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Relationship between extracellular T-wave height, T-wave alternans amplitude, and tissue action potential alternans: a 1-dimensional computer modeling study*

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Abstract

T-wave alternans (TWA) is a useful marker of cardiac instability, but not much is known about the factors that affect its measurement, such as electrode placement. We used a 1-dimensional myocardial fiber computer model of alternans to investigate the effect of electrode position on TWA measurement. Results demonstrated that TWA amplitude and T-wave amplitude change proportionally if both recording electrodes are symmetrically moved toward or away from the tissue. However, TWA amplitude and T-wave amplitude change out of proportion to one another when one electrode is moved while the other electrode remains stationary. These disproportionate changes result from beatwise alternation in the asymmetric potential field around the tissue. In summary, nonlinear changes in tissue repolarization during alternans result in nonlinear changes in T-wave amplitude and TWA amplitude.

Keywords

T-wave alternans; Action potential duration alternans; Electrocardiogram; Computer model

Introduction

T-wave alternans (TWA), alternation in the amplitude or morphology of the electrocardiogram (ECG) T wave, has long been associated with cardiac electrical instability and sudden cardiac arrest. Accordingly, clinical TWA testing has been shown to be a promising risk stratification tool for sudden death in several patient populations.¹ Although it is known from previous animal studies that alternans of cellular action potential duration (APD) within the myocardium is manifest as TWA in the ECG,² the relationship between the magnitude of cellular alternans within the tissue, the amplitude of TWA in the ECG, and the position of the ECG lead is unclear. Knowledge of this relationship is important to understanding and developing more sensitive TWA testing methods.

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The effect of electrode lead placement on the measured TWA amplitude may be affected by the amplitude of the ECG T wave. Intracardiac effects, such as the degree of cellular alternans and electrophysiologic heterogeneity of the tissue, and extracardiac effects, such as heterogeneity of the volume conductor, all likely affect measured T-wave and TWA amplitudes. To control and isolate the effects of these factors, we investigated a simple 1-dimensional fiber model of cellular alternans in an unbounded homogeneous volume conductor. By idealizing the tissue geometry as a fiber, considering it in a large, homogeneous volume conductor, and controlling the degree of cellular APD alternans, general inferences can be made about the effects of electrode placement on the measurement of TWA.

In this study, we created a 1-dimensional model of a multicellular myocardial fiber. We investigated the effects of various degrees of APD alternans and various electrode positions within the volume conductor on measured T-wave amplitude and TWA amplitude. We hypothesize that there is a nonlinear relationship between the amplitude of the measured T wave, the amplitude of TWA, and the position of the recording electrode.

Methods

Membrane and tissue model

A 1-cm long, 1-dimensional, multicellular fiber computer model of ventricular myocardium was designed to qualitatively represent action potential conduction from the endocardial surface to epicardial surface of the left ventricular free wall. The fiber was created by positioning 100 nodes, spaced 0.01 cm apart, in a straight line within a 2-dimensional coordinate system. Each node is a voltage point source representing a 100- μm long cylindrical cell with diameter 22 μm . Adjacent nodes are electrically coupled by a gap junction of conductance 1.5 μS , such that conduction velocity along the fiber is 44 cm/s, approximating left ventricular transmural conduction velocity recorded in vitro.³

Current flow through the fiber is described by Equation 1,

$$\frac{\partial}{\partial x} \left(D \frac{\partial V_m}{\partial x} \right) = \beta \left(C_m \frac{\partial V_m}{\partial t} + I_{ion} \right) \quad (1)$$

where D is axial conductivity (150 $\mu\text{S}/\text{cm}$); V_m is the transmembrane voltage in millivolts, β is surface-area-to-volume ratio (1818.2 cm^{-1}), C_m is membrane capacitance (1 $\mu\text{F}/\text{cm}^2$), and I_{ion} is the sum of ionic currents in microampere per square centimeter described by the ionic model by Fox et al.⁴ For all simulations, “sealed end” (no flux) boundary conditions were used. The fiber model is considered to be surrounded by a 2-dimensional, unbounded, homogeneous volume conductor of conductivity 20 mS/cm, equal to that of saline at 37°C.⁵ Virtual electrodes are placed at various points within the volume conductor, at distance d from the center of the fiber and at angle θ from the fiber axis (Fig. 1A).

Transmural dispersion of APD and APD alternans magnitude within the fiber were controlled by adjusting the G_{K1} and τ_{fCa} parameters of the Fox-McHarg-Gilmour model.

The fiber consisted of 3 electrophysiologically distinct regions, with the first 33 nodes representing endocardial ventricular cells, the middle 34 nodes representing midmyocardial ventricular cells, and the last 33 nodes representing epicardial ventricular cells. Values of G_{K1} for endocardial, midmyocardial, and epicardial nodes were set at 3.3, 1.8, and 5.0 mS/ μ F, respectively, resulting in a transmural APD profile qualitatively similar to that observed experimentally (Fig. 1B).³ To induce APD alternans within the fiber, τ_{fCa} of endocardial and epicardial nodes was set at 32 milliseconds, and τ_{fCa} of midmyocardial nodes was set at a value between 76 and 96 milliseconds, with a larger value of τ_{fCa} producing an increased degree of APD alternans in the fiber. For all simulations, the magnitude of APD alternans was largest near the endocardial end and smallest at the epicardial end (Fig. 1C).

Numerical methods and simulation

Integration of Equation 1 was accomplished using a semiimplicit Crank-Nicolson method with a dt of 0.004 milliseconds and dx of 0.01 cm. All simulations were run using the CardioWave software package⁶ on a Linux computing cluster. The leftmost node of the fiber was paced at suprathreshold strength at a basic cycle length of 220 milliseconds for 60 seconds in order for the system to reach steady state. The transmembrane voltage and extracellular potentials resulting from the final 2 stimuli were used for analysis.

Cellular activation and repolarization

For the 2 beats investigated, V_m was obtained from every node (every 0.01 cm) of the fiber. For each node, cellular activation time and cellular repolarization time were defined as the time after stimulus that V_m increased more than or decreased less than -81 mV (which roughly corresponds to 90% repolarization from peak V_m), respectively. Action potential duration was calculated as the difference between repolarization time and activation time. For each beat, the tissue repolarization gradient was approximated as a scalar quantity in milliseconds per centimeter by Equation 2,

$$\nabla_{repol} = -\frac{t_{repol}(\max) - t_{repol}(\min)}{x_{repol}(\max) - x_{repol}(\min)}, \quad (2)$$

where $t_{repol}(\max)$ and $t_{repol}(\min)$ are the maximum and minimum repolarization times, and $x_{repol}(\max)$ and $x_{repol}(\min)$ are the x-coordinates of the nodes with those times. A positive repolarization gradient signifies right-to-left repolarization in the fiber (repolarization opposite the direction of activation).

Extracellular signals

Potential at each virtual electrode in the volume conductor was calculated from the spatial gradient of transmembrane voltage using a current source approximation as described by Equation 3,

$$\phi_e(x', y', z') = \frac{a^2}{4\sigma_e} \int (-\nabla V_m) \times \left(\nabla \frac{1}{\sqrt{(x-x')^2 + (y-y')^2 + (z-z')^2}} \right) dx, \quad (3)$$

where $\phi_e(x', y', z')$ is the potential in mV of an electrode at coordinates (x', y', z') , a is the fiber radius in cm, σ_e is the conductivity of the volume conductor in millisiemens per centimeter, and (x, y, z) are the coordinates for each node. Psuedo-ECGs were obtained by subtracting an electrode potential on the left side of the fiber (the negative electrode) from one on the right side of the fiber (the positive electrode) (Fig. 1A). T-wave amplitudes were directly measured from the ECGs, and TWA amplitude was calculated as the difference between the 2 T-wave amplitudes (Fig. 2). The *TWA index*, defined as the ratio of TWA amplitude to minimum T-wave amplitude, was also calculated.

Studies conducted

T-wave amplitude relation to repolarization gradients—To determine the relation between T-wave amplitude and cellular repolarization, T-wave amplitudes in the ECG were compared to the corresponding repolarization gradients in the tissue for several degrees of cellular alternans. The TWA amplitude in the ECG was compared to the corresponding beatwise difference in repolarization gradient.

Effect of electrode position on T-wave amplitude and TWA amplitude—The effect of electrode position on T-wave amplitude and TWA amplitude was investigated by increasing the distance of coaxial electrodes from the fiber or by increasing the electrode lead angle relative to the fiber axis. To study the effects of electrode distance, 3 scenarios were considered: symmetric movement of both electrodes away from the fiber, asymmetric movement of the negative electrode away from the fiber while the positive electrode remained at 10.5 cm from the fiber center, and asymmetric movement of the positive electrode away from the fiber while the negative electrode remained at 10.5 cm from the fiber center. To study the effects of electrode lead angle on T-wave amplitude and TWA amplitude, the positive and negative electrodes were kept at an equal fixed distance away from the fiber center, but the angle θ between the fiber axis and the electrodes was increased from 0° to 80° . The effect of electrode lead angle was investigated for electrodes 1.5 cm, 3 cm, and 6 cm from the fiber center.

Results

T-wave amplitude relation to tissue repolarization gradients

For simulations with no APD alternans in the fiber, TWA was not present in any of the ECG leads examined. In contrast, for simulations with APD alternans in the fiber, alternation in the repolarization gradient produced TWA in all leads examined. Larger magnitudes of APD alternans in the fiber resulted in larger TWA amplitudes. Temporal matching of ECG T waves with simultaneous repolarization gradients during TWA revealed that the shorter alternating T wave is coincident with a smaller (shallow) repolarization gradient and that the taller alternating T wave is coincident with a larger (steep) repolarization gradient. Least

squares linear regression showed good correlation between T-wave amplitude from all simulations and corresponding repolarization gradient, with an r^2 value of 0.87. Thus, an increase in repolarization gradient produces an increase in T-wave amplitude. In addition, TWA amplitude from all simulations correlates well with the beatwise difference in the repolarization gradient in the fiber, with an r^2 value of 0.75. A larger beatwise difference in repolarization gradient results in a larger TWA amplitude. The strength of the correlation between T-wave amplitude or TWA amplitude and corresponding repolarization gradients was similar regardless of ECG lead configuration.

T-wave amplitude and TWA amplitude as a function of electrode position

To evaluate the effect of electrode position on T-wave amplitude and TWA amplitude, 4 scenarios were considered. In each case, the positive electrode was modeled to the right of the fiber and the negative electrode was to the left of the fiber (Fig. 1A). Scenarios 1, 2, and 3 involve varying electrode distance to the fiber center for electrodes that are along the fiber axis. Scenario 4 involves changing the lead angle (the angle of the fiber axis with respect to the line between the 2 electrodes) for electrodes at an equal fixed distance from the fiber center. T-wave amplitudes of consecutive beats and TWA amplitude were obtained for each electrode configuration. In addition, a “TWA index” was calculated by dividing the TWA amplitude by the T-wave amplitude of the short T wave (Fig. 2). For brevity, results are only presented for one magnitude of cellular alternans, though the trends described are similar for all degrees of cellular alternans investigated. Fig. 1B and C show the steady-state APD and APD alternans magnitude of each node for the fiber investigated. Results for this section are summarized in Tables 1 and 2.

Scenario 1—symmetric movement of recording electrodes

In this case, both electrodes are placed 1.5 cm from the fiber center and are moved symmetrically away from the fiber center along the fiber axis until each is 10.5 cm away. As distance between the electrodes increased, both TWA amplitude and T-wave amplitude decrease roughly as a function of the square of the inverse of the distance from either electrode to the fiber center. Because both TWA amplitude and T-wave amplitude decrease by the same proportion, the TWA index remained relatively constant for all electrode distances examined.

Scenario 2—asymmetric movement of positive electrode

In this case, the negative electrode is fixed at 10.5 cm from the fiber center while the positive electrode is moved from 1.5 cm to 10.5 cm away from the fiber center. As distance from the positive electrode to the fiber center increased, both TWA amplitude and T-wave amplitude decrease roughly as a function of the square of the inverse of the distance from the positive electrode to the fiber center. However, in contrast to scenario 1, as distance increases, T-wave amplitude of the short T wave decreases out of proportion to TWA amplitude, resulting in an increase in the TWA index.

Scenario 3—asymmetric movement of negative electrode

In this case, the positive electrode is fixed at 10.5 cm from the fiber center, while the negative electrode is moved from 1.5 cm to 10.5 cm away from the fiber center. The results of this scenario were essentially the reverse of scenario 2, but the magnitude of the effect was larger. As with scenarios 1 and 2, as distance from the negative electrode to the fiber center increased, both TWA amplitude and T-wave amplitude decrease roughly as a function of the square of the inverse of the electrode-fiber distance. In addition, as distance increases, TWA amplitude decreases out of proportion to T-wave amplitude, resulting in a large decrease in TWA index. The decrease in TWA index when the negative electrode is moved is larger than the increase in TWA index when the positive electrode is moved.

Scenario 4—rotation of electrode axis relative to fiber

To evaluate the effect of lead angle on T-wave amplitude and TWA amplitude, the positive and negative electrodes were kept at an equal fixed distance away from the fiber center, but the angle θ between the fiber axis and the electrodes was varied. As the angle increased from 0° to 80° , TWA amplitude and T-wave amplitude decreased monotonically in roughly the same proportion, giving a TWA index that is independent of lead angle. Slight fluctuations in TWA index were present for electrode configurations closer to the fiber but diminished at larger distances from the fiber.

Potential fields produced by alternating fibers

To further explore the effect of repolarization alternans on potential fields that are detected by ECG electrodes, we used Equation 3 to create plots of extracellular potential around the fiber at the instant of the peak of each T wave (Fig. 3). Fig. 3A illustrates extracellular potential during the peak of the taller alternating T wave, and Fig. 3B illustrates extracellular potential during the peak of the shorter alternating T wave. In both panels, the field is mostly negative on the left side of the fiber and slightly positive on the right side. This pattern indicates that repolarization is occurring from right to left, a finding that is confirmed by transmembrane voltage of each node at the peak of each T wave. The potential field is asymmetric in both magnitude and geometry. Specifically, the isopotential lines are closer together on the left end of the fiber than on the right end, indicating a greater change in potential for movement of a negative electrode over a certain distance than for movement of a positive electrode over that same distance. Consequently, the change in T-wave amplitude and TWA amplitude due to movement of the positive electrode differs in magnitude and direction from the change due to movement of the negative electrode.

Discussion

The results presented here demonstrate that changes in the repolarization gradient within tissue result in changes in the T wave that can be recorded distant from the tissue. As the tissue repolarization gradient increases (becomes more steep), T-wave amplitude increases. Similarly, a decrease in tissue repolarization gradient results in a decrease in T-wave amplitude. During cellular alternans, alternation in the tissue repolarization gradient leads to alternation of the T-wave amplitude. The potential fields created by alternating repolarization gradients are asymmetric and differ both in magnitude and in geometry on a

beatwise basis. Consequently, if an electrode is moved a certain distance away from the fiber, T-wave amplitude and TWA amplitude may decrease out of proportion to each other due to asymmetry and beatwise differences in potential field.

Current clinical TWA testing uses a set threshold of TWA amplitude in the microvolt range as an indicator of pathologic condition.⁷ However, as we have shown, an increased difference in intracardiac repolarization gradients results in increased TWA amplitude. Therefore, TWA amplitude may be indicative of the severity of the pathologic condition. However, we have also shown that TWA amplitude is sensitive to changes in distance and angle, making comparison of serial TWA amplitude measurements in the same patient difficult. Furthermore, 2 individuals with the same magnitude of cellular alternans may exhibit different TWA amplitude measurements due to differences in extracardiac factors such as torso size and shape. For these reasons, we investigated the effect of electrode position on the TWA index, which has been suggested as a correction factor for extracardiac effects.^{8,9} However, we have shown that even in an unbounded homogeneous volume conductor with a simple model of alternans, TWA index is dependent on electrode position, particularly when recording electrodes are at unequal distances from the tissue. Curiously, TWA index remained relatively constant with respect to changes in lead angle. This effect may be due to the geometry of the potential fields surrounding the fiber; as the lead angle was increased, the measuring electrodes moved across few isopotential lines, resulting in small and relatively symmetric changes in T-wave amplitude.

Although this study demonstrated that repolarization changes during alternans resulted in nonlinear changes in T-wave amplitude and TWA amplitude in a simple model, further work is needed to investigate how more complex intracardiac and extracardiac factors affect this phenomenon. Expanding the fiber model to a 3-dimensional model of the left ventricular free wall would give a more realistic potential field, particularly if apicobasal repolarization gradients were considered in addition to the transmural gradient investigated here. A 3-dimensional model would also allow investigation of the effects of an isolated population of alternating cells within a ventricle consisting mainly of nonalternating cells. Because the 1-dimensional fiber model involved fewer cells than a 3-dimensional model, electrotonic effects caused all cells within the fiber to alternate during APD alternans. Finally, investigation of alternating tissue in a bounded heterogeneous volume conductor would help describe the effects of conductivity changes on potential field magnitude and geometry.

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Fig. 1.

A, Position of positive and negative recording electrodes relative to fiber. (B) Steady-state APD of each node during APD alternans as a function of distance along the fiber. (C) Steady-state APD alternans magnitude during APD alternans as a function of distance along the fiber.

Fig. 2.

T-wave amplitude is directly measured from the ECG tracing. The TWA amplitude is calculated as the difference between the 2 T-wave amplitudes. The TWA index is calculated as TWA amplitude divided by T-wave amplitude of the short T wave.

Fig. 3.

Potential field surrounding fiber at the instant of the peak of the T wave, with isopotential lines shown in gray. A, Potential field at the peak of the shorter T wave during TWA. B, Potential field at the peak of the taller T wave during TWA.

Table 1

Steady-state T-wave measurements for selected electrode distances

Electrode distance from fiber center (cm)	1.5	3.5	6.5	10.5
Move both electrodes				
TWA amplitude (μV)	35.6	6.24	1.80	0.689
T-wave amplitude high (μV)	227	39.8	11.5	4.39
T-wave amplitude low (μV)	191	33.6	9.67	3.70
TWA index	0.170	0.170	0.170	0.170
Move positive electrode only				
TWA amplitude (μV)	15.5	3.24	1.21	0.689
T-wave amplitude high (μV)	161	25.3	8.32	4.39
T-wave amplitude low (μV)	146	22.1	7.11	3.70
TWA index	0.101	0.137	0.157	0.170
Move negative electrode only				
TWA amplitude (μV)	22.2	3.73	1.27	0.689
T-wave amplitude high (μV)	71.6	19.0	7.54	4.39
T-wave amplitude low (μV)	49.4	15.2	6.27	3.70
TWA index	0.366	0.218	0.184	0.170

Measurements of T-wave amplitude and TWA amplitude when moving colinear electrode(s) toward and away from the fiber center.

Table 2

Steady-state T-wave measurements for selected lead angles

Lead angle with respect to fiber axis (°)	0	30	60	80
Each electrode 1.5 cm from fiber center				
TWA amplitude (μV)	35.6	29.6	16.2	5.50
T-wave amplitude high (μV)	227	189	103	35.0
T-wave amplitude low (μV)	191	160	86.9	29.5
TWA index	0.170	0.169	0.171	0.171
Each electrode 3 cm from fiber center				
TWA amplitude (μV)	8.51	7.33	4.16	1.43
T-wave amplitude high (μV)	54.4	46.7	26.6	9.16
T-wave amplitude low (μV)	45.9	39.4	22.4	7.73
TWA index	0.170	0.170	0.170	0.169
Each electrode 6 cm from fiber center				
TWA amplitude (μV)	2.11	1.83	1.05	0.36
T-wave amplitude high (μV)	13.5	11.6	6.69	2.32
T-wave amplitude low (μV)	11.4	9.81	5.65	1.96
TWA index	0.170	0.170	0.170	0.170

Measurements of T-wave amplitude and TWA amplitude when increasing the angle of the ECG lead relative to the fiber axis.