EDITORIAL

Nondipolar Electrocardiographic Components and Myocardial Heterogeneity

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Already a quarter of a century ago, it has been established that nonuniform myocardial repolarization is an important contributor, if not the source of ventricular arrhythmogenicity.^{1,2} This prompted, among others, the search for an easily applicable clinical test documenting repolarization heterogeneity. As the standard 12-lead electrocardiogram (ECG) not only documents (in a global way) intracardiac electrophysiological processes, but is also very easily recorded, it quickly became the favorite object in attempts to quantify repolarization inconsistencies and nonuniformity. The attempts to use standard ECGs in diagnosing these repolarization abnormalities and relating them to ventricular arrhythmogenicity started some 20 years ago,^{3,4} and have continued ever since.

Unfortunately, in spite of occasional periods of enthusiasm for and excitement with a particular method, electrocardiographic research has not been particularly successful in these attempts. The so-called QT dispersion was perhaps the first of the passion and fashion triggering techniques, only to be later exposed as a mere methodological deception.^{5,6} Somewhat more recently, experiments performed in canine left-ventricular wedge preparation have shown that the interval between the peak and end of the T wave (the TpTe interval) characterizes repolarization heterogeneity.⁷ While this assertion was reasonably tested in the wedge preparation, its projection to clinical ECGs^{8,9} is potentially problematic since the wedge preparation contains transmural action potential gradient but

not other gradients such as the left-right, septum-free wall, and apex-base differences. Indeed, the usefulness of the TpTe interval derived from clinical 12-lead ECGs has been challenged both by some clinical studies,^{10–12} as well as by detailed electrocardiographic models.¹³ At present, it remains to be seen if some aspects of the TpTe concept will become clinically useful.

The experience with the failed and problematic approaches to the analysis of standard 12-lead ECGs suggests that quantification of repolarization heterogeneity will unlikely be achieved with simple measurements of intervals and voltages. While different ECG leads contain different diagnostic information, they are interlinked in an intricate way¹⁴ that is not easy to interpret in plain assessment and measurement (e.g., it is clearly wrong to assume—as was the case with QT dispersion—that leads V₄ and V₅ represent solely transmural signals of near apical left ventricular free wall). The search for a descriptor of repolarization heterogeneity thus started to use detailed ECG theory and mathematical elaboration of ECG signals¹⁵ that allows consideration of all the details of the spatial relationship between different leads.

One of these "mathematically" driven concepts is the measurement of the nondipolar contents of the T wave,¹⁶ also called, when applied to 12-lead ECGs, the T-wave residuum (TWR).¹⁷ The concept of TWR is rather simple; the spatial interrelationship between individual ECG leads allows representing the electrical signals of the whole heart by

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a moving 3-dimensional (3D) voltage dipole (i.e., moving pair of dots representing differences between anode and cathode) as in the standard vectorcardiogram. Special mathematic technique of algebraic matrix calculus (the so-called singular value decomposition¹⁹) extracts as much of the ECG signal that can be represented by a 3D dipole while also calculating the parts of the signals from individual leads that cannot be represented by a 3D dipole. The signals that cannot be represented by a 3D dipole correspond to discrepancies and asynchrony between different myocardial regions (synchronous signals from different regions contribute to the 3D vector). Since the regional differences and asynchrony are the essence of heterogeneity, these nondipolar signals measure the heterogeneity (Fig. 1). There are different ways of expressing the power of the dipolar and nondipolar signals but all allow quantifying the extent of nondipolar signals both absolutely and relatively (i.e., in relation to the dipolar signals).

While theoretically, there are good reasons for the nondipolar T-wave components or the TWR to quantify repolarization heterogeneity, the problematic experience with previous attempts to measure repolarization nonuniformity dictates that the concept needs to be very thoroughly tested. It is therefore pleasing that Kesek et al.²⁰ report on a detailed simulation study that shows a relationship between repolarization heterogeneity and nondipolar T-wave components. This article adds another piece to the mosaic of knowledge of nondipolar T-wave components.

At present, this mosaic is rather sparsely filled in. It contains both experimental studies with isolated animal hearts²¹ and clinical investigations that found expected predictive value of nondipolar T-wave components in cardiac patients²² and in a general population²³ as well as expected changes of the T-wave residuals by therapeutic interventions.²⁴ Apart from these investigations, physiologic studies exist showing sex differences in TWR,²⁵ its circadian pattern,²⁵ as well as its population-based relationship to heart rate.²⁶

In spite of the consistency of the previous reports with the present simulation study by Kesek et al.,²⁰ it is clearly too premature to be presently enthusiastic about the possibility offered by the measurement of the nondipolar contents of T wave. The embarrassing experience with the excitement by QT dispersion should not be forgotten. Many additional detailed studies are needed before it might

be claimed that the measurement of the nondipolar ECG contents provides a clinically useful tool. Problems that need solving are of technical, physiologic, and clinical nature.

Kesek et al.²⁰ also correctly point out that the assessment of T-wave residua is highly influenced by the ECG quality and noise contents. Relevant measurement of signal-to-noise ratio is needed together with investigations of whether the measurement might be corrected for the underlying noise. The result of singular value decomposition is also dependent on the analyzed ECG section. For the analysis of T-wave residua, only the T-wave signal should be used excluding the QRS complex that has a different interlead relationship. The stability of the result is thus, to some extent, dependent on the determination of T-wave onset, which is even more difficult to be made consistently than the T-wave offset. Although a relationship to heart rate has been found in populations of healthy subjects,²⁶ its implication for the possible usefulness of TWR is not known. It appears that, similar to other repolarization characteristics, heart rate dependency of TWR shows intrasubject stability with intersubject differences (Fig. 2) but relevant investigations are missing, possibly because of the lack of validated mathematical models of the relationship. In clinical applications, TWR might need to be corrected for heart rate but it is not presently known how such correction should be made. In some available clinical studies, TWR was calculated from representative median ECG patterns derived from 10-second recordings. At the same time, Figure 1 clearly shows that TWR exhibits marked beat-to-beat differences. Whether these differences have any physiologic and/or clinical meaning is also not known. Similarly, relationships to pathology progression, such as in ischemic heart disease or heart failure, have never been studied.

Hence, the list of gaps in the mosaic of our present knowledge of nondipolar T-wave components is substantial. At the same time, however, there are many clinically and physiologically well-characterized databases of digital ECG recordings and their processing for TWR assessment should be relatively easy to perform. The study by Kesek et al.²⁰ might thus also serve as encouragement to other researchers to fill in the knowledge gaps. Basic standardization is naturally needed when performing additional studies with 12-lead ECGs. Otherwise, the results might not be mutually comparable, as also shown in the simulation study by

Figure 1. There are eight independent leads in a standard 12-lead electrocardiogram (ECG; left panel). The algebra of singular value decomposition recalculates the ECG into an eight-dimensional system (middle panel). All the signals that can be represented in one direction are in the first dimension (S1), all remaining signals that can be represented in a direction perpendicular to S1 are in the second dimension (S2), and so on—up to the eighth dimension (S8). The signals in S1, S2, and S3 are the dipolar components that correspond to the three-dimensional vector movement; the signals in S4–S8 are the nondipolar components. The dipolar and nondipolar components may be used, for instance, to calculate their vector magnitude (VM) or the proportion of the nondipolar VM to the VM calculated from all eight dimensions S1 to S8—the relative nondipolar residuum (right panel). In the right panel, the vertical gains of the dipolar VM, nondipolar VM, and the relative residuum are shown in a 1:10:2000 proportion.

Figure 2. Relationship between heart rate and relative T-wave residuum assessed in four different healthy subjects. In each subject, the open, shaded, and closed marks correspond to different daytime 12-lead Holter recordings obtained with 2 to 5 week periods between repeated investigations. From each Holter recording, approximately 230 10-second ECG segments were selected, all preceded by stable heart rates. In each panel, the bold gray line shows a polynomial interpolation of the individual datapoints.

Kesek et al.²⁰ Potentially misleading conclusions from differently made analyses need to be carefully avoided. The standardization needs to include not only exact implementation of the algebraic computations, but also the definition of the analyzed ECG region. Perhaps, previous detailed description of an analytical system might be presently used for these standardization purposes.¹⁵ Hopefully, much more systematically gained knowledge and experience will accumulate soon. Only then it will be possible to decide whether TWR is a truly useful measure that might help in clinical practice.

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