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Analysis of T-wave alternans using the dominant T-wave paradigm

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Abstract The dominant T wave (DTW) reflects the derivative of the repolarization phase of the transmembrane potential of myocytes. *T-wave alternans* (TWA) is defined as an alteration of this repolarization that repeats every other beat. We investigate if the DTW can offer new insight on TWA.
We first proved that the DTW estimate obtained through singular value decomposition is optimal, because it minimizes the norm of the residuals. Then we suggested an optimal estimate of the vector of lead factors, in the case in which the DTW is given. Finally, we derived a mathematical relationship between observable TWA on electrocardiogram and DTW morphology. The relationship depends on the slope of the repolarization phase of the myocytes' transmembrane potentials and on the dispersion of the repolarization times. Based on this finding, a new index meant to quantify TWA was defined and termed *amplitude of dominant T-wave alternans* (ADTWA).
A preliminary validation of the index was performed using the synthetic records contained in the Computers in Cardiology 2008 data set. They were obtained from 5 electrocardiogram models to which TWA was added at different extents. We found a linear relationship between the TWA amplitude and the ADTWA metric (R^2 = 0.9898 ± 0.100 across all models). Moreover, the root mean square error between actual and estimated TWA amplitudes was 10.9 μV (ADTWA) vs 12.9 μV obtained with the classical spectral method.

Keywords: T-wave alternans; Cardiac transmembrane potentials; Repolarization analysis

Introduction

T-wave alternans (TWA) is a repolarization abnormality manifesting itself as a periodic alternation of the T-wave morphology on the electrocardiogram (ECG).[1] It is an important indicator of risk of sudden cardiac death[2] and has been associated to malignant arrhythmias susceptibility.[3]

TWA alternans on the surface ECG is the epiphany of alternans in the repolarization patterns at the level of myocytes.[1] Indeed, individual cardiac cells can alternate in respect to action potential duration,[4] whereas alternans in the repolarization phase of transmembrane action potentials (TMPs) have been observed in guinea pigs using optical techniques.[5] This phenomenon may invest a particular region of ventricular myocardium (concordant alternans) or different regions, which alternate with opposite phases (discordant alternans) creating a large spatial gradients of repolarization. In both situations, cellular alternans results in a different dispersion of repolarization timings of cardiac cells between even and odd beats.

The dominant T-wave paradigm

A mathematical relationship between the repolarization phase of TMP, their dispersions, and observable T-waves morphologies has been formalized by van Oosterom.[6] In his formulation, the potentials recorded at the skin during ventricular repolarization are represented by $\mathbf{\Psi}$, an $[L \times N]$ matrix containing the N ECG samples recorded from L leads. Assuming linearity of the conductive medium,[7] these potentials can be related to the repolarization phase of TMP, $D(t)$, occurring at the level of myocytes, through the following equation

$$\mathbf{\Psi} = \boldsymbol{A} \begin{bmatrix} D(t-\rho_1) \\ D(t-\rho_2) \\ \cdots \\ D(t-\rho_M) \end{bmatrix}, \tag{1}$$

where $\mathbf{A}$ is an $[L \times N]$ transfer matrix that accounts for both the volume conductor properties (geometry and conductivity) and

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the solid angle under which the single source contributes to the potential $\mathbf{\Psi}$ in each lead.

In Eq. (1), $D(t)$ is supposed to be identical across cells, but time shifted by a factor ρ_i, which identifies the specific repolarization time of each cell. Writing ρ_i in terms of its distance from the mean repolarization time $\overline{\rho}$, (ie, $\rho_i = \overline{\rho} + \Delta\rho_i$) and assuming $\Delta\rho_i \ll \overline{\rho}$, the function $D(t)$ can be expanded in series around $\overline{\rho}$ leading to the following model[6]

$$\mathbf{\Psi} = -A\begin{bmatrix}\Delta\rho_1\\ \Delta\rho_2\\ \cdots\\ \Delta\rho_M\end{bmatrix}\frac{\mathrm{d}D(\tau)}{\mathrm{d}\tau}\bigg|_{\tau=t-\overline{\rho}} + o\left(\Delta^2\rho_m\right). \tag{2}$$

In most situations, the linear term in Eq. (2) dominates, and when this happens, we have

$$\mathbf{\Psi} \approx -A\Delta\varrho\frac{\mathrm{d}D(\tau)}{\mathrm{d}\tau}\bigg|_{\tau=t-\overline{\rho}} = wT_{\mathrm{D}} \tag{3}$$

where $\Delta\varrho$ is the vector composed of the different delays $\Delta\rho_i$. The first derivative of the repolarization curve, $T_{\mathrm{D}} = \mathrm{d}D(\tau)/\mathrm{d}\tau$, becomes the dominant contribute to T waves and was therefore termed *dominant T wave* (DTW).[8] It is worth noticing that when the approximation (3) holds, the T waves measured on the thorax are only a rescaled version of T_{D}, being $w = -\mathbf{A}\Delta\varrho$ a vector of lead factors determining amplitude and signs of the T waves. Interestingly, this form shows that measured T wave on the skin depends on both the repolarization curve of TMP and the dispersion of repolarization times, two entities that are affected by alternans at cellular levels. We therefore speculate that analysis of DTWs can be used to quantify TWA on the ECG. We verify the idea in this study.

Quantification of TWA via DTW

The link between DTW and TWA

Studies performed at cellular level demonstrated the existence of alternans in TMP of myocytes, which involves action potential duration as well as action potential morphology in phases 2 and 3. Interestingly, looking at the down-slope during phase 3 of the TMP, it appears that the steepness of the recovery phase does not change between even and odd beats, especially for moderate or moderately high heart rate. This observation is evidenced in Fig. 1, which mimics the experimental findings presented in Fig. 2 of the paper by Pastore et al. This means that, in first approximation, the DTW *is not affected during alternans*, and thus, we will keep it as a constant in our analysis.

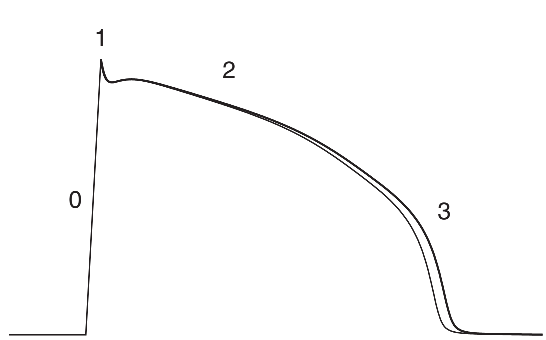

Fig. 1. Sketch of cardiac action potentials for even (thin line) and odd (thick line) beats during alternans.

We termed $\mathbf{\Psi}_{\mathrm{e}}$ and $\mathbf{\Psi}_{\mathrm{o}}$ the surface T waves for even and odd beats, respectively. Under the previous assumption, their first-order (rank 1) approximations are given by

$$\mathbf{\Psi}_e \approx w_e T_{\mathrm{D}} \tag{4}$$

$$\mathbf{\Psi}_o \approx w_o T_{\mathrm{D}}. \tag{5}$$

where the DTW T_{D} is, as stated before, taken to be constant across beats, for example, $(\mathbf{\Psi}_{\mathrm{e}} + \mathbf{\Psi}_{\mathrm{o}})/2 = \mathbf{\Psi} \approx wT_{\mathrm{D}}$. Following its definition, we quantify TWA alternans by considering the maximum absolute differences in the T waves of even and odd beats

$$\begin{aligned}\mathrm{TWA} &= \max_t |\mathbf{\Psi}_e - \mathbf{\Psi}_o| \approx |w_e - w_o| \max_t |T_{\mathrm{D}}|\\ &= |A(\Delta\varrho_e - \Delta\varrho_o)| \max_t |T_{\mathrm{D}}|.\end{aligned} \tag{6}$$

The remarkable aspect of Eq. (6) is that information on TWA is summarized into 2 factors: The $\max_t |T_D|$ term, which is related to the repolarization phase of the TMPs, and the difference $|\mathbf{A}(\Delta\varrho_{\mathrm{e}} - \Delta\varrho_{\mathrm{o}})|$, which accounts for differences in the repolarization times among even and odd beats. Thus, relation (6) provides a direct link between TWA and factors that are supposed to have originated it. To compute it, we need a first method to estimate T_{D} and a second one to obtain the weights w_{e} and w_{o} once given T_{D}. They will be described in the following sections.

Estimation of the DTW

An estimate of the DTW can be obtained through the minimization of the Frobenius norm of the error

$$\varepsilon = ||\mathbf{\Psi} - wT_{\mathrm{D}}||_{\mathrm{F}}, \tag{7}$$

between the measured T waves, $\mathbf{\Psi}$, and their approximations by the first-order term of Eq. (3). The T_{D} obtained with this procedure is optimal in the sense that (through w) provides the best fit to the data (smaller Frobenius norm of the residual). In Eq. (7), both w and T_{D} are unknown and have to be estimated.

Using a classical result of linear algebra, the Schmidt's approximation theorem (often called the *Eckart-Young theorem*), we know that the best rank 1 approximation $\mathbf{\Psi}^1$ to $\mathbf{\Psi}$, which minimizes

$$\varepsilon = ||\mathbf{\Psi} - \mathbf{\Psi}^1||_{\mathrm{F}}, \tag{8}$$

is[9]:

$$\mathbf{\Psi}^1 = u_1\lambda_1 v_1^T, \tag{9}$$

where u_1 and v_1 are the unit-norm, first columns of the matrices $\mathbf{U}$ and $\mathbf{V}$ obtained by singular value decomposition (SVD) of $\mathbf{\Psi} = \mathbf{USV}^T$, and where λ_1 is the corresponding largest singular value.