanabe N, Kobayashi Y, Tanno K, Miyoshi F, Asano T, Kawamura M, Mikami Y, Adachi T, Ryu S, Miyata A, Katagiri T. Transmural dispersion of repolarization and ventricular tachyarrhythmias. *J Electrocardiol* 2004;37:191–200. [PubMed: 15286932]

11. Schwartz PJ, Priori SG, Spazzolini C, Moss AJ, Vincent GM, Napolitano C, Denjoy I, Guicheney P, Breithardt G, Keating MT, Towbin JA, Beggs AH, Brink P, Wilde AA, Toivonen L, Zareba W, Robinson JL, Timothy KW, Corfield V, Wattanasirichaigoon D, Corbett C, Haverkamp W, Schulze-Bahr E, Lehmann MH, Schwartz K, Coumel P, Bloise R. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001;103:89–95. [PubMed: 11136691]
12. Yamaguchi M, Shimizu M, Ino H, Terai H, Uchiyama K, Oe K, Mabuchi T, Konno T, Kaneda T, Mabuchi H. T wave peak-to-end interval and QT dispersion in acquired long QT syndrome: a new index for arrhythmogenicity. *Clin Sci (Lond)* 2003;105:671–6. [PubMed: 12857349]
13. Topilski I, Rogowski O, Rosso R, Justo D, Copperman Y, Glikson M, Belhassen B, Hochenberg M, Viskin S. The morphology of the QT interval predicts torsade de pointes during acquired bradyarrhythmias. *J Am Coll Cardiol* 2007;49:320–8. [PubMed: 17239713]
14. Antzelevitch C. T peak-Tend interval as an index of transmural dispersion of repolarization. *Eur J Clin Invest* 2001;31:555–7. [PubMed: 11454006]
15. Opthof T, Coronel R, Wilms-Schopman FJ, Plotnikov AN, Shlapakova IN, Danilo P Jr, Rosen MR, Janse MJ. Dispersion of repolarization in canine ventricle and the electrocardiographic T wave: T(p-e) interval does not reflect transmural dispersion. *Heart Rhythm* 2007;4:341–8. [PubMed: 17341400]
16. Akar FG, Yan GX, Antzelevitch C, Rosenbaum DS. Unique topographical distribution of M cells underlies reentrant mechanism of torsade de pointes in the long-QT syndrome. *Circulation* 2002;105:1247–53. [PubMed: 11889021]
17. Aiba T, Shimizu W, Hidaka I, Uemura K, Noda T, Zheng C, Kamiya A, Inagaki M, Sugimachi M, Sunagawa K. Cellular basis for trigger and maintenance of ventricular fibrillation in the Brugada syndrome model: high-resolution optical mapping study. *J Am Coll Cardiol* 2006;47:2074–85. [PubMed: 16697328]
18. Castro HJ, Antzelevitch C, Tornos BF, Dorantes SM, Dorticos BF, Zayas MR, Quinones Perez MA, Fayad RY. Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. *J Am Coll Cardiol* 2006;47:1828–34. [PubMed: 16682308]