T_{peak}-T_{end} Interval as an Index of Transmural Dispersion of Repolarization and Risk for Development of Torsade de Pointes

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Amplification of transmural dispersion of repolarization (TDR) within the ventricular myocardium has been suggested to underlie arrhythmogenesis in the Brugada, short QT and long QT syndromes. Recent studies have identified TDR and other forms of spatial dispersion of repolarization as the principal substrate and early afterdepolarization (EAD)-induced extrasystoles as the most common trigger for the development of TdP in LQTS.[1] One of the challenges ahead is to identify a means to quantitate TDR non-invasively. This brief paper discusses the value of the interval between the peak and end of the T wave (Tpeak-Tend, Tp-Te) as an index of TDR.

Recent studies have highlighted the heterogeneity that exists among the cells that comprise ventricular myocardium, demonstrating unique electrophysiologic and pharmacologic profiles for epicardial, endocardial and M cells in a number of species, including man. (see [2;3] for reviews) Ventricular epicardial and M cells display action potentials with a prominent transient outward current (I_{to})-mediated phase 1, giving rise to a notched appearance of the action potential. M cells are characterized by the ability of their action potential to prolong more than that of epicardial or endocardial cells in response to a slowing of rate and/or in response to drugs that prolong action potential duration (APD).

Differences in the time-course of repolarization of these three predominant ventricular myocardial cell types appear to be largely responsible for the inscription of the electrocardiographic T wave.[4] Currents flowing down voltage gradients on either side of the M region contribute prominently to inscription of the T wave (**Fig. 1**). [4]

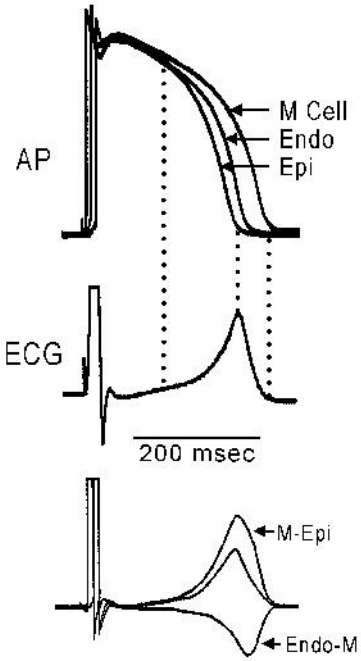

Figure 1

Figure 1. Voltage gradients on either side of the M region are responsible for inscription of the electrocardiographic T wave. **Top:** Action potentials simultaneously recorded from endocardial, epicardial and M region sites of an arterially-perfused canine left ventricular wedge preparation. **Middle:** ECG recorded across the wedge. **Bottom:** Computed voltage differences between the epicardium and M region action potentials ($\Delta V_{M\text{-}Epi}$) and between the M region and endocardium responses ($\Delta V_{Endo\text{-}M}$)

The interplay between these opposing transmural forces determines the height and width of the T wave and the extent to which the T wave may be interrupted, resulting in a bifid or notched appearance.

The T wave begins when the plateau of epicardial action potential diverges from that of the M cell. As epicardium repolarizes, the voltage gradient between epicardium and the M region continues to grow giving rise to the ascending limb of the T wave. The voltage gradient between the M region and epicardium ($\Delta V_{M\text{-}Epi}$) reaches a peak when the epicardium is fully repolarized - this marks the peak of the T wave. On the other end of the ventricular wall, the endocardial plateau deviates from that of the M cell, generating an opposing voltage gradient ($\Delta V_{Endo\text{-}M}$) and corresponding current that limits the amplitude of the T wave and contributes to the initial part of

the descending limb of the T wave. The voltage gradient between endocardium and the M region reaches a peak when the endocardium is fully repolarized. The gradient continues to decline as the M cells repolarize. All voltage gradients are extinguished when the longest M cells are fully repolarized.

When the T wave is upright, the epicardial response is the earliest to repolarize and the M cell action potential is the latest. Full 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. It therefore follows that the duration of the M cell action potential determines the QT interval, whereas the duration of the epicardial action potential determines the QTpeak interval. Another interesting finding stemming from these studies is that the $T_{peak}–T_{end}$ interval may provide an index of transmural dispersion of repolarization [2;4]. Figure 2 illustrates these relationships under baseline and long QT conditions.

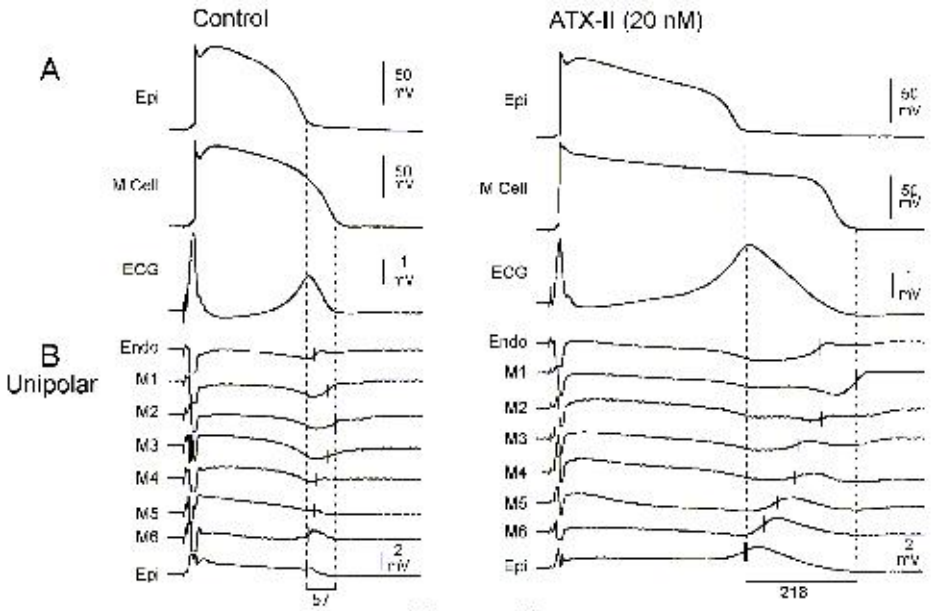

Figure 2

Figure 2. Correspondence among transmembrane, unipolar, and ECG recordings in he absence (left) and the presence (right) of ATX-II (20 nmol/L). Each panel shows: **A.** Transmembrane action potentials recorded from M (M2) and epicardial sites of a canine left ventricular wedge preparation together with a transmural ECG recorded across the bath (BCL of 2000 msec); **B.** Eight intramural unipolar electrograms recorded approximately 1.2 mm apart from endocardial (Endo), M (6 sites; M1–M6) and epicardial (Epi) regions (120 um silver electrodes insulated except at the tip) inserted midway into the wedge preparation. Dashed vertical lines in the unipolar electrograms denote the time maximum of the first derivative (V_{max}) of the T wave (end of activation-recovery interval – ARI). Close correspondence between the repolarization time of the cells deep within the wedge and those at the cut surface attest the uniformity of the electrical activity in the respective transmural layers. Modified from [2], with permission.

ATX-II, a sea anemone toxin, mimics the LQT3 form of the long QT syndrome by augmenting the late sodium current, which helps to sustain the plateau of the action potential. ATX-II, like most agents that prolong the action potential, causes a preferential prolongation of the M cell response, thus producing a dramatic accentuation of the transmural dispersion of repolarization, which is reflected on the ECG as a prolongation of the Tpeak-Tend interval. An increase in transmural dispersion of repolarization is a common feature of all LQTS models and has been shown to provide the substrate for the development of Torsade de Pointes under long QT conditions. [2;5;6].

The available data suggest that Tpeak-Tend measurements should be limited to precordial leads since these leads may more accurately reflect *transmural* dispersion of repolarization. Recent studies have also provide guidelines for the estimation of transmural dispersion of repolarization in the case of more complex T waves, including negative, biphasic and triphasic T waves.[7] In these cases, the interval from the nadir of the first component of the T wave to the end of the T wave provides an accurate electrocardiographic approximation of transmural dispersion of repolarization.

The clinical applicability of these concepts remains to be fully validated. An important step towards validation of the Tpeak-Tend interval as an index of transmural dispersion was provided in a report by Lubinski et al.[8], which showed an increase of this interval in patients with congenital long QT syndrome. Recent studies suggest that the Tpeak-Tend interval may be a useful index of transmural dispersion and thus may be prognostic of arrhythmic risk under a variety of conditions [9-11].

Figure 3 illustrates the typical effect of exercise in patients with LQT1 and LQT2 syndromes, demonstrating exercise-induced accentuation of the T_{peak}-T_{end} interval in LQT1, but not LQT2. [12]

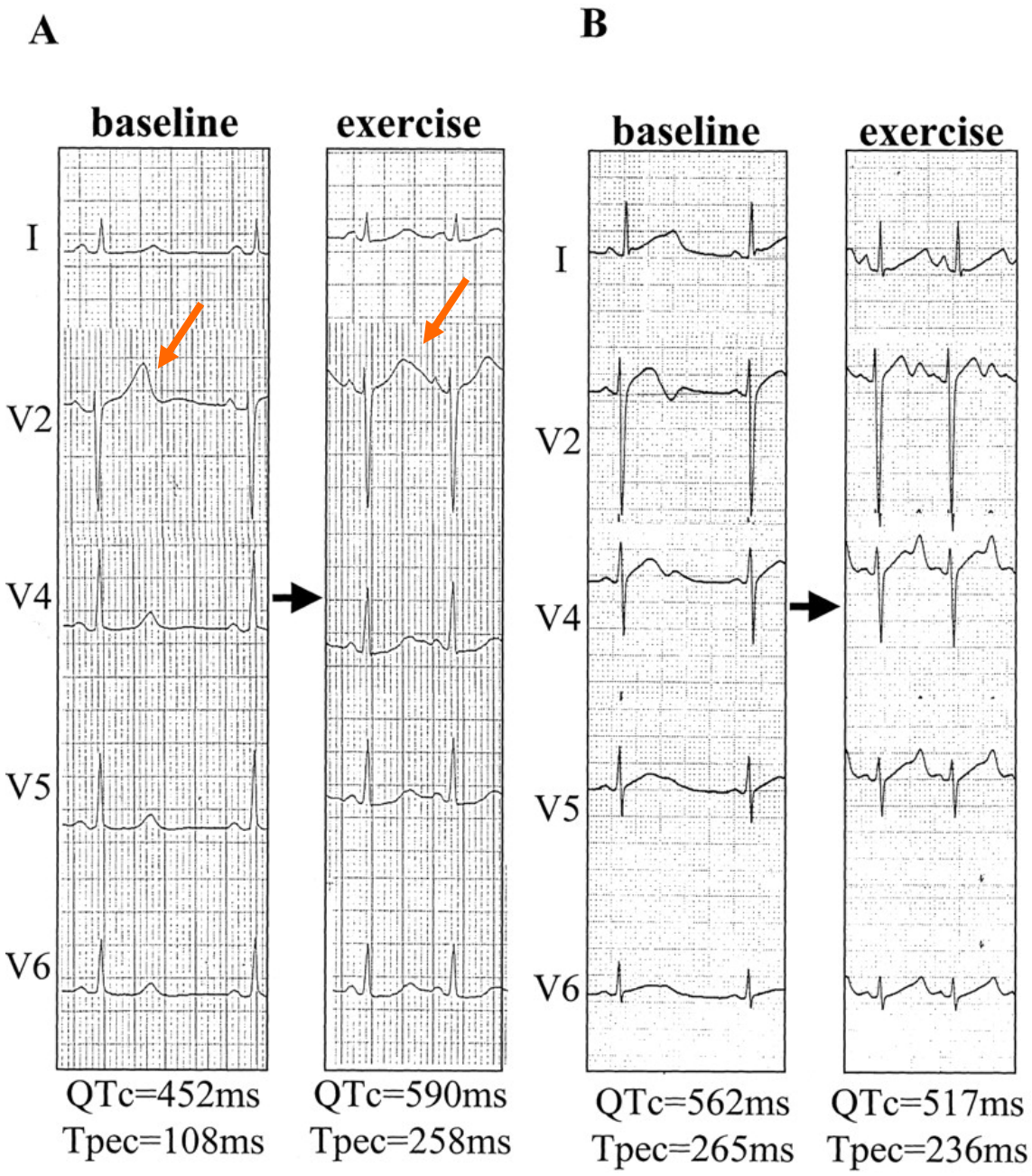

Figure 3. Representative morphologic changes in the 5 leads of ECGs during exercise in patients with LQT1 (A) and LQT2 (B). Measured values for QTc and corrected Tpeak-Tend (Tpec; Tpe/R-R1/2) are shown at the bottom of each column. From [12] with permission.

These observation coupled with those of Schwartz et al. [13] 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 TdP.

Direct evidence in support of Tp-Te as a valuable index to predict TdP in patients with long QT syndrome was provided by Yamaguchi and co-workers.[14] These authors concluded that Tp-Te is more valuable than QTc and QTdispersion as a predictor of TdP in a patients with acquired LQTS.

Recent studies involving the wedge preparation have shown that the area under the second half of the T wave ($Tpeak–Tend_{Area}$) can provide a still more reliable index to gauge changes in transmural dispersion of repolarization (Tsuboi M, Antzelevitch C. Non-invasive index of transmural dispersion of repolarization (TDR) from the ECG. PACE, 26:II-958, 2003).

Although additional work is needed to assess the value of these non-invasive indices of electrical heterogeneity and their prognostic value in the assignment of arrhythmic risk, evidence is mounting in support of the hypothesis that TDR rather QT prolongation underlies the substrate responsible for the development of TdP (Table 1).

Table 1. Association of increased transmural dispersion of repolarization and early afterdepolarizations activity in canine left ventricular myocardium with occurrence of Torsade de Pointes in humans

	Canine LV Tissues Studied				Effect in Canine LV		Effect in Humans	
Drug/Condition	**M**	**Epi**	**PF**	**Wedge**	**EADs**	**⇑TDR**	**⇑QT**	**TdP**
Amiodarone[15]	✓	✓			–	–	+	±
Azimilide[16]	✓	✓			+	+	+	+
Cisapride[17]	✓	✓	✓	✓	+	+	+	+
Erythromycin[18]	✓	✓		✓	+	+	+	+
$\Downarrow I_{Ks}$ with β adrenergic stimulation[6]	✓	✓	✓	✓	–	+	+	+
$\Downarrow I_{Ks}$ with β adrenergic block[6]	✓	✓	✓	✓	–	–	+	–
Sodium Pentobarbital[19]	✓	✓		✓	–	–	+	–
Quinidine, low concentration[20]	✓	✓	✓		+	+	+	+
Quinidine, high concentration[20]	✓	✓	✓		–	–	+	–
Sotalol[5;6;21]	✓	✓	✓	✓	+	+	+	+
Terfenadine*	✓	✓		✓	+	+	+	+
Verapamil*	✓	✓	✓	✓	–	–	–	–
Mibefradil*				✓	+	+	+	+
Moxifloxacin*	✓	✓		✓	+	+	+	+
Ranolazine*	✓	✓	✓	✓	–	–	+	–

Epi = epicardial cells; M = M cells; PF = Purkinje fibers; $\Downarrow I_{Ks}$ = LQT1 (I_{Ks} defect) or drug-induced I_{Ks} block; *unpublished observation.

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