Imaging Dispersion of Myocardial Repolarization, I
Comparison of Body-Surface and Epicardial Measures

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Background—Body-surface ECG measures (QT dispersion [QTd], QRST integrals) have been used as indices of myocardial repolarization abnormalities with the goal of identifying patients at risk of fatal arrhythmias. The clinical utility of these measures has been questioned. We investigate the complex relationship between epicardial and body-surface potentials in the context of regionally abnormal myocardial repolarization.

Methods and Results—Epicardial potentials were recorded with a 224-electrode sock from an open-chest dog during control, regional epicardial warming, cooling, and adjacent warming and cooling to induce localized alterations in myocardial repolarization and regions of increased repolarization dispersion. Body-surface potentials were generated from these epicardial potentials in a human torso model. Epicardial estimates of repolarization (activation recovery intervals [ARIs] and QRST integrals) were evaluated for their ability to identify regions with increased repolarization dispersion. Body-surface QRST integrals and QTd in 12-lead ECG and 64-lead body-surface potential maps were evaluated for their ability to detect increased dispersion of myocardial repolarization. Epicardial ARI and QRST integral maps successfully located epicardial regions with increased dispersion of repolarization. The increased dispersion was not consistently reflected in the 12-lead or 64-lead ECG QTd or in the body-surface QRST integral maps.

Conclusions—This study demonstrates the inadequacy of body-surface measures that are thought to reflect myocardial dispersion of repolarization. In contrast, measures based on epicardial electrograms (ARI or epicardial QRST integral maps) provide physiologically relevant information about myocardial repolarization and can locate regions of increased dispersion. (Circulation. 2001;104:1299-1305.)

Key Words: arrhythmia ■ electrocardiography ■ electrophysiology ■ imaging ■ potentials

Dispersion of myocardial repolarization contributes to arrhythmia vulnerability by creating arrhythmogenic substrates for reentry.1 QT interval dispersion (QTd) and QRST integral maps of the body-surface ECG have been used to characterize myocardial repolarization with the goal of noninvasively identifying patients at risk of fatal arrhythmias.2–8 Several studies found QTd to be a useful predictor of sudden cardiac death in several patient populations, including long-QT syndrome (LQTS),3,4 congestive heart failure,5 and after myocardial infarction.6,7 Other studies showed that QTd has either borderline or no predictive value.8–10 Furthermore, the QTd measure was shown to depend on variables not related to myocardial repolarization.11 These factors have combined to call into question the clinical usefulness of QTd.12,13

A major assumption of QTd and QRST integral maps is that body-surface potentials preserve the spatial distribution of epicardial potentials and associated cardiac electrical sources. In fact, each electrode on the body surface measures an integrated potential generated by all bioelectric sources from the entire heart.14 Therefore, in general, body-surface potentials do not preserve the spatial pattern of myocardial repolarization and its dispersion. The ability of these methods to predict arrhythmia vulnerability successfully depends on the specific myocardial source configuration during repolarization and its geometric relationship to the body surface.

In this study, we used local interventions (epicardial warming and cooling) to create areas with increased dispersion of myocardial repolarization. We examine how these regional repolarization abnormalities are reflected in measures of dispersion on the epicardium and body surface. We also evaluate whether body-surface indices that are currently used to infer heterogeneity of myocardial repolarization reflect such heterogeneities accurately and reliably and compare their performance with that of epicardial measures of dispersion.

Methods

Experimental Methods
All studies were performed in accordance with guidelines specified by our Institutional Animal Care and Use Committee, the American Heart Association Policy on Research Animal Use, and the Public Health Service Policy on Use of Laboratory Animals. Epicardial
Measurements of Repolarization Dispersion

QT intervals were determined on body-surface leads as the difference between the Q-onset time on ECG lead II and the local T-offset times. T-offset was determined from the baseline intersection of a linear fit to the steepest portion of the T wave after its peak. QT dispersion (QTd) was defined as the difference between the maximum and minimum QT intervals for either the 12-lead ECG or 64-lead BSPM. Activation recovery intervals (ARIs) were determined from epicardial electrograms as the difference between activation and recovery times. Activation was set at the time of maximum negative derivative of the QRS. Recovery was set at the time of maximum positive derivative of the T wave. ARI dispersion (ARId) was defined as the difference between the maximum and minimum ARIs on the epicardial surface. Standard deviations of the QT interval (QTstd) and ARI (ARId) were also computed. The T-offset, T-peak, activation, and recovery times were automatically determined by computerized algorithms, individually verified, and when necessary, manually edited. The QRST integral map was computed on both the epicardial and body surfaces by summation of the potentials for each lead over the entire QRST complex.

Results

Heterogeneities in action potential duration (APD) across the myocardial wall produce a transmural repolarization gradient that is reflected in the T wave. Figure 1A illustrates this relationship for an epicardial electrogram in a normal LV during sinus rhythm (activation propagates from endocardium to epicardium). For clarity of presentation, the contribution of the endocardial layer is not shown, because the cooling/warming interventions are applied to the epicardial surface and influence its repolarization. In addition, the important fiducial points of the T wave (peak and end) are determined by the repolarization of the epicardium and midmyocardium, respectively. In the absence of intervention, although activated last, the epicardial cells repolarize first because of their shorter APDs compared with midmyocardial cells. This creates a transmural gradient of transmembrane potential (\(\nabla V_m\)) from epicardium to midmyocardium that constitutes a dipolar source that generates the epicardial T wave. This source is reversed in polarity relative to the potential gradient, ie, it points toward the epicardium. The unipolar epicardial electrogram therefore records a positive T wave, with its peak corresponding to the time of epicardial repolarization (when the transmural gradient is greatest).

Epicardial warming exaggerates the transmural repolarization gradient by increasing the rate of repolarization that shortens epicardial APDs. This is reflected in a T wave that is more positive and starts earlier compared with control (Figure 1B). Epicardial cooling decreases or even reverses the transmural repolarization gradient by slowing repolarization kinetics and lengthening epicardial APDs. A flat T wave is generated if the epicardial cells repolarize simultaneously with the midmyocardial cells, whereas a negative T wave reflects reversal of the repolarization gradient, with epicardium repolarizing later than midmyocardium (Figure 1C). In Figure 2, results from localized epicardial warming confirm the analysis of Figure 1B, with electrograms in the warmed region showing augmented positive T waves compared with control (Figure 2B, sites 1, 2, 3, and 5). Electrodes farther from the warmed region show little or no T-wave alteration (sites 4 and 6). Localized epicardial cooling results in the pronounced negative T waves observed at sites 1, 2, 4,
Adjacent warming and cooling results in enhanced positive T waves near the warmed region (Figure 2D, site 3) and deep negative T waves near the cooled region (Figure 2D, sites 4, 5, and 6).

ARIs determined from unipolar epicardial electrograms have been shown to correlate with underlying epicardial APDs. Epicardial ARI maps can be constructed from an array of epicardial electrograms to provide information about the spatial distribution of repolarization over the epicardium. The epicardial ARI map during warming (Figure 3B) shows decreased ARIs relative to control (black) over the warmed region. Comparison with control (Figure 3A) shows that regional epicardial warming increases spatial epicardial ARI gradients from the fairly uniform control map. The decrease in epicardial ARI over the warmed region reflects the shortened APDs in this region. As explained above (Figure 2), this is reflected in the epicardial electrogram T waves and results in earlier recovery times (Figure 2B, vertical lines, sites 1, 2, 3, and 5). Regional cooling results in the expected ARI increase (white) over the cooled region (Figure 3C).

Figure 2. Epicardial electrograms altered by regional warming and/or cooling. A, Anterior epicardial surface with right ventricle (RV), left anterior descending coronary artery (LAD), and LV marked. Regions of warming and cooling are outlined by solid and dashed lines, respectively. Numbers in boxes identify locations of recorded electrograms. B, Electrograms during control (black) and regional warming (gray). Vertical lines mark recovery (repolarization) times. C, Electrograms during regional cooling. Same format as B. D, Electrograms during simultaneous adjacent warming and cooling. Same format as B. During this protocol, only part of circle not covered by rectangular cryoprobe is heated.
caused by cooling-induced APD increases and delayed recovery times (Figure 2C). Adjacent warming and cooling (Figure 3D) creates large ARI gradients (dispersion of repolarization) across a small distance on the LV epicardium, in sharp contrast to the smooth ARI distribution observed in control. The spatial epicardial repolarization gradient can be represented by quantitative indices such as ARId or ARIstd shown graphically in Figure 4A. As expected, warming leads to increased epicardial ARId (thick black bars) and ARIstd (white error bars) because of a reduced minimum ARI, cooling leads to increased ARId and ARIstd because of an increased maximum ARI, and simultaneous warming and cooling results in an even larger ARId with both an increased maximum and decreased minimum ARI. Thus, the increased spatial dispersion of repolarization caused by regional warming and/or cooling observed in ARI maps is correctly reflected in the epicardial ARId and ARIstd indices.

Body-surface QTd and QTstd for the same protocols are shown for the 12-lead ECG and 64-lead BSPM in Figure 4B. Note that during control, the BSPM shows much larger QTd (gray) than the 12-lead ECG (black). This demonstrates that the 12-lead ECG is not adequately sampling the body surface to measure QTd accurately. QTstd is only slightly larger in the BSPM than the 12-lead ECG. Furthermore, the QTd and QTstd in both the 12-lead ECG and 64-lead BSPM show a paradoxical decrease during epicardial warming despite the increase in dispersion of repolarization on the epicardial surface. This demonstrates that these body-surface indices do not necessarily reflect the underlying dispersion of myocardial repolarization. Figure 5 shows the 12-lead ECG for the control (black lines) and warming (gray lines) protocols. Most warming-induced ECG changes cause the T wave to become more pronounced without major changes in the general T-wave morphology. The small changes of T-wave morphology that occur make the distribution of T-offset times more uniform, leading to a decreased QTd and QTstd. In contrast to epicardial warming, epicardial cooling increases the body-surface QTd and QTstd from control in both the 12-lead ECG and 64-lead BSPM (Figure 4B). Evaluation of the 12-lead ECG during cooling (Figure 6) shows that the T-wave morphology undergoes significant changes in leads V2, V3, and V4, resulting in very different T-offset times, which contributes to increased QTd and QTstd in body-surface lead sets. During simultaneous warming and cooling, the BSPM shows the same QTd as during cooling alone, whereas the 12-lead ECG shows a decreased QTd (Figure 4B). This once again highlights how the 12-lead ECG inadequately samples the QTd on the body surface.

The epicardial QRST integral map has been shown theoretically and experimentally to reflect local myocardial repolarization independently of the activation sequence. The epicardial QRST integral map during warming shows increased values over the warmed area (Figure 7B, white), indicating increased repolarization gradients in this region (compare with control, Figure 7A). The increased QRST integrals with warming can be attributed to the enhanced T waves observed in the electrograms of Figure 2B. Cooling the epicardium results in decreased QRST integrals over the cooled region (Figure 7C), reflecting the large repolarization gradients created through cooling. The complexity of this map can be explained by the complex T-wave changes with cooling (Figure 2C), which include T-wave inversion and
enhancement of negative T waves. The QRST integral map during adjacent warming and cooling (Figure 7D) shows an even larger spatial gradient across the LV free wall, with the maximum and minimum QRST integral values separated by only 1.3 cm. QRST integrals can also be computed on the body surface, as shown in Figure 7, E through H. Unlike the epicardial QRST integral maps, the body-surface QRST integral maps do not reflect the degree of myocardial repolarization heterogeneity and the complexity of its spatial pattern. All protocols show smooth body-surface QRST integral maps with only minor differences from control.

Discussion

The ability of the body-surface ECG to provide noninvasive, reliable information on the degree of repolarization heterogeneity in the heart has been a subject of much debate. In particular, the clinical usefulness of QTd as an identifier of patients at risk of fatal arrhythmias remains questionable. The results of this study demonstrate that regions of increased dispersion of myocardial repolarization are not reflected faithfully in the ECG. This principle is demonstrated for several QT-interval indices, including QTd and QTstd in 12-lead ECGs and in 64-lead BSPMs. Similar lack of sensitivity characterizes the body-surface QRST integral maps.

The failure of body-surface QT interval indices to reflect regional changes in myocardial repolarization is because each electrode on the body surface records a potential that is a distance-weighted integral of the potential over the entire epicardial surface (or alternatively, over all cardiac electrical
sources generated by the process of activation or repolarization. Therefore, spatial properties of the cardiac source configuration and of the epicardial potential distribution are not preserved in the body-surface potential distribution, and spatial differences (dispersions) that are pronounced on the epicardium may be lost on the body surface. It should be stated that under special circumstances, spatial properties and dispersions of myocardial repolarization could be reflected in the body-surface potential distribution. This requires a favorable situation in which the region of increased dispersion is proximal to the body surface, the orientation of the associated dipolar sources maximizes the body-surface potential magnitude, and activity in other regions of the heart does not cancel or mask the body-surface potentials generated by the cardiac region of interest. The existence of such favorable circumstances could explain the usefulness of QTd as an index of arrhythmia risk in some cases of the long-QT syndrome. Another example is the Brugada syndrome, in which increased transmural dispersion of repolarization (shortened epicardial APD due to reduced sodium current on the background of a large transient outward current) occurs preferentially in the right ventricular epicardium in close proximity to the right anterior chest and is reflected as ST-segment elevation in the right precordial leads of the body-surface ECG. It should be emphasized in this context that QTd, a measure derived from the body-surface ECG, should not be used interchangeably with (or equated to) dispersion of repolarization, a physiological process that occurs in the excitable tissues of the heart.

In contrast to the body-surface potential and its derived indices of repolarization dispersion (QTd, QTstd, QRST integrals), epicardial measures (ARI and epicardial QRST integral maps) are shown in this study to reflect repolarization heterogeneities and to locate regions of increased dispersion. The ARI and QRST integral measures are derived from the epicardial electrograms and have a sound physiological basis in the context of underlying myocardial repolarization. The ARI estimates the local epicardial APD from the unipolar electrogram. The QRST integral reflects the local repolarization gradient independently of the activation sequence. The regional epicardial cooling and/or warming creates areas with altered repolarization due to accelerated (warming) or slowed (cooling) kinetics of repolarizing ionic currents. The resulting spatial dispersion of repolarization is clearly mapped by the epicardial ARI and QRST integral maps. The statistical ARId and ARIdst measures compress this information into a single index for global quantification of the degree of dispersion. The ARI and QRST integral maps, however, provide a more detailed description of the spatial organization of myocardial repolarization gradients.

In conclusion, this study shows that epicardial indices of repolarization (ARI and epicardial QRST integral maps) are reliable measures of repolarization heterogeneity and its spatial distribution, whereas body-surface indices (QTd, QT-
std, body-surface QRST integrals) are not. In particular, QT dispersion in the 12-lead ECG is not a reliable index of dispersion of repolarization in the heart. An important property of epicardial ARI and QRST integral maps, not shared by the body-surface measures, is their ability to locate the substrate of increased dispersion (possibly for specific diagnosis and targeted intervention). At present, obtaining epicardial information requires invasive intraoperative mapping. Recent developments of a noninvasive imaging modality for cardiac electrophysiology (ECG imaging), however, have demonstrated that epicardial potentials and electrograms can be reconstructed with good accuracy over the entire epicardial surface in normal hearts and in the presence of arrhythmogenic substrates associated with myocardial infarction. Application of ECG imaging during repolarization to noninvasively reconstruct epicardial potentials and associated measures of dispersion, such as ARI and epicardial QRST integral maps, could provide detailed information on repolarization abnormalities. Such information could then be used to noninvasively identify patients at risk for developing arrhythmias, obtain more specific diagnosis of repolarization disorders, and monitor the effects of therapies that modify repolarization (e.g., antiarrhythmic agents with class III action). The possibility of noninvasive reconstruction of repolarization heterogeneities is addressed in the accompanying article.

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References
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