Role of Dipolar and Nondipolar Components of the T Wave in Determining the T Wave Residuum in an Isolated Rabbit Heart Model

MARCELO O. BIAGETTI, M.Sc., PEDRO D. ARINI, E.Eng., ESTEBAN R. VALVERDE, E.Eng., GUILLERMO C. BRETRAN, M.Sc., and RICARDO A. QUINTEIRO, M.D., Ph.D.

From the Cardiac Electrophysiology Laboratory, Department of Physiology, Favaloro University, Buenos Aires, Argentina

Dipolar and Nondipolar Components of the T Wave. ***Introduction:*** **Repolarization heterogeneity has been shown to constitute a substrate for malignant ventricular arrhythmias. Noninvasive measurement of abnormal repolarization through assessment of QT interval dispersion from the resting standard 12-lead ECG initially had shown promise in assessing arrhythmia risk but was challenged recently. The relative T wave residuum (TWR) has been proposed recently to reflect regional repolarization dispersion more accurately. We analyzed the role played by the dipolar and nondipolar components in determining TWR.**

Methods and Results: **Singular value decomposition was applied to the repolarization signals obtained from isolated rabbit hearts using a 5 × 8 array multielectrode recording system during premature beats (N = 11) and after d-sotalol (N = 9) exposure. Both the dipolar and nondipolar components of the T wave increased significantly during premature stimulation and after d-sotalol exposure. The relative TWR decreased significantly during premature stimulation but did not change after d-sotalol. Changes in the dipolar and nondipolar components of the second half of the T wave were significantly greater than those corresponding to the first half during premature stimulation, and a significant correlation was observed between the nondipolar components of the second half of the T wave and the $T_{peak\text{-}end}$ interval.**

Conclusion: **Conditions exist during which both the dipolar and nondipolar components can change simultaneously. Under these conditions, the relative TWR may not reflect regional heterogeneity of repolarization with accuracy. The nondipolar components of the second half of the T wave can be linked to assessment of the transmural dispersion of repolarization.** *(J Cardiovasc Electrophysiol, Vol. 15, pp. 356-363, March 2004)*

T wave residuum, electrocardiographic repolarization signal analysis, transmural repolarization dispersion, sotalol, premature ventricular stimulation

Introduction

Historically, dispersion of repolarization is the phenomenon under which neighboring areas of the myocardium exhibit different timings in action potential durations. The duration of action potentials differs not only between myocytes of different ventricular layers but also between those of the apex and the base of both ventricles, between those of the posterior and anterior endocardial surfaces, and between the right and left ventricles.[1-4] Moreover, ventricular repolarization is a complex series of events that occur nonuniformly in space and over time, with the T wave on the surface ECG representing an integrated signal from multiple repolarization wavefronts.[5]

Repolarization heterogeneity has been shown to constitute a substrate for malignant ventricular arrhythmias.[6-9] Noninvasive measurement of abnormal repolarization through assessment of QT interval dispersion from the resting standard 12-lead ECG initially had shown promise[10] but was challenged recently.[11-14]

The difficulty in measuring the end of the QT interval on the surface ECG and the still yet undefined significance of QT dispersion have led to the development of several new ECG indices proposed to better characterize repolarization abnormalities. Among these, the so-called *T wave residuum* (TWR) has been linked to regional repolarization dispersion. By applying singular value decomposition (SVD), a previously described technique, to the eight independent leads of the 12-lead standard ECG (I, II, V_1–V_6), it is possible to reconstruct the repolarization ECG signals in an orthogonal eight-lead system. In such a system, the first lead contains the maximum energy of the T wave in one single direction, the second lead the maximum energy perpendicular to the first lead, the third lead the maximum energy perpendicular to the first two leads, etc. Therefore, the energy contained in the first three orthogonal leads corresponds to the energy of the T wave vector (dipolar components), and the summed energy in the remaining leads 4 to 8 correspond to the nondipolar components of the original ECG.[15,16] The TWR was proposed to represent these so-called *nondipolar components* and can be quantified as its absolute value or as the relative TWR, which is the proportion by which the extent of nondipolar components contribute to the complete ECG repolarization signal.

The morphology of the normal T wave in itself represents the existence of a normal degree of dispersion of repolarization; hence, any increase beyond this normal limit should be associated with changes in T wave morphology.

Address for correspondence: Ricardo A. Quinteiro, M.D., Ph.D., Solis 453, 4th floor, Buenos Aires 1078, Argentina. Fax: 5411-4381-0323; E-mail: quinteiro@favaloro.edu.ar

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We hypothesized that these abnormalities in T wave morphology should be reflected in changes of both the dipolar and nondipolar components of the T wave. Therefore, the relative TWR would either increase, decrease, or remain without changes, depending on the relative changes of both the dipolar and nondipolar components.

In the present study, we analyzed the role played by both the dipolar and nondipolar components in determining TWR. To achieve this goal, we induced abnormalities of repolarization in an isolated rabbit heart model using premature ventricular stimulation or d-sotalol exposure, and SVD techniques were used to analyze repolarization signals obtained from multiple body surface ECG signals.

Methods

General

Twenty New Zealand white male rabbits (weight 2.8–3.8 kg) were heparinized (500 U/kg IV) 10 minutes before being killed and anesthetized by intramuscular injection of a combination of ketamine (35 mg/kg) and lidocaine (5 mg/kg).

The animals were killed by cervical dislocation. The heart was removed via thoracotomy and arrested by immersion into ice-cold Tyrode's solution. The aorta was cannulated, the heart placed in a Langendorff perfusion apparatus in which the coronary arteries were perfused with oxygenated temperature-controlled Tyrode's solution at a constant pressure, and immersed into a heart chamber filled with warmed normal Tyrode's solution. Time from chest opening to aorta cannulation ranged from 2 and 3 minutes. Silver-silver chloride electrodes of 2-mm diameter were fixed to the wall of the heart chamber distributed in an array of five rows (10-mm interelectrode distance) and eight columns (45° angular distance between electrodes) in order to obtain multiple precordial leads. Care was taken to always place the hearts in the same position relative to the electrodes. The flow rate of the Langendorff perfusion apparatus was adjusted using a variable-speed roller pump (Extracorporeal M2102 Infusion Pump) to maintain a perfusion pressure of at least 80 mmHg. The general characteristics of our preparation were described previously.[17] The Tyrode's solution was of the following composition (in mM): 140 NaCl, 5 KCl, 1 $MgCl_2$, 0.33 NaH_2PO_4, 5 HEPES, 11.1 glucose, and 2.2 $CaCl_2$. The pH of the solution was adjusted to 7.4 with NaOH. The temperature of the perfusion and the reservoir Tyrode's solution was fixed at 38°C ± 0.5°C and gassed with 100% O_2. The sinus node was crushed and the hearts were paced from either the right atrium or from the right or left ventricle, depending on the experimental protocol, at a constant basic cycle length (BCL) of 500 or 400 ms, respectively, with 2-ms duration and twice diastolic threshold stimuli delivered by a programmable stimulator (DTU 101, Bloom Associates Ltd., Reading, PA, USA).

To assess the stability of the preparation, in five preliminary experiments the ECG signals were monitored continuously during 4 to 5 hours of Langendorff perfusion. The signals were stable in both amplitude and shape, and no evidence of ST-T changes suggestive of ischemia were observed. The hearts had good contractility (as determined by visual evaluation), were free of arrhythmias, and had uniform coloration, suggesting adequate perfusion of the organs. Although these preliminary experiments were stable for more than 3 hours, typically the experiments included in the present study were concluded in <2 hours.

Experimental Protocol

After an equilibration period consisting of 30 minutes of perfusion with normal Tyrode's solution, hearts were randomly separated into two groups: group I in which premature ventricular stimulation was applied, and group II in which the hearts were exposed to a high concentration of d-sotalol (60 μM). It has been well recognized that cellular repolarization and action potential duration are highly sensitive to the timing of a premature stimulus or to the effect of several potassium channel-blocking drugs. Due to heterogeneous shortening of action potential duration as a consequence of the heterogeneous distribution of the restitution kinetics[8] or to the heterogeneous distribution of action potential lengthening induced by potassium channel-blocking drugs,[18,19] a true dispersion of repolarization can be obtained.

Group I consisted of 11 hearts in which premature stimuli with coupling interval equal to the effective refractory period + 5 ms (ERP+5 ms) were given to both the right and left ventricles. The hearts were stimulated at a BCL of 400 ms with rectangular pulses of 2-ms duration at twice diastolic threshold using bipolar electrodes having Teflon-coated stainless steel wires. ERP+5 ms stimuli were applied, after the 50-pulse trains, at the base of both ventricles below the atrial appendages. The effective refractory period was estimated with premature stimuli applied after the 50-pulse trains, at decreasing coupling intervals in 10-ms steps until a coupling interval of 250 ms was reached, and at 5-ms steps thereafter until ventricular refractoriness. Group II consisted of 9 hearts that were exposed to d-sotalol 60 μM. The hearts were paced from the right atrium at a BCL of 500 ms with rectangular pulses of 2-ms duration and twice diastolic threshold using bipolar electrodes having Teflon-coated stainless steel wires. Data were obtained after 30 minutes of d-sotalol exposure.

Data Acquisition and Analysis

The signals were amplified by custom-built amplifiers with a gain between 1,000× and 10,000× and a bandwidth between 0.05 and 300 Hz. Recordings were digitized at 1 kHz and 12-bit resolution with a digital acquisition board (LabPC+, National Instruments, Austin TX, USA). If necessary, the signals were digitally filtered for 50-Hz noise. All data were processed using custom-built software written in Borland C++ running under Microsoft Windows 98. Depending on the experimental group, 50 consecutive beats plus the premature beat were acquired simultaneously by the 40-electrode array and stored on hard disk. For the purpose of analysis, the 48th to 50th beats of each pulse train were averaged. Variables were measured for these selected beats and for the premature beats. The software allowed us to manually define a window in which the longest T wave was included. This window then was automatically repeated for all the other leads, and these 40 T waves were further used for SVD analysis.

Singular Value Decomposition

Theoretical and technical details of SVD analysis have been previously described.[15,16,20] In brief, a new orthogonal 40-lead system was built from the original 40 lead signals using the SVD method, and the corresponding 1 to 40

eigenvalues were obtained (σ_1^2 to σ_{40}^2).[19] The principle of SVD transformation is based on the redundancy concept. Using mathematical tools such as correlation, all repeated information is discarded in each new component. In this manner, σ_i^2 represents the energy of the T wave in the ith direction or projection. In the new lead system, the vector projection of the T wave is included in the first three components(σ_1^2 to σ_3^2), which represents the movements of the T vector in the three spatial axes.[13,14,20] These components are called the *dipolar components* and contain the common energy detected from all the electrodes. Normally the dipolar components represent >98% of the total T wave energy. The nondipolar components are represented by the remaining 4 to 40 reconstructed waves and are expressed by the absolute value of σ_4^2 to σ_{40}^2. These components are a minor part of the signal energy but include information that is only partially viewed from any of the electrodes and reflect regional inequalities in repolarization. In addition, all the T waves were partitioned into two portions: the first, from the beginning of the T wave until the time corresponding to the peak of the first eigenvector, and the second, from this point to the end of the ECG signal. The time to the peak of the first eigenvector was chosen in order to obtain a common single reference for dividing all the T waves. After this division, both the dipolar and nondipolar components of each half of the T wave were calculated.

An illustrative example of SVD method is shown in Figure 1. The 40 spatially distributed T wave signals obtained from each single electrode were converted to 40 new linearly independent waves that represent the new transformed space. Both the dipolar and nondipolar sums of components also are plotted on a logarithmic-based scale for better comparison of these components.

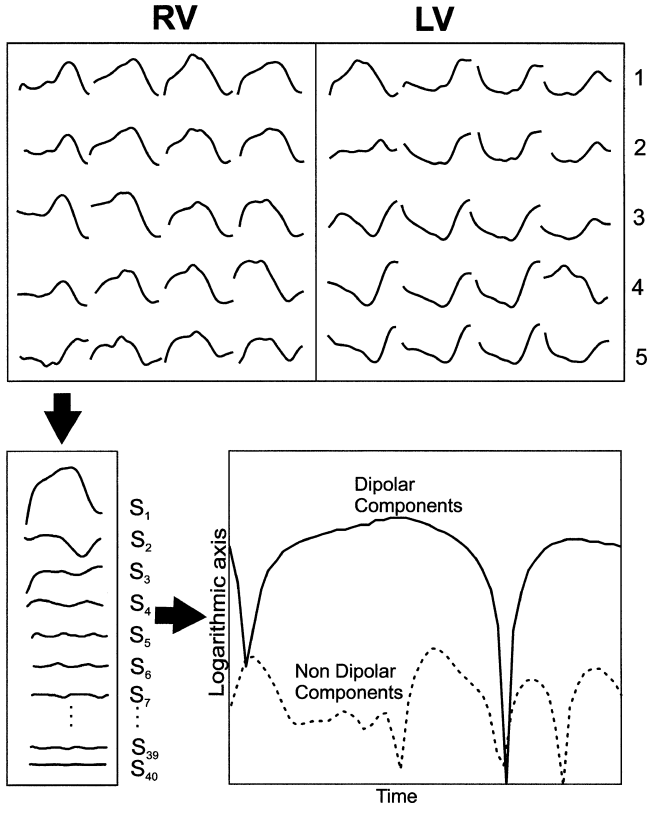

Figure 1. *Data obtained from a single experiment illustrating singular value decomposition. Top: Corresponding T waves from the original 40 ECG signals (8 columns × 5 rows). The 40 reconstructed orthogonal leads (s_1 to s_{40}) are shown in the bottom left panel. s_1, s_2, and s_3 signals correspond to the dipolar components; the remaining s_4 to s_{40} signals represent the nondipolar components. Bottom right panel: Logarithmic plot of the power of both the dipolar (solid line) and nondipolar (dashed line) components for each time instant within the T wave.*

ECG and SVD Variables Characterizing Repolarization Heterogeneity

QT_{end} and $T_{peak\text{-}end}$ intervals were manually measured for each of the 40 recording electrodes. These intervals were measured from the beginning of the QRS and the peak of the T wave, respectively, to the end of the T wave and expressed in milliseconds. The standard deviation of the QT_{end} interval ($SDQT_{end}$) expressed in milliseconds was used to assess the dispersion of repolarization.

The absolute value of the sum of the first three eigenvalues ($\sigma_{1\text{-}3}^2$) expressed in mV^2 quantifies the dipolar components of the T wave.

The absolute value of the sum of the 4 to 40 eigenvalues ($\sigma_{4\text{-}40}^2$) expressed in mV^2 defines the TWR and quantifies the nondipolar components of the T wave.

The relative TWR (dimensionless) is expressed as the proportion between the sum of the 4 to 40 eigenvalues to the sum of all 1st to 40th eigenvalues (relative TWR $= \sigma_{4\text{-}40}^2/\sigma_{1\text{-}40}^2$).

Statistical Analysis

Unless specified otherwise, data in the tables are given as mean ± SD and as mean ± SEM in the figures. Comparisons between groups were made using one-tailed Wilcoxon or Mann-Whitney and Kruskal-Wallis with Dunn tests. $P < 0.05$ was considered statistically significant. A Spearman correlation was used to analyze the relationship between the $T_{peak\text{-}end}$ interval and the nondipolar components of the 2nd half of the T wave during both premature stimulation and d-sotalol exposure.

Results

Ventricular repolarization signals obtained from each of the 40 unipolar ECG leads were decomposed using an SVD-based algorithm. During premature stimulation, based on the site of ventricular pacing no significant differences were found between repolarization variables; therefore, these data were pooled together.

The distribution pattern of the first 10 eigenvalues (expressed as a percentage) with respect to the total energy contained within the T wave is shown in Figure 2. Only the first 10 eigenvalues (not all 1–40) are plotted for simplicity. An exponential decay is clearly seen in both experimental groups ($\tau = 2.30 \pm 0.80$ vs 1.92 ± 0.75, $P = 0.035$, $r = 0.999 \pm 0.002$ and 0.997 ± 0.006 for control and the premature beat, respectively; $\tau = 2.68 \pm 1.32$ vs 1.87 ± 0.80, P = NS, $r = 0.992 \pm 0.018$ and 0.991 ± 0.023 for control and d-sotalol, respectively). From Figure 2 it is clear that the sum of the first three eigenvalues ($\sigma_1^2 + \sigma_2^2 + \sigma_3^2$) represents >98% of the total energy contained within the T wave and defines the so-called *dipolar components.* The remaining σ_4^2 to σ_{40}^2 eigenvalues represent <2% of the total energy, the so-called *nondipolar components,* and, as stated in the Methods section, the sum of these nondipolar components ($\sigma_{4\text{-}40}^2$) is defined as the absolute TWR.

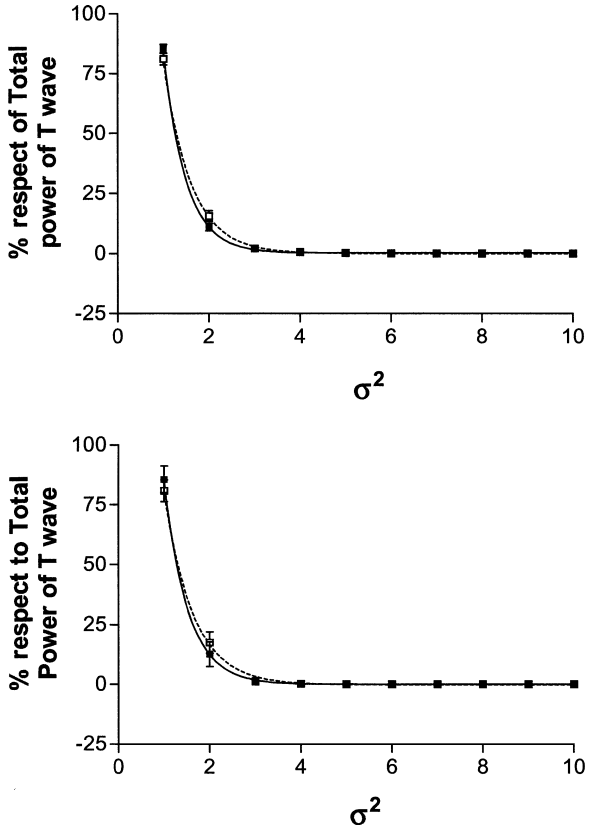

Figure 2. *Distribution pattern of each of the first 10 σ^2 expressed as a percentage with respect to total power of the T wave (mean ± SEM) during premature ventricular stimulation (top panel) and after d-sotalol exposure (bottom panel). In each plot, filled squares represent control conditions and open squares correspond to test conditions. Solid (control) and dotted (test) lines are single-exponential decay fittings during both experimental conditions.*

We found a significant increase in the total energy of the T wave during premature stimulation and after d-sotalol exposure. Moreover, we also found that both the dipolar and nondipolar components of the T wave increased significantly during premature stimulation and after d-sotalol exposure. However, despite a significant increase in the absolute TWR, the relative TWR decreased significantly during premature stimulation and remained unchanged after d-sotalol exposure. These results are summarized in Tables 1 and 2. To gain insight into the mechanisms of these changes, the first three components were analyzed separately. Each of the three eigenvalues, representing the dipolar component of the T wave, were increased significantly during premature ventricular stimulation. However, only σ_2^2 exhibited a significant increase after d-sotalol exposure. In Figure 3, the nondipolar components ($\sigma_{4\text{-}40}^2$), together with each of the three components (σ_1^2, σ_2^2 and σ_3^2) normalized with respect to control values, are shown. It can be clearly seen that, during premature stimulation, all the variables analyzed increased significantly with respect to control conditions. Moreover, σ_2^2 exhibited the greatest change compared with σ_1^2, σ_3^2, or $\sigma_{4\text{-}40}^2$. In contrast, after d-sotalol exposure, only σ_2^2 and $\sigma_{4\text{-}40}^2$ exhibited significant changes with respect to control conditions, and no significant differences in the percentage

TABLE 1

T Wave Morphology Variables During Premature Ventricular Stimulation

Variable	Control	Premature Beat
Relative TWR	0.0157 ± 0.006	0.0106 ± 0.0054*
Dipolar (mV^2)	12.09 ± 10.59	23.05 ± 19.33*
σ_1^1 (mV^2)	10.20 ± 8.9	19.02 ± 15.92*
σ_2^2 (mV^2)	1.58 ± 1.7	4.26 ± 4.63a*
σ_3^3 (mV^2)	0.316 ± 0.508	0.538 ± 0.582*
Nondipolar (mV^2)	0.193 ± 0.181	0.285 ± 0.259*

*P < 0.05 vs control.
TWR = T wave residuum.

TABLE 2

T Wave Morphology Variables During d-Sotalol Exposure

Variable	Control	d-Sotalol 60 μM
Relative TWR	0.003 ± 0.002	0.0043 ± 0.0026
Dipolar (mV^2)	25.80 ± 15.46	66.49 ± 60.50
σ_1^1 (mV^2)	23.24 ± 14.65	58.34 ± 58.11
σ_2^2 (mV^2)	2.26 ± 2.28	7.56 ± 5.19*
σ_3^3 (mV^2)	0.289 ± 0.277	0.587 ± 0.455
Nondipolar (mV^2)	0.0998 ± 0.126	0.195 ± 0.119*

*P < 0.05 vs control.
TWR = T wave residuum.

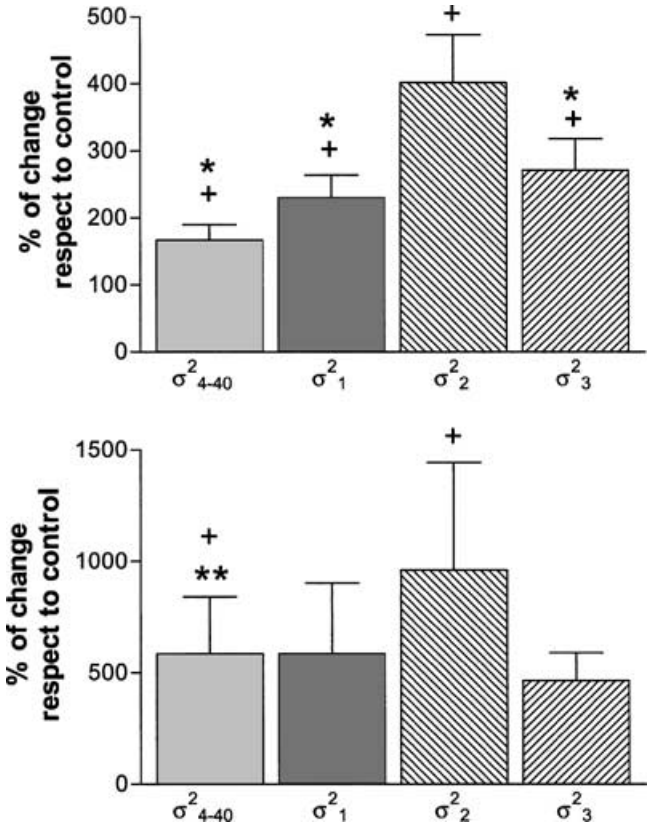

Figure 3. *Amount of change (mean ± SEM) with respect to control conditions of $\sigma_{4\text{-}40}^2$, σ_1^2, σ_2^2, and σ_3^2 plotted for both premature ventricular stimulation (top panel) and d-sotalol exposure (bottom panel). *Significant differences of $\sigma_{4\text{-}40}^2$, σ_1^2, and σ_3^2 against σ_2^2, respectively. **Significant differences between both experimental groups. +Significant differences against respective control values.*

of change for each of these parameters with respect to control were observed. Finally, when comparisons between premature stimulation and d-sotalol data were made, significant differences were found only for the nondipolar components, which exhibited a greater change after d-sotalol exposure.

To address the question of whether dipolar and nondipolar components changed differently between the first and second half of the T wave, we partitioned all the T waves into two portions: the first one from the beginning of the T wave until the time corresponding to the peak of the first eigenvector, and the second from this point to the end of the ECG signal. The dipolar and nondipolar components of each part of the T wave were calculated and the results, expressed as the percentage of change with respect to control conditions, are shown in Figure 4. During premature stimulation, both the dipolar and nondipolar components of either the first and second half of the T wave were significantly different than those obtained during control conditions. However, the changes observed in the dipolar and nondipolar components of the second half of the T wave were significantly greater than those corresponding to the first half. Finally, although the dipolar components exhibited a greater relative change respect to control, only during the first half of the T wave did these differences achieve a significant level.

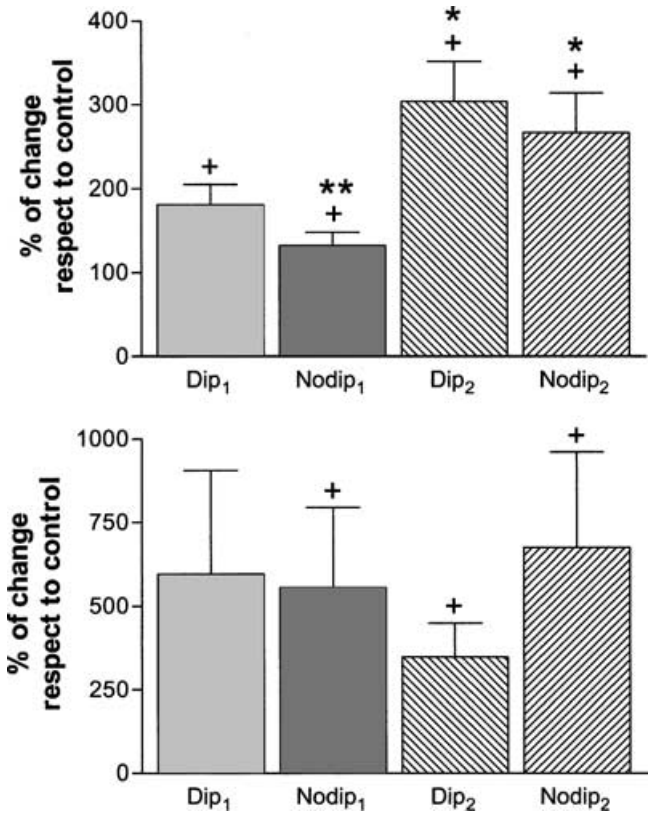

Figure 4. *Analysis of the changes observed in the first and second half of the T wave for the corresponding dipolar and nondipolar components during premature ventricular stimulation (top panel) and after d-sotalol exposure (bottom panel). Data represent mean ± SEM values and are expressed as a percentage with respect to control conditions. *Significant differences between first and second half of the T wave. **Significant differences between dipolar and nondipolar components. +Significant differences against respective control values.*

In contrast, after d-sotalol, although important changes were found in the dipolar and nondipolar components, only the nondipolar components of the first half and the dipolar and nondipolar components of the second half exhibited significant differences with respect to control conditions. Moreover, opposite to that observed during premature stimulation, no significant differences were found between both the dipolar and nondipolar components of the first half against those of the second half of the T wave.

On the other hand, only in the second half of the T wave did the nondipolar components exhibit a greater relative change with respect to control than the dipolar components, although these differences were not significant.

Finally, because the nondipolar components of the second half of the T wave increased significantly with respect to control conditions during premature stimulation and after d-sotalol exposure, we looked for differences in the $T_{peak\text{-}end}$ interval with the assumption that changes in the second half of the T wave also should be reflected in this interval. Significant increases in the $T_{peak\text{-}end}$ interval also were found either during premature stimulation (53.7 ± 7.2 ms vs 66.3 ± 11.9 ms, $P < 0.0002$) and after d-sotalol exposure (38.4 ± 3.1 ms vs 65.4 ± 16.0 ms, $P < 0.001$). Moreover, a significant correlation between the nondipolar components of the second half of the T wave and the $T_{peak\text{-}end}$ interval was found during premature stimulation and after d-sotalol exposure ($r = 0.511$, $P = 0.01$; and $r = 0.725$, $P = 0.004$ for correlations during premature ventricular stimulation and d-sotalol exposure, respectively). On the other hand, dispersion of repolarization was evaluated by assessing $SDQT_{end}$. A significant increase of this variable was found during premature stimulation (7.7 ± 2.4 ms to 12.8 ± 3.8 ms for control and premature stimulation, respectively) and after d-sotalol exposure (6.2 ± 1.3 ms to 11.6 ± 1.7 ms before and after d-sotalol exposure, respectively).

Discussion

Findings of the Present Study

Among the chief findings of this study were as follows. (1) Both the dipolar and nondipolar components of the T wave increased significantly during premature stimulation with very short coupling intervals and after d-sotalol exposure. (2) In contrast, the relative TWR either did not change, as occurred after d-sotalol exposure, or decreased significantly during premature stimulation. (3) The changes in the dipolar and nondipolar components of the second half of the T wave were significantly greater than those corresponding to the first half during premature stimulation. (4) A significant correlation was observed between the nondipolar components of the second half of the T wave and the $T_{peak\text{-}end}$ interval during premature stimulation and after d-sotalol exposure.

Significance and Interpretation of Data Derived from SVD

Dipolar components

Classic ECG has been based on the assumption that the electrical activity of the heart could be represented as a dipole located inside the thorax, which changes its amplitude and direction throughout the cardiac cycle. During electrical propagation in the heart, the ECG electrodes sense this phenomenon as different morphologic signals, because these

morphologies are dependent on their projections over the lead axes. If the nature of the ECG signal is, in fact, exclusively dipolar, any number of electrode leads could be condensed in only three new leads, that is, only those necessary to describe the movement of the dipole in three-dimensional space. SVD analysis is a mathematical process that transforms any number of signals (i.e., ECG leads) into a new set of data in which all redundant information is eliminated. SVD analysis has been applied to the study of abnormalities of repolarization and defines the principal nonredundant spatial components into which the T waves are decomposed and that contribute, in descending order of significance, to its morphology. The significance of each component is measured by its eigenvalue. The so-called σ_1^2, σ_2^2, and σ_3^2 are the first three eigenvalues that normally carry >98% of the total energy of the T wave. Its sum defines the dipolar component and represents the global morphologic pattern of the T waves analyzed. Furthermore, any change in its value represents a global repolarization alteration (global heterogeneity) because this change is seen or detected by all the electrodes. When repolarization is uniform, most of the information on its morphology is contained in the first main principal component. When the T wave becomes more complex, the relative value of the next, smaller components of the T wave increases, that is, their eigenvalues increase.

Previous studies of ventricular repolarization demonstrated that the first component or eigenvalue accounts for most of the energy in repolarization when applied to the normal T wave vector, whereas inhomogeneous repolarization is indicated by a relevant contribution of the second and third components.[21-23] Assuming an entirely dipolar nature of the T wave, the ratio of the second to the first eigenvalue ($PCA_{ratio} = \sigma_2^2/\sigma_1^2$) was proposed as a variable that quantifies the complexity of repolarization, where a high PCA_{ratio} reflects a more complex T wave morphology. Moreover, the PCA_{ratio} provides information that can be visualized by analogy as the long and short axes of the three-dimensional T wave loop and provides an estimate of the relative roundness of the T wave loop.

We have shown that the dipolar components increased during premature stimulation and after d-sotalol exposure. Moreover, as shown in Figure 3, the second component (σ_2^2) exhibited the greatest change and was a determinant of the decrease in relative TWR during premature stimulation. Also, the increase of this component may play an important role in the lack of change of the relative TWR observed after d-sotalol exposure. On the other hand, it also could be assumed that the changes of σ_2^2 reflect a rise in global heterogeneity of repolarization and, hence, determine an increase in the T wave complexity.

Nondipolar components

An entirely dipolar nature is true for a substantial portion, but not for the entire extent, of the ECG signal of repolarization. SVD analysis previously has been used to distinguish between those parts of the ECG signal that can be explained by the changes in the three-dimensional dipole (dipolar components) and those that cannot be explained by these changes and, therefore, are called nondipolar components.

It has been hypothesized recently that nondipolar contents of the T wave, that is, the signal beyond the three-dimensional T wave vector, reflect the true heterogeneity of repolarization, and the TWR analysis has been proposed to quantify these nondipolar signal components. Consistent with the concept that heterogeneity of repolarization increases with myocardial diseases, it was shown that both the absolute and relative TWR increased significantly in patients with different classes of myocardial diseases.[15,16] In the present study, we also showed a significant increase in the nondipolar components during premature ventricular stimulation and after d-sotalol exposure. However, in contrast to previous studies, relative TWR was found to either decrease or remain unchanged.

Physiopathologic considerations

An increase in the relative TWR, as previously reported by others, implies that the dipolar components remain unchanged or change slightly and that this behavior must be associated with an important change in nondipolar components.

The simultaneous increase in both the dipolar and nondipolar components that we observed should not be an unexpected finding because abnormal repolarization should be associated with an increase in the global energy within the T wave. Because dipolar components represent >98% of the energy of the T wave, it is logical to assume that an increase in both the dipolar and nondipolar components should be associated with abnormal repolarization. Hence, an increase, no change, or even a decrease in the relative TWR would be the consequence, depending on the magnitude of the changes induced in both components.

Spatial and temporal irregularities of ventricular repolarization are the consequence of the combination of two factors, the timing of activation, and the local duration of recovery.

It could be hypothesized that under conditions of severe and heterogeneous anatomic damage of the myocardium (myocardial infarction or cardiomyopathies), the asynchrony of repolarization (due to the important intramyocardial conduction disturbances) would induce an almost exclusive increase in the nondipolar components. In contrast, in other pathologic conditions such as long QT syndrome, proarrhythmic effects of Class III antiarrhythmic agents, or during ventricular premature beats, an increase in both the dipolar and nondipolar components would be observed. In the first case, an increase in the relative TWR will be the consequence. In contrast, an increase, no change, or even a decrease in the relative TWR should be expected to occur in the second case, depending on the relative changes in both the dipolar and nondipolar components.

First and Second Half of T Wave Analysis

An increase in the transmural dispersion of repolarization may play an important role in arrhythmogenesis during ventricular repolarization. In this regard, several lines of evidence indicate that an increase in the $T_{peak\text{-}end}$ interval is associated with a high risk for the development of torsades de pointes or sudden cardiac death.[24-28]

It was demonstrated recently that regional differences exist in the electrophysiology of ventricular cells. Numerous laboratories have provided evidence for the existence of several electrophysiologically and functionally distinct cell types, including epicardial, endocardial, and M cells. The durations

of the action potentials of these three cell types are different. The epicardial cells have the shortest duration and the endocardial and mid-myocardial, or M, cells have the longest durations.[1,29,30] These inequalities in the durations of the action potentials develop transmural voltage gradients that play an important role in the inscription of the ECG T waves. Although the epicardium is activated last, it repolarizes earlier than the endocardium and M cells because of its shorter repolarization time. Therefore, repolarization of endocardial and mid-myocardial M cells is temporally aligned with the end of the T wave (T_{end}), whereas repolarization of the epicardium is coincident with the peak of the T wave (T_{peak}).[31] As a result, at the peak of the T wave the transmural voltage gradient reaches the maximum and, therefore, the descending limb represents the extent of transmural dispersion of repolarization.

According to this model, the first half of the T wave would be considered an index of the epicardial action potential durations, whereas the second half would be considered an index of the endocardial and mid-myocardial action potential durations. During premature stimulation, shortening of action potential durations should be expected to occur, although this shortening would not necessarily be the same in the three types of myocardial cells. Previous studies have shown that epicardial ventricular pacing and premature ventricular beats increase the transmural dispersion of repolarization reflected by an increase in the $T_{peak\text{-}end}$ interval.[32,33] Moreover, shortening of the epicardial action potential duration should be reflected by an earlier timing of the peak of the T wave, whereas an increase in the duration of the endocardial or mid-myocardial action potentials should be reflected as an increase in the T_{end} interval. In SVD analysis, these changes will be reflected as variations of the dipolar components. We analyzed from the first component obtained after SVD (Fig. 1) the percentage of the time to peak with respect to the total duration of this component and observed significant shortening during premature stimulation ($71.5\% \pm 7.1\%$ vs $57.4\% \pm 8.9\%$, $P < 0.0002$). In contrast, no significant differences were found after d-sotalol exposure ($70.8\% \pm 9.8\%$ vs $65.4\% \pm 6.6\%$). These results would be in agreement with a preferential shortening of epicardial action potentials during premature stimulation. Accordingly, preferential changes occurring during the second half of the T wave will necessarily be reflected by variations in the dipolar components of this portion of the T wave.

We also showed a significant correlation between the nondipolar components of the second half of the T wave and the $T_{peak\text{-}end}$ interval. Therefore, it seems reasonable to assume that the increase of the nondipolar components of the second half would be indicative of the degree of heterogeneity in endocardial and mid-myocardial action potential durations. Interestingly, we showed an increase of the nondipolar components of the second half of the T wave both during premature stimulation and after d-sotalol exposure. However, this increase was preferential only during premature stimulation, probably reflecting the heterogeneous effect over the endocardial and mid-myocardial action potentials.

In contrast, the changes in the dipolar and nondipolar components of both the first and second half of the T wave, observed after d-sotalol exposure, could be explained by a more global effect of this drug on epicardial, endocardial, and mid-myocardial cells.

Study Implications

To the best of our knowledge, we showed for the first time that normalization of any component of those obtained after SVD analysis with respect to any other component derived from the same technique could be a source of misinterpretation. From the present results, it becomes clear that both the dipolar and nondipolar components of the T wave are important determinants of variables reflecting heterogeneous repolarization derived from SVD analysis. Therefore, care should be taken when the absolute value of any component derived from SVD analysis is normalized with respect to any other SVD components because, as we have shown, conditions exists in which σ_1^2, σ_2^2, σ_3^2, and $\sigma_{4\text{-}40}^2$ can change simultaneously. Under these conditions, the relative value of these variables should not reflect regional heterogeneity of repolarization with accuracy. Finally, analysis of SVD-derived variables corresponding to the second half of the T wave would be helpful in the assessment of transmural dispersion of repolarization.

Efforts should be made to integrate both dipolar and nondipolar factors in a single index in order to assess abnormalities of repolarization more accurately.

Moreover, it is clear that efforts should be made to carry out prospective epidemiologic studies in order to define the normal limits of these new indices that characterize ventricular repolarization.

Study Limitations

In the present study, we used the protocols of premature ventricular stimuli and d-sotalol exposure to increase ventricular dispersion of repolarization to induce changes in the repolarization process of the ventricles. We then analyzed the role of the changes in both the dipolar and nondipolar components of the T wave in reflecting heterogeneities of repolarization. However, no attempt was made to measure heterogeneities of repolarization on the epicardial surface or in mid-myocardial or endocardial muscle layers. In fact, we limited our analysis to ECG signals obtained from recording electrodes embedded in the wall of the tissue bath chamber in which the hearts were immersed. We consider this to be an important limitation of the study. Nevertheless, it has been well established by others that with either very close ventricular premature beats[8] or exposure to d-sotalol doses $>10\ \mu$M,[17,18] a significant increase in ventricular repolarization dispersion actually was induced.

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