Imaging Dispersion of Myocardial Repolarization, II
Noninvasive Reconstruction of Epicardial Measures

Raja N. Ghanem, MS; John E. Burnes, PhD; Albert L. Waldo, MD; Yoram Rudy, PhD

Background—Dispersion of myocardial repolarization supports the development and maintenance of life-threatening arrhythmias. Current noninvasive approaches for detecting substrates with increased dispersion based on ECG measures (eg, QT dispersion) have shown limited success and inconsistencies. The companion article shows that, in contrast, epicardial potentials and derived measures reflect local dispersion of repolarization. Here, using a recently developed ECG imaging method, we evaluate the feasibility of noninvasive reconstruction of such epicardial measures from body-surface ECG data.

Methods and Results—Epicardial potentials were recorded with a 224-electrode sock from an open-chest dog during control, regional warming, cooling, and simultaneous adjacent warming and cooling to induce localized changes in myocardial repolarization and regions of increased dispersion. Body-surface potentials were generated from these epicardial potentials in a human torso model. Realistic geometric errors and measurement noise were added to the torso data, which were then used to noninvasively reconstruct epicardial measures of repolarization dispersion (activation recovery intervals [ARIs] and QRST integrals). Repolarization properties were accurately depicted by ECG imaging, including (1) shortened ARIs and increased QRST integrals over the warmed region, (2) prolonged ARIs and decreased QRST integrals over the cooled region, and (3) high gradients of ARIs and QRST integrals over the adjacent warmed and cooled regions.

Conclusions—ECG imaging can reconstruct repolarization properties accurately and localize areas of increased dispersion of repolarization in the heart noninvasively. Its clinical significance lies in the possibility of noninvasive risk stratification and in guidance and evaluation of therapy. (Circulation. 2001;104:1306-1312.)

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

Dispersion of myocardial repolarization results in regional variation in refractoriness, which is highly arrhythmogenic.1,2 This creates abnormal electrophysiological substrates that support initiation and maintenance of potentially fatal reentrant arrhythmias. From a clinical perspective, it is essential to identify patients with such substrates and to stratify their risk of developing malignant arrhythmias so that prophylactic measures can be prescribed. In addition, characterization of the high-dispersion substrate in terms of severity and location in the heart can be very helpful in deciding on therapeutic strategy. Attempts to do so noninvasively with body-surface ECG indices (eg, QT dispersion3) have met with only partial success and suffer from lack of consistency.4–6 As shown in the companion article,7 the inconsistency results from a fundamental property of the spread of the cardiac electrical field within the torso. Such a spread does not preserve spatial relationships, and the potential measured at a given body-surface point (ECG electrode) reflects potentials over the entire heart. In contrast, the companion article shows that epicardial potentials, and in particular such derived epicardial measures as activation recovery intervals (ARIs) and QRST integrals, accurately reflect spatial heterogeneities of myocardial repolarization. In this article, we examine the possibility of noninvasively reconstructing epicardial potentials and epicardial measures of dispersion from body-surface potentials during interventions (regional epicardial warming and cooling) that create regions with increased repolarization dispersion. We do so using noninvasive ECG imaging (ECGI) methods developed in our laboratory8–11 and recently applied to reconstruct activation during reentrant arrhythmias.12,13 The results demonstrate the feasibility of the approach in terms of its ability to noninvasively detect and locate substrates with high dispersion of repolarization in the heart.

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

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Health Service Policy on Use of Laboratory Animals. Epicardial potentials were recorded from an anesthetized dog (pentobarbital, 30 mg/kg IV) during control conditions and during induced regional dispersion of repolarization. Details of the experimental procedure are presented in the companion article. Briefly, localized epicardial warming to 42°C and cooling to 28°C were used to induce regions of shortened and prolonged repolarization, respectively. Four different protocols were studied during right atrial pacing: control, localized left ventricular (LV) warming, localized LV cooling, and adjacent LV warming and cooling. An idle time of 5 minutes between protocols allowed the heart to return to its baseline temperature. Unipolar epicardial electrograms were acquired at 1 kHz from 224 uniformly distributed silver-silver chloride electrodes embedded in an elastic sock.

Computational Methods

As in previous studies, recorded potentials were placed on a digitized 3D canine heart model and aligned on the basis of the positions of coronary arteries. The heart was then placed in the correct anatomic position inside a computer model of the human torso that contained lungs, spine, sternum, and skeletal muscle. The measured epicardial potentials were used to compute ECG potentials at 458 nodes on the body surface. Gaussian noise (50 μV peak-to-peak) was added to the computed torso potentials to simulate measurement noise. Gaussian geometrical error (1 mm) was added to each body-surface node to simulate errors in determining electrode positions in the clinical setting. By use of the perturbed body-surface potentials and node positions, epicardial potentials and electrograms were noninvasively reconstructed with our previously described ECGI methodology. Reconstructed electrograms were low-pass–filtered (cutoff frequency of 100 Hz) for display. In the previous studies, a Tikhonov zero-order scheme that constrains epicardial potential magnitudes was used to regularize the reconstruction of epicardial potentials from body-surface potentials. Here, Tikhonov second-order regularization was used instead (Appendix). In this scheme, the curvature (laplacian) of the computed potential distribution on the epicardial surface is constrained. The use of second-order regularization was dictated by the importance of repolarization waveforms (electrogram T waves and their magnitudes) in this study and the property that T-wave amplitudes are better reproduced by the second-order scheme than by the zero-order scheme (Figure 1).

Measures of Repolarization Dispersion

ARIs (defined as the difference between activation and recovery times) were computed on the epicardium from measured and noninvasively reconstructed epicardial electrograms. Activation times were set at the maximum negative derivative of the QRS (“intrinsic deflection”). Recovery times were set at the maximum positive derivative of the T wave. The activation and recovery times were automatically detected with computerized algorithms, verified, and when necessary manually edited. If a maximum positive derivative was absent, the recovery time was manually set at the time when (1) the electrogram amplitude decreased to <10% to 25% of T peak or (2) reached baseline in the case of an absent obvious T wave. ARI dispersion (ARIstd) was computed as the difference between the maximum and minimum ARIs on the epicardial surface for both measured and noninvasively reconstructed ARIs. Standard deviations of the ARIs (ARIstd) were also computed for measured and reconstructed ARI maps. QRST-integral maps were computed on the epicardial surface from measured and noninvasively reconstructed electrograms. For each electrode measured, QRST integrals were computed by summing the recorded potentials over the entire QRST complex. These values were displayed as a QRST-integral map on the epicardial surface. Noninvasive epicardial QRST-integral maps were constructed by 2 different approaches: (1) computation of QRST integrals from the reconstructed epicardial electrograms or (2) reconstruction of epicardial QRST-integral maps from body-surface QRST-integral maps. The first approach required multiple reconstructions, because electrograms were assembled from potentials computed at multiple times (every 1 ms) during the cardiac cycle. The second approach required only a single reconstruction. The accuracy of noninvasive ARI and QRST-integral maps was assessed by visual comparison and by computing correlation coefficients (CCs) relative to the directly measured maps.

Results

Noninvasively Reconstructed Electrograms

In Figure 2, measured and noninvasively reconstructed epicardial electrograms are compared during control, regional LV warming, regional LV cooling, and simultaneous warming and cooling at adjacent LV locations. Electrograms from 7 recording sites are shown for each electrogram, the change in ARI (ΔARI) relative to control is shown for measured (gray) and noninvasively reconstructed (black) epicardial data. Compared with control, measured and reconstructed electrograms during LV warming show augmented positive T waves and shorter ARIs in the warmed region (Figure 2B, second column, sites 1, 2, 3, and 5). Minor or no T wave changes are observed in sites outside the warmed region. At site 4, the reconstructed electrogram has a very shallow T wave, which is not suitable for recovery time determination by the maximum positive derivative criterion. Manual editing is used in this case. During LV cooling, measured and reconstructed electrograms reveal negative T-wave morphologies and longer ARIs in the cooled region (Figure 2B, third column, sites 1, 2, 4, 5, and 6). During adjacent warming and
cooling, positive T waves and shorter ARIs are accurately reconstructed over the warmed region (Figure 2B, right column, sites 1, 2, and 3), and negative T waves and longer ARIs are reconstructed over the cooled region (sites 4, 5, and 6). In most cases, changes in electrogram morphologies and ARIs caused by the 3 interventional protocols are faithfully reconstructed. Figure 2C shows similar data for a location away from the warmed and cooled regions. Note that, as expected, T-wave morphology is unaltered by the remote interventions, and DARI relative to control for reconstructed (black) and measured (gray) ARIs is shown for all electrograms. Vertical lines during T wave mark determined recovery time.

**Noninvasively Reconstructed ARI and QRST-Integral Maps**

Directly measured (top row) and noninvasively reconstructed (bottom row) epicardial ARI maps are compared in Figure 3. ARId and ARIstd are provided as quantitative measures of spatial variations in ARIs. During control, a relatively uniform ARI distribution (202±14 ms) is reconstructed over the whole heart. During warming, short ARIs (172±7 ms) are reconstructed over the warmed region, whereas during cooling, prolonged ARIs (234±2 ms) are reconstructed over the cooled region. The noninvasively reconstructed map during simultaneous warming and cooling captures the adjacent areas of short and long ARIs (214±34 ms) and the large repolarization gradient in this region. The effects of temperature alterations on ARId and ARIstd are also faithfully reconstructed (Table). They include increased ARId and ARIstd during warming due to reduced ARIs in the warmed region, increased ARId and ARIstd during cooling due to increased ARIs over the cooled region, and further increased ARId and ARIstd during simultaneous warming and cooling due to the introduction of both shorter and longer ARIs by this protocol. Importantly, a visual comparison of the noninvasively reconstructed and measured ARI maps shows that the noninvasive maps capture the extent and location of the regions with accelerated repolarization (shaded light gray).
and slowed repolarization (shaded black) for all interventional protocols. Quantitative comparison is provided in the Table.

Figure 4 compares measured and noninvasively reconstructed epicardial QRST-integral maps during the 4 experimental protocols. The top row shows the measured epicardial QRST-integral maps. The middle and bottom rows display the corresponding, noninvasively reconstructed QRST-integral maps computed by integrating the reconstructed epicardial electrograms (middle row) or by single reconstruction from the body-surface QRST-integral maps (bottom row). During warming or simultaneous warming and cooling, QRST-integral values are higher than control in the warmed region as a result of augmented positive T waves in this area. The regions of increased QRST-integral values (shaded white) are faithfully reconstructed in the noninvasive maps for both protocols. The resulting nonuniformity of the QRST-integral maps is indicative of increased dispersion of repolarization in this region. The effect of cooling is to reduce QRST-integral values relative to control. During cooling alone, a region of reduced QRST integrals appears over the LV and is reconstructed in the noninvasive maps. An intense and very localized minimum that appears in the measured maps during cooling alone or simultaneous cooling and warming (black in the measured maps), however, is not reproduced in the noninvasive maps. This is a consequence of the spatial smoothing property of the regularization procedure, which tends to underweigh highly localized events. Note that the noninvasive maps computed from the reconstructed electrograms (middle row) or from the body-surface QRST-integral maps (bottom row) are virtually identical.

Homogeneous Torso Approximation

Up to this point, all reconstructions were performed in an inhomogeneous torso that contained the lungs, sternum, spine, and skeletal muscle. Here, we examine the possibility of approximating the torso by a simplified, homogeneous volume conductor without these inhomogeneities for noninvasive reconstruction of repolarization properties. Noninvasive ARI and QRST-integral maps reconstructed in homogeneous and inhomogeneous torsos during LV warming are compared in Figure 5. Note that the body-surface potentials that constitute the data for the noninvasive reconstructions are generated in an inhomogeneous torso for both cases, to represent the clinical situation. Short ARIs and large QRST-integral values are successfully reconstructed over the warmed region by use of the homogeneous torso approximation. In general, the ARI maps and QRST-integral maps reconstructed in the homogeneous and inhomogeneous torsos are very similar (CC is 0.87 for ARI and 0.98 for QRST

<table>
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<tr>
<th>Comparison of ARI Statistics for Measured and Reconstructed (Computed) Data During Control and Interventional Procedures</th>
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<td>Control</td>
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<td>Average difference between measured and computed ARIs*</td>
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ARId over ROI indicates mean ARI over region of interest (control, warmed, cooled, and warmed and cooled regions). All statistics except for ARId avg over ROI are computed over the whole heart. All units are in ms.

*Note that these differences are an order of magnitude smaller than the average ARI changes due to the interventions.
integrals), with only small differences in the shape of the areas with reduced ARIs (shaded light gray) and increased integrals (shaded white).

**Discussion**

Because of asymmetry of excitability properties, dispersion of repolarization creates conditions for the formation of unidirectional block and reentry. Therefore, myocardial regions with large repolarization heterogeneities constitute an arrhythmogenic substrate with the potential for developing life-threatening arrhythmias. Abnormally high dispersion can be associated with genetic disorders, such as the long-QT syndrome,2,17,18 or with substrate remodeling, such as occurs during infarction1 or cardiomyopathies.19 The companion article7 established the principle that dispersion of repolarization is faithfully reflected in epicardial electrophysiological measures but not in noninvasive ECG measures on the body surface (eg, QT dispersion). Here, we evaluate the ability to noninvasively reconstruct epicardial regions with increased dispersion and to obtain a measure of its severity. The reconstruction is performed from body-surface potentials by use of a previously developed and validated methodology.8–14 Our previous work on ECGI9–14 was limited to noninvasive reconstruction of myocardial activation. This article describes the first application of ECGI during myocardial repolarization. Our approach has always been to reconstruct epicardial potentials, from which epicardial electrograms and activation isochrones are then computed.9 This approach has several advantages over methods that directly compute epicardial activation isochrones20,21: (1) epicardial potentials reflect activity in the depth of the myocardium even when the epicardium is not activated10; (2) it can be validated through direct comparison with measured epicardial potentials8–10 (activation isochrones require determination of activation times, which is subject to editing and interpretation and therefore less direct); and (3) importantly, as demonstrated here, it can be applied during repolarization as well as activation, a property not shared by the activation imaging methods.

Successful application of ECGI during repolarization required one modification to the previous methodology. Previously, Tikhonov zero-order regularization15 was used to stabilize epicardial potential reconstruction. In this scheme, epicardial potential amplitudes are constrained. Consequently, reconstructed epicardial electrogram amplitudes are often suppressed (Figure 1). Although this has minimal effect during activation, it introduces large errors to the determination of recovery time and QRST integrals during repolarization.
tion because of T-wave suppression. We therefore use Tikhonov second-order regularization, which uses the laplacian operator to constrain epicardial potential curvature (rather than amplitude), with better preservation of T-wave amplitude and morphology (Figure 1). As demonstrated here, this strategy permits an accurate determination of recovery times and QRST integrals in the majority of reconstructed electrograms. The laplacian operator exerts a spatial smoothing effect on the reconstructed epicardial potential distribution, however. This results in loss of localized features, such as the local minimum associated with LV cooling (Figure 4), and puts a limit on the spatial resolution of the approach.

Two measures of repolarization, ARI and QRST integrals, are reconstructed on the epicardium to provide noninvasive indices of dispersion. Both measures have a clear physiological basis. ARI is determined as the difference between activation and recovery times in a unipolar electrogram and has been shown to correlate with the local action potential duration. \(^{16}\) QRST integrals reflect intrinsic spatial heterogeneities of repolarization independently of the activation sequence. \(^{22}\) In general, the repolarization sequence is determined by the preceding activation sequence and by local repolarization properties. The QRST integration cancels the activation-dependent component, thereby uncovering the local intrinsic component of repolarization \(^{22}\) and its spatial dispersion. As shown in Figure 4, epicardial QRST-integral maps can be computed in a single reconstruction from body-surface QRST-integral maps. This property makes them computationally efficient and particularly suitable for rapid screening of patients for the existence of arrhythmogenic substrates with abnormal repolarization and increased regional dispersion. These maps can also provide a first noninvasive estimate of the location, extent, and degree of dispersion (severity) of the substrate.

In conclusion, this study demonstrates the feasibility of noninvasively reconstructing regional repolarization properties on the epicardial surface of the heart with ECGI. Given the important role of repolarization abnormalities in arrhythmogenesis, the ability to image substrates with abnormal repolarization noninvasively is of clinical significance, especially in view of the limitations of methods that rely on body-surface ECG data alone (eg, QT dispersion). The clinical implementation of the approach will be simplified by the finding that torso inhomogeneities have only a minimal effect on the reconstruction of epicardial repolarization (Figure 5), a property that we have observed previously during activation as well. \(^{14}\) Such a method could be used for risk stratification, for more specific diagnosis of repolarization abnormalities, and for monitoring the effects of therapeutic interventions (eg, repolarization-modifying antiarrhythmic drugs).

Appendix

Body-surface potentials are related to epicardial potentials through Green’s second theorem. \(^{23}\) The resulting discretized problem can be expressed as follows for each time instant in the cardiac cycle:

\[
V_t = AV_E
\]

where \(V_t\) is the vector of body-surface potentials, \(V_E\) is the vector of epicardial potentials, and \(A\) is the transfer matrix describing the geometric relationship between the body and heart surfaces and the geometry and conductivities of the various torso inhomogeneities.

The objective of ECGI is to solve the inverse problem of electrocardiography to compute epicardial potentials from measured body-surface potentials. Because of the ill-posed nature of the inverse problem, one cannot simply invert the \(A\) matrix (equation 1) and compute \(V_E\) from \(V_t\). Tikhonov regularization is therefore used to solve the following minimization problem:

\[
\min_{V_E} \|AV_E - V_t\| + \lambda\|LV_E\|
\]

where \(\lambda\) is the regularization parameter and \(L\) the regularization operator. In this study, the regularization parameter \(\lambda\) is chosen by use of the modified composite residual and smoothing operator method for higher-order Tikhonov regularization, \(^{15,24}\) and \(V_E\) is computed from \(V_t\) for each time instant. The regularization operator, \(L\), is chosen to be the laplacian such that the curvature of the epicardial potential distribution is constrained. The \(L\) matrix is constructed as follows:

\[
L_{ij} = \begin{cases} 
1 & \text{if } i = j \\
\frac{1}{d_{ij}} & \text{if } j \text{ is a 4-connected neighbor of } i 
\end{cases}
\]

where \(d_{ij}\) represents the euclidean distance between node \(j\) and node \(i\). When this \(L\) matrix is multiplied by \(V_E\), a discretized laplacian of \(V_E\) is obtained. This is illustrated below for the following 4-connected-node arrangement, in which the laplacian is computed at node 3:

\[
L_{3\times3} = \begin{bmatrix}
1 & 1 & 1 & \ldots \\
1 & 1 & 1 & \ldots \\
1 & 1 & 1 & \ldots \\
\vdots & \vdots & \vdots & \ddots
\end{bmatrix}
\]

When \(L\) is multiplied by the vector \(V_E= [V_{e1} V_{e2} V_{e3} V_{e4} V_{e5}]^T\), the expression for the laplacian of \(V_E\) at node 3 is obtained:

\[
\|LV_E\| = \|V_{e1} + \frac{V_{e2}}{d_{12}} + \frac{V_{e3}}{d_{13}} + \frac{V_{e4}}{d_{14}} + \frac{V_{e5}}{d_{15}} \|.
\]

The \(L\) matrix is formed for all epicardial nodes. The solution to the Tikhonov minimization problem using the \(A\) and \(L\) matrices is computed by generalized singular-value decomposition. \(^{25}\)

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