Electrocardiographic Imaging
Noninvasive Characterization of Intramural Myocardial Activation From Inverse-Reconstructed Epicardial Potentials and Electrograms

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Background—A recent study demonstrated the ability of electrocardiographic imaging (ECGI) to reconstruct, noninvasively, epicardial potentials, electrograms, and activation sequences (isochrones) generated by epicardial activation. The current study expands the earlier work to the three-dimensional myocardium and investigates the ability of ECGI to characterize intramural myocardial activation noninvasively and to relate it to the underlying fiber structure of the myocardium. This objective is motivated by the fact that cardiac excitation and arrhythmogenesis involve the three-dimensional ventricular wall and its anisotropic structure.

Methods and Results—Intramural activation was initiated by pacing a dog heart in a human torso tank. Body surface potentials (384 electrodes) were used to compute epicardial potentials noninvasively. Accuracy of reconstructed epicardial potentials was evaluated by direct comparison to measured ones (134 electrodes). Protocols included pacing from five intramural depths. Epicardial potentials showed characteristic patterns (1) early in activation, central negative region with two flanking maxima aligned with the orientation of fibers at the depth of pacing; (2) counterclockwise rotation of positive potentials with time for epicardial pacing, clockwise rotation for subendocardial pacing, and dual rotation for midmyocardial pacing; and (3) central positive region for endocardial pacing. Noninvasively reconstructed potentials closely approximated these patterns. Reconstructed epicardial electrograms and epicardial breakthrough times closely resembled measured ones, demonstrating progressively later epicardial activation with deeper pacing.

Conclusions—ECGI can noninvasively estimate the depth of intramyocardial electrophysiological events and provides information on the spread of excitation in the three-dimensional anisotropic myocardium on a beat-by-beat basis. (Circulation. 1998;97:1496-1507.)

Key Words: electrocardiography ■ imaging ■ pacing ■ epicardium ■ potentials ■ anisotropy
or other arrhythmias associated with the long QT syndrome.\textsuperscript{17} It is important, therefore, to develop noninvasive methods for obtaining information on activity inside the volume of the ventricular wall. The objective of the current study was to extend the use of ECGI and to evaluate its ability to detect and locate, noninvasively, electrical events in various depths inside the myocardium. Specifically, intramural pacing sites at several depths and at various locations are used to simulate intramural foci of activation. In addition, the ability of ECGI to provide information on the spatio-temporal propagation of intramural activation as the activation-front traverses the myocardium is examined.

Methods

Computational Methods

Details of the computational methodology have been documented previously.\textsuperscript{3,10,16–20} Briefly, ECGI requires solving the inverse problem of electrocardiography, a procedure that involves two major steps. The first entails discretization of the relation between potentials on the epicardium and those on the body surface. This relation is provided by Laplace's equation and the boundary element method. The second step is the inversion of this relation to obtain an expression for computing epicardial potentials from the measured body surface potentials. Because the inverse problem in electrocardiography is ill posed (ie, unstable in the presence of noise), solving for the epicardial potentials requires regularization. In this study, as in our previous studies,\textsuperscript{8,12,18} Tikhonov zero order regularization is used to stabilize the solution, and the regularization parameter is found using the CRESO (Composite Residual and Smoothing Operator) method.\textsuperscript{2} Computing the epicardial potentials in this way is completely noninvasive and requires only knowledge of the geometry and of the electric potential distribution on the torso.

Electrograms, measured and reconstructed, are examined for purposes of identifying the time of epicardial activation ("breakthrough") near the intramural pacing sites. Noninvasive reconstruction of the electrograms is accomplished in the following way: First, potential maps are reconstructed for each time frame, then the time series of maps is organized by lead to provide temporal electrograms. The time of activation for a given electrode is taken as the maximum \(-dV/dt\). Details of the reconstruction method can be found in our previous work.\textsuperscript{12}

Experimental Methods

The inverse epicardial solutions were verified using a human torso-shaped tank described in detail previously.\textsuperscript{12} The tank (Fig 1A) was molded from the torso of a 10-year-old boy, was filled with an electrolytic solution, and contained an isolated dog heart suspended with part of the anterior surface removed to reveal the heart and the rods. The rods project from the surface of the body, inward toward the heart. The rods were located along an imaginary line parallel to the atrioventricular groove and approximately halfway between it and the apex. Site 1 was located near the septum (see Fig 1B); site 2 was \(50\) mm to the anatomic left of site 1. The ventricle was paced at depths of 0 mm (ie, rhythms used.\textsuperscript{20} In this study (as in our earlier work of epicardial and endocardial reconstructions),\textsuperscript{8,10,12,21,22} we noninvasively compute and directly measure the epicardial potentials in the same heart. The measured epicardial potentials provide a high-resolution gold standard for evaluating the noninvasive reconstruction by direct comparison over the entire epicardial surface and over the entire cardiac cycle. Such detailed and rigorous evaluation is essential for correct development of reconstruction methods for both epicardial potentials (from body surface data) and endocardial potentials (from a noncontact catheter).\textsuperscript{21,22}

Fig 1B displays four overlapping views of the epicardium. Anatomic landmarks are displayed and identified beneath the plot, and two asterisks identify the needles that contain the pacing electrodes. Pacing was performed using electrode pairs along two needles in the left ventricle and an additional electrode pair on the right atrium near the sinoatrial node. The ventricular pacing sites were located along an imaginary line parallel to the atrioventricular groove and approximately halfway between it and the apex. Site 1 was located near the septum (see Fig 1B); site 2 was \(50\) mm to the anatomic left of site 1. The ventricle was paced at depths of 0 mm (ie,
at the epicardium), 3.2 mm, 6.4 mm, 9.6 mm, and 12.8 mm relative to the epicardial surface. Ventricular pacing was accomplished with current pulses of 2 ms duration and intensity just above threshold (generally 0.2 to 0.5 mA). Stimuli were delivered simultaneously to the ventricular pacing leads and to the right atrial pacing leads to prevent sinus beats from capturing the ventricles. Cycle length of pacing (the longest to capture the heart and exceed the sinus rate) was 380 ms.

Fig 2, modified from Taccardi et al.,1 is a schematic of the basic patterns of potentials and currents associated with point stimulation. With single-site pacing (from the position of the central asterisk), a region of negativity forms (inside the ellipse in the figure). Because of the preferential activation and the dominant electric sources along the fibers (shown as gray lines in the background), maxima (plus signs) form outside this negative region along the axis of the fibers. Notice that two corresponding minima (minus signs) form inside the negative region and that neither minimum coincides with the pacing site. This potential pattern is consistent with an equivalent source configuration of two opposite dipoles pointing from each minimum toward its corresponding maximum (ie, in the fiber direction).1 For epicardial pacing, the potential pattern is oriented along the epicardial fibers. For intramural pacing, the orientation of the epicardial maxima early after pacing reflects the fiber orientation at the depth of pacing (fibers rotate in the counter clockwise, CCW, direction with increasing depth relative to the epicardial surface).1

On the basis of these properties, we determine the pacing site to be at the center of the region of negativity in both the measured and the inverse-computed maps.

Results

Anterior Pacing (Epicardial and at Varying Intramural Depth)

Fig 3 (left column) shows the measured epicardial potential distributions for pacing sites at four different depths along the anterior needle. All maps in this figure display the potentials recorded 13 ms after the pacing stimulus. This time frame was chosen because it is the first with sufficiently high torso potential magnitude (above the noise) to show detailed patterns. Each of the four rows of maps represents a different depth of stimulation, from 0.0 mm (at the epicardium) to 9.6 mm deep relative to the epicardial surface. From the set of four overlapping views in Fig 1B, only the two views (anterior and left) that contain important information for this pacing protocol are shown. On these measured epicardial maps associated with each depth of stimulation, one can identify the intense minimum that reflects the position of the pacing site as well as the flanking maxima (one on
Measured Torso, Anterior Pacing Sites

Anterior

12 msec

Min = -400 μV; Interval = 100 μV

Depth

0.0 mm

Max/Min = 125/345 μV; Interval = 100 μV

3.2 mm

Max/Min = 65/475 μV; Interval = 98 μV

6.4 mm

Min = 290 μV; Interval = 40 μV

9.6 mm

Posterior

Figure 4. Measured torso potentials for anterior pacing sites. Measured body surface potentials for pacing sites at various depths along the anteriorly inserted needle of Fig 3. The body surface is displayed as two nonoverlapping views: anterior and posterior. Potentials are displayed as contour plots. Positive potentials are drawn with solid lines (first solid line is the zero line); negative potentials with dashed lines. Minima are identified with a minus sign (−), and their magnitudes as well as the contour intervals are printed (in microvolts) beneath the plots. Maxima are identified with a plus sign (+). The potentials are plotted for the same depths (provided to the right of the maps) and at the same instant in time (13 ms) as those of Fig 3.

depth. Notice in this figure that there is a minimum in the anterior superior region of the torso, reflecting the minimum seen on the anterior region of the heart. Notice also that for the pacing depths of 3.2 and 6.4 mm, there is a slight rotation of a maximum (solid contour line) in a CCW direction, as seen on the epicardium. Of course, it is impossible to make more than a general qualitative correlation between the locations of torso extrema and the site of myocardial activity.

Fig 3 (right column) displays the series of inverse-reconstructed epicardial maps that correspond with the measured epicardial maps of the same figure (left column). Epicardial potentials are computed noninvasively from the body surface data of Fig 4. The measured data of Fig 3 serves as a gold standard for evaluating the reconstructed maps. The errors in the positions of the reconstructed pacing sites (asterisks) relative to the corresponding sites in the measured maps are 4, 6, 2, and 2 mm (average, 3.5 mm) for pacing depths increasing from 0 to 9.6 mm, respectively. Note that in the measured maps of Fig 3, the estimated location of the pacing site varies slightly for different pacing depths. This implies that there is some uncertainty in locating the pacing site even from measured epicardial maps due to several factors. For example, the needle might not be exactly perpendicular to the epicardium, and the fibers could be tilted in an epicardial to endocardial direction. Importantly, the location errors of the noninvasively reconstructed pacing site are smaller than this uncertainty in the measured maps. Thus the noninvasive reconstruction does not add a significant error to the original uncertainty that exists in the invasively measured data. The errors in the positions of the maxima are 0 and 20 mm for epicardial pacing, 16 and 17 mm for pacing at 3.2-mm depth, 16 and 14 mm for pacing at 6.4-mm depth, and 0 mm for pacing at 9.6-mm depth. There is no clear posterior maximum seen at this deepest level. All errors are within the distance of one epicardial electrode position.

The magnitude of the reconstructed minimum increases somewhat with increasing depth, except for that reflecting the 9.6-mm depth of pacing, in which the minimum is reduced significantly. The magnitudes of the inverse-reconstructed potentials (Fig 3, right column) are different (usually smaller) from those of the measured potentials (left column), but the dependence on depth is similar. Note that the shape of the reconstructed regions of negativity also matches those of the measured regions of negativity, with a quasi-elliptic shape for pacing closer to the epicardium that becomes more circular for pacing closer to the endocardium. Most important, the orientation of the computed maxima displays the same pattern of CCW rotation with depth, as seen in the measured epicardial potentials, reflecting the fiber orientation at the level of the stimulation site.

Temporal Progression of Potentials for Anterior Epicardial PACing

Fig 5 shows the time progression of epicardial potential distributions after epicardial pacing. In Fig 3, epicardial potential distributions were displayed for anterior pacing at different intramural depths. In this figure, the pacing is
epicardial only, and each row of the figure displays a different time frame (identified in the center of the figure; time is measured in milliseconds after the stimulus). Consequently, the asterisk that identifies the pacing site early in the activation sequence (top row) remains in the same place in all other time frames even though the region of negativity and its center evolve over time.

In the left column of Fig 5, the measured epicardial potentials are displayed for 13, 23, 33, and 43 ms. The map for 13 ms is identical to the map in the first row (also 13 ms, epicardial pacing) of Fig 3. With time, both the spatial size and the potential magnitude of the negative region increase, and although the minimum shifts somewhat from the site of the initial pacing minimum and even fragments, it does remain in the same general location. The anterior maximum rotates with time in a CCW direction, reflecting penetration of the activation front into deeper layers and the progressive CCW rotation of fibers with depth. Notice that the region of positivity broadens, and that more than one local maximum is seen. The broadening of the positive region reflects the combined effects of activating both the superficial as well as the deeper layers of the myocardium. Fragmentation of the maxima may reflect nonmyocyte heterogeneities (eg, connective tissue or blood vessels), geometric properties, or an effect of the highly conductive blood in the ventricular cavity.

The noninvasively computed potentials, displayed in the right column of Fig 5, show very similar patterns. Again, the map in the first row is identical to that of the first row of Fig 3. The negative region expands, fragments, and grows in magnitude with time. The error in location of the pacing site at 13 ms is 4 mm. The anterior maximum rotates CCW and expands while the pacing minimum remains almost stationary as the activation proceeds from epicardium to endocardium. The errors in location of these maxima are 0, 0, 18, and 13 mm for each respective time frame. In both the measured and the computed potentials, the more posterior maximum shows somewhat of a tendency to rotate but not as clearly as the anterior maximum. The errors in locating each of the posterior maxima are 20, 27, 0, and 14 mm for each respective time frame.

Posterolateral Pacing (Epicardial and at Varying Intramural Depth)

All of the above figures have dealt with pacing from the anterior portion of the heart that is situated relatively close to the body surface. Figs 6 and 7 deal with pacing from the posterolateral portion of the heart. This is a more challenging situation for the noninvasive reconstruction procedure because of the large distance from the torso surface and consequential loss of detail and resolution in the body surface potential maps. (The torso potential map is not shown here because it contains even less detail than the map for anterior pacing, Fig 4.) Fig 6 shows a single time frame of epicardial potentials for four pacing sites at different depths within the myocardium (analogous to Fig 3); Fig 7 shows epicardial potential maps for the time progression of epicardial potentials as activation due to epicardial pacing spreads into the myocardial depth (four time frames, analogous to Fig 5, are shown).

In Fig 6, the left and posterior views of the epicardium are shown. In the measured (left) column, one can see a clear epicardial minimum reflecting the site of myocardial activation. Similar to anterior pacing, epicardial potentials reflecting posterolateral pacing show a CCW rotation of the more anterior maximum relative to the minimum as a function of...
pacing depth. The magnitudes of the extrema decrease monotonically with depth of pacing. In the computed potentials, the center of the quasi-elliptical negative region (asterisk) is identified for each pacing depth with an error of 6, 6, 4, and 9 mm (average, 6.25 mm) for pacing depths of 0, 3.2, 6.4, and 9.6 mm, respectively. The more anterior maximum is reconstructed with errors of 12, 12, 16, and 25 mm for each respective pacing depth. The more posterior maximum is difficult to characterize in both the measured and the computed epicardial potential maps (except for the maximum in the measured potentials seen for 9.6-mm depth pacing) because its region of positivity becomes fused with the positive region associated with right atrial activation. The magnitudes of the minimum and the anterior maximum decrease monotonically as the pacing site nears the endocardium. This behavior is observed in both the measured and inverse-computed epicardial potentials.

**Temporal Progression of Potentials for Posterolateral Epicardial Pacing**

Fig 7 follows the time progression of epicardial potential distributions for posterolateral epicardial pacing site. Note that in the top row, the left views (measured and computed) are identical to the corresponding left views plotted in Fig 6. In this figure, however, anterior and left views are displayed instead of the left and posterior views of Fig 6. This is done to capture the rotation through time of the more anterior maximum.

![Figure 7](image-url)

**Noninvasive Computed Potentials**

The maxima are reconstructed with location errors of 12, 0, 19, and 0 mm for each respective time frame. Note that the time required to achieve a comparable rotation is ~15 ms longer for posterolateral pacing than for anterior pacing (compare with Fig 5).

**Temporal Progression of Potentials for Anterior Intramural Pacing**

Figs 8 and 9 display epicardial potential distributions for intramural pacing sites along the anterior pacing needle.

![Figure 8](image-url)

![Figure 9](image-url)
Pacing in Fig 8 is accomplished from electrodes at a depth of 9.6 mm, close to (3.2 mm from) the endocardium. Note that the top row of this figure is identical to the bottom row of Fig 3. At 13 ms from the pacing stimulus, the maximum is in a mostly inferior position. With time, the anterior maximum expands and fragments as it does in Fig 5 (epicardial activation), but rotation occurs in a clockwise (CW) rather than in a CCW direction, reflecting the CW rotation of fibers as activation spreads mostly from subendocardium to epicardium. The pacing site (asterisk) is reconstructed to 2 mm from its measured location; the initial anterior maximum is reconstructed in its exact measured location. Note that in the bottom row (43 ms), the most superior maximum, which reflects the fiber rotation, is also reconstructed in its exact measured location. The more posterior region of positivity also undergoes a CW expansion and rotation, but this is much less prominent than the expansion/rotation of the anterior positive region in both the measured and the reconstructed potentials. At 23 ms, the anterior maxima are reconstructed 26 and 13 mm from their measured locations. Note, however, that the reconstructed inferior maximum (error of 26 mm) is associated with a secondary maximum located in the exact location of the corresponding measured maximum. At 33 ms, although the entire expanded region of positivity is reconstructed, only one individual maximum is seen. It is reconstructed 13 mm from its measured location.

Fig 9 shows the potentials for midwall pacing (6.4 mm—approximately equidistant from both epicardium and endocardium). The top row of this figure is the same as the third row of Fig 3. Again, in both the measured and reconstructed epicardial potentials, the maxima expand and rotate as they do in Figs 5 and 8, but the rotation here is both CCW and CW, reflecting fiber rotation in both directions relative to the midwall site of pacing. The pacing site is reconstructed to 2 mm of its measured position. At 13 ms, the reconstructed dominant anterior maximum is 16 mm from the measured dominant anterior maximum; it is in the exact location of the secondary maximum seen in the map of measured potentials. Careful inspection of the anterior positive region reveals that both maxima are actually present in both the measured and computed epicardial maps, suggesting that at 13 ms, two levels of fibers with sufficiently different orientations are already activated. At 23 ms, the measured anterior maxima are reconstructed in their exact locations. An additional maximum is reconstructed as well (just above the pacing asterisk). At 33 ms, the two anterior maxima are reconstructed at 13 (inferior) and 11 mm from their measured locations and at 43 ms, 11 (inferior) and 0 mm from their measured locations. The 43-ms frame also contains an additional reconstructed anterior maximum (most inferior) not seen in the measured map.

**Temporal Progression of Potentials for Anterior Endocardial Pacing**

All pacing-initiated activation presented up to this point (epicardial and intramural) has been reflected in epicardial potentials as a negative region flanked by positive extrema. Fig 10 demonstrates a phenomenon seen in both experimental work and model studies for epicardial potentials that are measured early after endocardial pacing. In this situation, instead of the intense epicardial minimum over the pacing site, there is a region of positivity. As time progresses, a minimum forms within that region of positivity and then the regions of positivity around that minimum rotate as they would during activation spread from a deep intramural pacing site (Fig 8). The initial positive region is seen in the measured and reconstructed potentials in the top row of Fig 10 (17 ms). The central minimum forms at 31 ms (second row), and the flanking regions of positivity rotate in a CW direction (third and fourth rows). The initial maximum at 17 ms is reconstructed 13 mm from its measured location. The minimum in the second row is reconstructed 15 mm from its measured location.

**Epicardial Electrograms and Breakthrough Times**

Fig 11 demonstrates the noninvasive reconstruction of epicardial electrograms that reflect intramural activation with the use of ECGI. In this figure, electrograms are reconstructed for the two epicardial electrode positions (identified as I and II in the figure) closest to the anterior pacing needle. Panel A shows the measured and the corresponding noninvasively reconstructed (computed) epicardial electrograms associated with increasing pacing depth (top to bottom). The vertical bar in each electrogram identifies the position of the steepest negative slope (maximal $-dV/dt$), which indicates when the activation wave front has reached the epicardium at that location ("breakthrough"). There is very good correspondence between the noninvasively computed and the measured electrograms and breakthrough times. Note that as expected, the position of the bar occurs progressively later in time with increasing depth of pacing. This point is amplified in panel B, which shows, for the same two electrodes, the time of breakthrough (ie, time of maximal $-dV/dt$) versus depth of pacing. Note also that with deeper pacing, the time to
The study presented here examines, in the same heart, the dependence of epicardial potential patterns on the three-dimensional architecture of the myocardium and the ability of ECG imaging to noninvasively reconstruct these patterns. The results demonstrate that ECGI can reconstruct, from body surface potentials, epicardial potentials that reflect not only the electrical activity near or at the epicardium but also within the depths of the myocardial wall. The measured potential patterns were correlated with histological findings and in theoretical simulations using bidomain models of cardiac tissue. As a general principle, epicardial potentials during intramural pacing are characterized by a central negative region and two flanking maxima (although at times only a single maximum is apparent in the epicardial recordings). The center of the negative region provides a close estimate of the location of the underlying pacing site. During the early stage of activation, the orientation of the maxima relative to each other and to the central minimum reflects the orientation of the myocardial fibers at the depth of pacing. At later stages, the rotation and expansion of the positive epicardial regions in time correlates with the helical spread of excitation as it travels through layers of rotating fibers (fiber direction undergoes CCW rotation with increasing depth relative to the epicardial surface). In addition, multiple maxima appear in the expanding positive areas. For endocardial pacing, a central positive epicardial region develops during early activation. In this study, all of these characteristics are reconstructed noninvasively from measured body surface potentials using ECGI. Discussion of these reconstructions for different locations and intramural depths of the stimulation site is provided below.

**Theoretical Basis: Equivalent Sources**

To assist in the interpretation of the reconstructed epicardial potentials, we provide certain basic concepts of source-field relations in the anisotropic myocardium. The activation front produced by point stimulation is nearly ellipsoidal, with its major axis along the fiber direction (the direction of high conductivity and fast velocity) and its minor axis perpendicular to the fiber direction (the direction of low conductivity and slow velocity). The electrical sources associated with this wave front are described within the framework of the oblique dipole layer model and can be represented as the superposition of a uniform double-layer that is normal to the activation front and a nonuniform, axial double-layer oriented along the fiber direction. Such source distribution is shown schematically in Fig 12A, in which a closed wave front is shown early after intramural stimulation. For a closed wave front, the uniform (normal) component does not contribute to the potential and the potential is determined solely by the axial component. The axial dipole strength increases as propagation becomes more axial (it is zero on the broad portion of the wave front and maximal on the narrow portion where propagation is along fibers, as indicated in Fig 12A by the increase in axial arrows towards the narrow portion). A consequence of these properties is that a simplified representation of the source by two equal and opposite axial dipoles located on the major axis of the wave front (bold arrows in Fig 12A and 12B) provides a reasonable approximation of the field at some distance away from the wave front. Note that this configuration was used in Fig 2 in “Methods” to provide the basis for locating the pacing site. Fig 12B shows the direction of current flow associated with this source configuration. The resulting epicardial potential distribution exhibits a central region of negativity (depicted with dashed contours in Fig 12B) above the pacing site and two peripheral maxima (indicated schematically by solid contours and plus signs) whose orientation reflects the fiber direction at the intramural depth of pacing.

For endocardial pacing (Fig 12C), the situation is different because the wave front is open and its rim is in contact with the intracavitary blood (a highly conductive medium). Under such
conditions, the uniform double-layer component that is normal to the wave front contributes to the potential field (its contribution is zero only when the wave front is closed). Moreover, the proximity of the myocardium-blood interface acts to augment the normal component and to attenuate the axial component (a phenomenon known as the Brody effect\(^27\)) that can be explained by introducing “image” sources to account for boundary conditions at this interface.\(^1\) As a result, the potential field is no longer dominated by the axial component. The normal component projects positive potentials intramurally and acts to diminish the axial component. The result is a typical epicardial potential distribution with a central negative region.

**Epicardial Potentials and the Intramural Depth of Pacing**

The results confirm earlier experimental results that the epicardial maxima flanking the negative region rotate as a function of stimulation depth (Figs 3 and 6), reflecting the fiber orientation at the depth of pacing. The ECG inverse method is able to reconstruct the epicardial potential pattern and its dependence on the intramural depth of the pacing site. In fact, for anterior pacing (Fig 3) the site of the minimum was computed to within 6 mm (average, 3.5 mm) of its measured position, and the sites of the maxima for the different pacing depths were all within 20 mm of their measured positions. With posterolateral pacing (Fig 6), for which one may have expected a poorer reconstruction because of the greater distance from the body surface, the results were similar, with the pacing site reconstructed no further than 9 mm (average, 6.25 mm) from its measured location and all except one of the maxima to within 16 mm of their measured locations (one was 25 mm from its measured location). Another phenomenon found here in both the measured and inverse reconstructed epicardial potentials is a general increase in the distance between the epicardial maxima and the minimum with increased pacing depth.

Although the absolute magnitudes of the epicardial maxima and minima are not reconstructed with great accuracy (the regularization of the reconstruction procedure acts to diminish the potential magnitudes), their dependence on the depth of pacing is preserved by the noninvasive reconstruction. For example, one expects that the magnitude of epicardial potentials early in activation will decrease with pacing depth simply because the epicardium is progressively further from the point of stimulation. This is seen in Fig 6 (posterolateral pacing) for both the measured and computed epicardial potentials. For anterior pacing (Fig 3) the trend is different and “atypical” with magnitudes of both maxima and minima first increasing with depth of pacing and then decreasing as the pacing site approaches the endocardium. The initial increase could be due to geometrical factors (e.g., an increase in the activation front that overcompensates for the increase in distance from the epicardium) or to conductivity factors, and this needs further clarification. The important result in the context of this study is that independent of the mechanism, this nonmonotonic behavior of epicardial magnitudes is preserved in the noninvasively reconstructed epicardial potentials (Fig 3).

In this study, the heart was suspended in the torso tank, exposing the epicardium to a conductive electrolytic solution that filled the tank. Consequently, epicardial pacing is influenced by the proximity of an interface with a highly conductive medium, similar to endocardial pacing. Since for epicardial pacing, propagation is from epicardium toward the endocardium, the normal component projects negative potentials epicardially and adds to the contribution of the axial component. The result is a typical epicardial potential distribution with a central negative region.

![Figure 12](image-url)
Temporal Evolution of Epicardial Potentials Reflects Intramural Spread of the Activation Front

The rotation of the epicardial potential maxima with time (Figs 5 and 7 to 10) is clearly observed in the measured epicardial potentials and is correctly reproduced in the noninvasively computed epicardial potentials. For the case of epicardial pacing (Figs 5 and 7), the regions of epicardial positivity grow and the maxima rotate in the CCW direction as the activation front penetrates deeper into myocardial layers, reflecting the CCW rotation of fibers with depth.5 For anterior epicardial pacing (Fig 5), the anterior maximum spreads out and actually fragments by 43 ms. This fragmentation is captured in the noninvasively computed potentials as well and is consistent with earlier experimental findings.5 The reason for maxima fragmentation needs further clarification. It is possible that the main anterior maximum, identified by a plus sign, reflects activation of deeper layers, whereas the other maximum reflects continued activation of layers closer to the epicardium. However, this hypothesis is not supported by theoretical simulations that reproduce the expansion of positive epicardial regions in time but not the maxima fragmentation.24 More recent theoretical simulations, performed in our laboratory, reproduce the fragmentation of epicardial maxima as activation spreads intramurally.25 The model used in these simulations is a bidomain model of ventricular activation in a whole heart that contains the intracavitary blood and represents the variable thickness of the ventricular wall (ie, tapering from base to apex). Without the blood and tapering, the regions of positivity expand smoothly, without fragmentation. This suggests a role for the intracavitary blood and for the myocardial tapering in the maxima fragmentation. Other anatomic factors can play a role in the fragmentation of the epicardial maxima, including discontinuities introduced by connective tissue septa or by the presence of blood vessels in the wall. As stated above, determination of the contribution of these various factors to the appearance of multiple epicardial maxima awaits further experimental and theoretical investigation. For subendocardial pacing (Fig 8), the epicardial maxima rotate in a CW direction, reflecting the CW rotation of the fibers as the activation front propagates from endocardium toward the epicardium. For midwall pacing (Fig 9), the wave front propagates both toward the epicardium and toward the endocardium. This results in a “double rotation” of the epicardial maxima in both CW and CCW directions, reflecting CW rotation of the fibers from midwall to epicardium and CCW rotation of the fibers from midwall to endocardium. Importantly, these dynamic patterns are well reconstructed noninvasively from the torso potential data, and the temporal progression of the computed and measured epicardial potentials is very similar. Endocardial pacing (Fig 10) generates a somewhat different epicardial potential distribution than midwall or epicardial pacing. Instead of the typical minimum over the pacing site, an early potential maximum develops. As discussed in the beginning of this section (Fig 12 and related text), this is a consequence of the intracavitary blood and its effect on the pattern of current flow generated by the nearby activation front. As the activation front propagates away from the endocardium, an intense minimum develops within this positive epicardial region (Fig 10, 31 ms) and the newly formed flanking maxima rotate in a CW direction as expected. Again, this temporal progression is faithfully reconstructed in the noninvasively computed epicardial potentials. Temporal epicardial electrograms (Fig 11) are also faithfully reconstructed from the body surface data. One notices not only the progressively later time of breakthrough for increasing depth of pacing (vertical bars in panel A and stars in panel B) but also that this progression is not linear and levels off as the pacing site nears the endocardium. This phenomenon is apparent in both the computed and the measured breakthrough times and has been seen in other studies of measured epicardial electrograms for various pacing depths.26 It seems to indicate that there is faster transmural wave front propagation closer to the endocardium than in the more superficial layers. The reason for this behavior is not entirely clear and requires future investigation; however, it might reflect greater obliqueness of myocardial fibers in layers close to the endocardium.21

Significance of the Study

In a previous study, we demonstrated the ability of ECGI to reconstruct epicardial potentials, electrograms, and isochrones noninvasively from measured body surface potential data.12 The earlier study was limited to epicardial pacing and epicardial activation. The present study extends the approach to electrical events in the depth of the ventricular wall. As discussed above, epicardial potentials during ectopic focal excitation reflect the direction of myocardial fibers through which excitation is spreading. Taking advantage of this relation, the noninvasively reconstructed epicardial potentials can be used to characterize activity in the depth of the myocardium. As demonstrated in this study, the center of the epicardial region of negativity in the early stages of activation provides the location of the focal activation site, whereas the orientation of the potential maxima reflects the fiber orientation at the intramural depth of this site. Consequently, from the reconstructed epicardial potential pattern together with knowledge of the fiber orientation pattern across the ventricular wall it is possible to estimate, noninvasively, the location and depth of a site (or sites) of ectopic activity and of initial myocardial activation. The results also demonstrate that noninvasive ECGI can provide information on the transmural spread of excitation by reconstructing the rotation of epicardial maxima that reflects propagation across the wall. CCW rotation reflects epicardial-endocardial spread, CW rotation reflects endocardial-epicardial spread, and the presence of both CCW and CW rotation indicates helical spread in both transmural directions. This temporal evolution of the reconstructed epicardial potentials provides another clue to the depth of initial activation: Pure CCW rotation implies that the initiation site is close to the epicardium; CW rotation only (or an initial epicardial maximum followed by the development of a minimum with flanking maxima that then rotate CW) implies that the site is close to the endocardium; and double rotation in both CCW and CW directions indicates that the site is intramural. In addition, the time of epicardial activation (breakthrough) as detected in the
temporal electrograms (Fig 11) also provides an indication of the pacing depth.

The ability to estimate the locations and depths of sites of initial activation suggests a potential use of noninvasive ECGI in guiding interventional procedures (eg, ablation). Its ability to obtain information on the transmural spread of activation in a noninvasive fashion is also of potential clinical importance because in general arrhythmogenic reentrant activity can involve three-dimensional transmural propagation, and the reentry pathway is not confined to the epicardial or endocardial surfaces of the ventricular wall. The results reported in this study were obtained with the use of normal hearts in the absence of structural heart disease. In the next stage of development, ECGI will be evaluated in terms of its ability to reconstruct potentials, electrograms, and isochrones in the presence of infarction and during reentrant ventricular tachyarrhythmias.

The inverse procedure requires knowledge of the heart-torso geometry. In the experimental torso tank setup, the heart is accessible so that the geometry of the epicardium and of the torso surface (including body surface electrode positions) can be measured directly. In the clinical setting, this information must be obtained noninvasively. In preparation for the clinical implementation of ECGI, we have begun development of a computed tomographic–based method that noninvasively determines both the body surface electrode positions and an epicardial envelope that closely encloses the heart. Simpler imaging modalities (eg, radiography in combination with echocardiography) will be investigated as well. The same noninvasive imaging methods could provide information on the geometry of internal torso structures (inhomogeneities, eg, lungs) that affect the electric field. This will permit us to incorporate such effects into the ECGI reconstruction procedure. It should be noted, however, that previous studies have indicated that torso inhomogeneities affect only epicardial potential magnitudes and not the potential patterns or the sequences of epicardial activation (isochrones). In addition to noninvasive determination of geometry, clinical application of ECGI will benefit from computational efficiency that reconstructs epicardial potentials in close to real time. We have optimized our computational scheme to the point where it now runs on a local workstation (instead of a CRAY supercomputer). After initial general computation that requires ~1 minute, each epicardial map (single time frame) can be computed in ~60 ms.

The principle that noninvasive ECGI can provide information on intramural electrical processes is not limited to myocardial activation. Intramural repolarization processes are also reflected in epicardial potentials that can be reconstructed noninvasively from body surface potential data. This is an important property because nonuniformities of repolarization are associated with the development of cardiac arrhythmias. Intramural nonuniformity of repolarization can result from various physiological and pathophysiological conditions. One example is the recently discovered presence of transmural heterogeneity of cellular electrical properties. Importantly, a unique population of midmyocardial cells (M-cells) has been described and is characterized by a longer action potential duration (APD) than epicardial or endocardial cells. M-cell APD prolongs much more upon reduction in rate (eg, bradycardia or after a pause), in response to class III antiarrhythmic drug application, and possibly due to ion-channel mutations associated with the long QT syndrome. Because epicardial potentials are determined by the intramural spatial gradients of the transmembrane potential, such APD heterogeneities are reflected in the epicardial potential distribution. By reconstructing the epicardial potentials using ECGI, such heterogeneities could be evaluated noninvasively. It is well established that heterogeneity of APD (or “dispersion of repolarization”) creates conditions for the development of unidirectional block and reentry and that the risk of arrhythmogenesis is related to the degree of intramural heterogeneity. The ability to obtain, noninvasively, information on intramural heterogeneity could provide a basis for identifying patients at risk and for evaluating the effects of interventions (eg, antiarrhythmic drug treatment) on the degree of heterogeneity and the consequential vulnerability to arrhythmogenesis.

Similar to the potential clinical usefulness of noninvasive ECGI in the context of intramural activity, one can envision its potential as an experimental tool for the study of cardiac excitation and arrhythmias that involve deep myocardial layers. This could include studies of intramural focal arrhythmias or transmural reentry in the nonanesthetized, intact animal under physiological conditions. It could also be used for noninvasive studies of arrhythmogenic activity that involve intramural excitation in patients, in whom mechanisms and characteristics of arrhythmias might be very different from those in animal models, or where adequate animal models do not exist.

Acknowledgments

This study was supported by NIH-NHLBI grants HL-33343 and HL-49054 (Dr Rudy) and HL-43276 (Dr Taccardi). Additional support was provided by awards from the Nora Eccles Treadwell Foundation and the Richard A. and Nora Eccles Harrison Fund for Cardiovascular Research. We thank Younild Vyhmeister, BS, for her assistance with the experiments.

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Howard S. Oster, Bruno Taccardi, Robert L. Lux, Philip R. Ershler and Yoram Rudy

Circulation. 1998;97:1496-1507
doi: 10.1161/01.CIR.97.15.1496

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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