Effect of Myocardial Fiber Direction on Epicardial Potentials

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Background Understanding the relations between the architecture of myocardial fibers, the spread of excitation, and the associated ECG signals is necessary for addressing the forward problem of electrocardiography, that is, predicting intracardiac and extracardiac ECGs from known intracardiac activity. So far, these relations have been studied experimentally only in small myocardial areas. In this study, we tested the hypothesis that potential distributions measured over extensive epicardial regions during paced beats reflect the direction of superficial and intramural fibers through which excitation is spreading in both the initial and later stages of ventricular excitation. We also tried to establish whether the features of the epicardial potential distribution that correlate with fiber direction vary as a function of pacing site, intramural pacing depth, and time elapsed after the stimulus. An additional purpose was to compare measured epicardial potentials with recently published numerical simulations depicting the threedimensional spread of excitation in the heart muscle and the associated potential fields.

Methods and Results The hearts of 18 mongrel dogs were exposed and 182 to 744 unipolar electrograms were recorded from epicardial electrode arrays (2.3×3.0 to 6.5×6.5 cm). Hearts were paced at various intramural depths through an intramural needle. The overall number of pacing sites in 18 dogs was 241. Epicardial potential distributions, electrographic waveforms, and excitation time maps were displayed, and fiber directions in the ventricular wall underlying the electrodes were determined histologically. During the early stages of ventricular excitation, the position of the epicardial maxima and minima revealed the orientation of myocardial fibers near the pacing site in all cases of epicardial and intramural pacing and in 60% of cases of endocardial or subendocardial pacing. During later stages of propagation, the rotation and expansion of the positive areas correlated with the helical spread of excitation through intramurally rotating fibers. Marked asymmetry of potential patterns probably reflected epicardial-endocardial obliqueness of intramural fibers. Multiple maxima appeared in the expanding positive areas.

Conclusions For 93% of pacing sites, results verified our hypothesis that epicardial potential patterns elicited by ventricular pacing reflect the direction of fibers through which excitation is spreading during both the initial and later stages of propagation. Epicardial potential distributions provided information on the site of origin and subsequent helical spread of excitation in an epicardial-endocardial, endocardial-epicardial, or double direction. Results were in agreement with previously published numerical simulations except for the asymmetry and fragmentation of the positive areas. (Circulation. 1994;90:3076-3090.)

Key Words • potentials • electrocardiography • electric stimulation • anisotropy • mapping

When an excitation wave front initiated by point stimulation propagates through atrial or ventricular heart muscle, it assumes an oblong shape that reflects faster conduction along the direction of myocardial fibers.1-4 ECG waveforms and potential distributions generated by the spreading wave front are also affected by fiber direction. Previous studies showed that in the initial stages of propagation, when excitation spreads through quasi-parallel fibers, ECG R waves and positive potentials are recorded primarily from those regions toward which excitation propagates along fibers.3-5 Potential distributions elicited by point stimulation showed a central negative area surrounding the pacing site and, just outside the negative area, two positive regions, each of which contained a positive maximum (site where the potential value was positive and higher than that measured at all surrounding sites3-7) (see Fig 2D). The axis joining the two maxima was always nearly parallel to the direction of the fibers near the pacing site. Thus, potential patterns elicited by point stimulation revealed both the site of origin of excitation (center of negative area) and the direction of the nearby fibers. These effects have been observed in superfused myocardial laminae,3 on the epicardial and endocardial surfaces,4-7 and in volume conductors surrounding an isolated heart.8 The counterclockwise (CCW) rotation of fiber direction from epicardium to endocardium9-11 further affected wave front shapes and potential distributions both on the epicardium and in the ventricular walls.5,6,12-14

On the basis of the above studies, we made the hypothesis that epicardial potential patterns recorded in the initial stages of a paced beat, when excitation spreads through quasi-parallel fibers, would reveal the orientation of the fibers near the site of pacing, even when the pacing site was intramural or subendocardial and, importantly, even before the arrival of excitation at the epicardial surface. A second hypothesis to be tested was that in later stages of ventricular excitation, intramural propagation through rotating fibers would also affect epicardial potentials in a recognizable way. To test both hypotheses, we recorded epicardial potentials from the ventricular surface of exposed dog hearts.
during ventricular pacing, and we tried to identify those features of the potential distribution (e.g., number and location of potential extrema, voltage of extrema, shape of equipotential lines) that best correlated with the direction of the myocardial fibers through which excitation was spreading. We also tried to establish whether the features that best correlated with fiber direction varied as a function of pacing site, intramural pacing depth, and time elapsed after the stimulus.

Our initial, tentative prediction, based on past studies, was that for all pacing depths, epicardial potentials would show a central negative area, revealing the epicardial projection of the pacing site, and two peripheral maxima indicating the direction of the fibers near the pacing site. This information cannot be obtained from epicardial excitation time (isochrone) maps, which depict the spread of excitation only after excitation has reached the ventricular surface. We also expected that the magnitude of the epicardial potentials would be lower for deep wave fronts, in view of the greater distance between the current sources (wave front) and the measuring site (epicardium). Finally, we tentatively expected that during later stages of ventricular excitation, propagation from epicardium to endocardium, through CCW-rotating fibers, would produce a progressive CCW rotation of the epicardial potential pattern during the QRS interval and endo-epicardial propagation would produce a clockwise (CW) rotation. Verification of the second hypothesis would show that epicardial potentials reveal whether intramural propagation is occurring in an epicardial-endocardial or endo-epicardial direction or in both directions (from a midwall site). Preliminary experimental studies\(^{5,14}\) and model simulations\(^{15}\) support these predictions.

An additional purpose of the study was to provide a detailed description of epicardial potentials, as affected by fiber directions, for a number of different excitation sequences. Knowledge of these patterns is necessary for addressing the forward problem of electrocardiography (predicting ECGs and potential distributions from known intracellular sources). Epicardial potential maps help in solving the forward problem because they simultaneously show (1) the epicardial current sources (wave front), (2) the potential distribution generated by the sources, and (3), indirectly, the relevant electrograms. Electrograms are, in fact, just local samples of the potential distribution as it varies during the cardiac cycle. The ultimate solution to the forward problem can be provided only by mathematical simulations,\(^{12,15-17}\) but the accuracy of the simulations can be evaluated only by comparison with measured data of the type collected in this investigation. These aspects of our study will be addressed in the “Discussion.”

To achieve the purposes stated above, we recorded 182 or more epicardial electrograms while pacing the left or right ventricle of exposed dog hearts at various intramural depths. The recorded data were used to display potential maps and excitation time (isochrone) maps. Ventricular pacing rather than sinus rhythm was used to create wave fronts that would start from a known site, spread for several milliseconds through fibers with constant, known orientation near the pacing site, and subsequently reach intramural regions where fiber direction rotated in a known way. Fiber directions in myocardial regions of various sizes were determined histologically in 15 dogs.

**Methods**

Eighteen mongrel dogs weighing 10 to 25 kg were anesthetized with 30 mg/kg IV sodium pentobarbital. Additional amounts of anesthetic were administered during the experiments as needed. The heart was exposed through a left thoracotomy (14 dogs) or a longitudinal sternotomy (4 dogs) and suspended in a pericardial cradle. In each experiment, unipolar epicardial electrograms were recorded with one of four different electrode arrays containing 182, 250, 525, or 744 electrodes, respectively (Fig 1). The arrays were fabricated by fastening 0.002-in or 0.003-in silver wires to a piece of nylon stocking as described by Arisi et al.\(^ {16}\) The arrays were applied to the right or left ventricular epicardium as shown in Fig 1. The nylon cloth had a thickness of 100 μm and was kept moist by addition of small amounts of saline every 15 minutes. The total distance between the electrodes and the outermost (subepicardial) myocardial fibers was 200 to 300 μm, of which 200 μm represents the thickness of the visceral pericardium\(^ {19}\) and 100 μm represents the thickness of the moist cloth. One to six intramural needles carrying 15 or 10 electrodes each, 1.0 or 1.6 mm apart, were inserted through the nylon cloth into the left or right ventricular wall with the purpose of delivering pacing stimuli at various intramural depths. Approximate positions of 34 pacing needles in all experiments were summarized in Fig 1. The total number of pacing sites was 241, distributed among the 18 dogs. Unipolar cathodal or bipolar stimuli were delivered through a single terminal or a pair of adjacent needle terminals. Stimulus duration was 2 milliseconds, and stimulus strength was just above threshold. The return electrode for unipolar pacing was a steel needle inserted into the chest wall. In most cases, the right atrium was also paced, 1 to 90 milliseconds after the ventricular stimulus, to prevent atrial captures. The pacing cycle length was 330 to 400 millise-
Fig 2. A. Position of 525-electrode array (40 × 48 mm) on right ventricle of dog 16. Double arrow indicates epicardial fiber direction near the pacing site. B. Distribution of equipotential lines on epicardial area explored by electrode array at 9 milliseconds after the stimulus. Internal rectangle delimits area shown at higher magnification in D. Star indicates pacing site. Negative lines are dashed, positive lines are continuous. Zero line is the first continuous line. Straight dashed line indicates the direction of epicardial fibers near pacing site. Values above panels B and D indicate time in milliseconds after the stimulus and potential values of negative and positive extrema in millivolts, followed by potential step between adjacent equipotential lines. C. Excitation time (isochrone) map. First isochrone line near the stimulus site was traced at 6 milliseconds after the stimulus. Time step between isochrones is 3 milliseconds. D. Potential distribution in area delimited by rectangle in B shows dense array of negative lines outlining the wave front. Numbers indicate voltage of two potential maxima and two minima. E. The ellipse diagrammatically represents a wave front elicited by epicardial stimulation. Two potential maxima near the narrow ends of the wave front and two minima inside the wave front schematize the linear quadrupole model. Four current lines (curved arrows) describe the flow of extracellular currents from the two maxima toward the minima.

Results
Epicardial Potentials in the Initial Stages of Ventricular Excitation (5 to 15 Milliseconds After the Stimulus)

Epicardial pacing produced well-defined excitation potential patterns at 5 to 8 milliseconds after the stimulus. For deeper pacing, well-defined patterns emerged from the background noise between 6 and 14 milliseconds from the stimulus. The delay increased with increasing pacing depth.

Epicardial Pacing

On both ventricles, epicardial pacing produced potential patterns with negative potentials surrounding the pacing site (−5 to −30 mV) and two positive maxima located along a straight line that passed near the pacing site (Fig 2B and 2D, sites at 3.16 and 2.91 mV). The two maxima had approximately equal voltages, ranging between 2.5 and 6 mV in different experiments. At 7 to 9 milliseconds after the stimulus, an array of roughly elliptical, densely packed, negative equipotential lines became clearly recognizable in the negative area (Fig 2B and 2D). This array outlined the intersection of the wave front with the epicardial surface. Its major axis was always parallel to fiber direction near the pacing site (dashed straight line in Fig 2B). Its position, shape, and orientation were similar to the position, shape, and orientation of the isochrone line corresponding to the same time instant within the limits of our space resolution. (Fig 2C). The close correspondence between isochrone lines and the array of negative equipotential lines could also be observed during later stages of propagation. From now on, we will use the term “wave front” to indicate either the isochrone line or the array of densely packed equipotential lines that outlined the wave front.

The potential distribution observed outside and inside the wave front in the initial stages of propagation (Fig 2D) was similar to that produced by two collinear dipoles at 180° from one another (linear quadrupole) as...
observed by Macchi et al.\textsuperscript{20} For a complete description of this simplified model, see Colli Franzone et al.\textsuperscript{21} Fig 2E schematizes an elliptical wave front and two dipoles at 180° that are located near the narrow ends of the wave front and represent the linear quadrupole model. The two plus signs and the two minus signs represent the two potential maxima and minima, which are also visible in the real distribution (Fig 2D, sites at 3.16 and 2.91 mV and -17.98 and -16.24, respectively). Some of the currents (arrows) flow from the maxima toward the resting tissue outside the wave front, then enter the excited region by crossing the wave front, and reach the two potential minima inside the wave front. It must be pointed out that this quadrupole model disregards an important feature of the potential distribution, namely, the continuous extracellular potential jump (15 to 40 mV) across the entire length of the elliptical wave front. This jump is revealed by the dense array of elliptical negative lines in Fig 2D. Despite this limitation, the model is useful as a simplified solution to the forward problem in the early stages of propagation of a paced beat because it approximately simulates the potential distributions in the conducting media outside the wave front (see “Discussion”).

During the initial 5 to 10 milliseconds after an epicardial stimulus, the two potential maxima either faced the narrow ends of the elliptical wave front (that is, those portions of the wave front that propagated along fibers) or, more often, were slightly shifted CCW (Fig 2B). The amount of CCW shift ranged between 0° and 15° at 10 milliseconds after the stimulus. The shift was also observed in model simulations\textsuperscript{15} and can be explained by considering that at 5 to 10 milliseconds, the wave front had reached an intramural depth of 2 or 3 mm and therefore was spreading through fibers whose direction underwent some degree of CCW rotation from the epicardium to the deepest point of the wave front. The position of the epicardial maxima reflected the average direction of the fibers through which the wave front was spreading at 5 to 10 milliseconds. The positive equipotential lines surrounding the two maxima had an oval, elongated shape and were slightly tilted CCW relative to the major axis of the wave front (Fig 2B).

Thus, in the early stages of an ectopic beat elicited by epicardial pacing, we observed four electrophysiological indicators of fiber direction near the pacing site: the orientation of the early isochrones, the orientation of the elliptical negative lines outlining the wave front, the orientation of the line joining the two maxima, and the elongated shape of the positive equipotential lines. When fiber direction varied in the area explored, pacing at different epicardial sites produced potential distributions in which the four indicators revealed the varying fiber directions. Differences of up to 75° were observed within the area explored. Thus, the distribution of fiber directions at the epicardium could be detected by multiple pacing, without histological examination. Previous work showed that a local necrosis of the superficial fibers in a very small epicardial region (<1 cm²) was revealed by the disappearance of the potential maximum in the necrotic area.\textsuperscript{5}

The distributions of potentials and currents described in Fig 2 are similar to those observed by Spach et al\textsuperscript{14} in a superfused myocardial lamina (see also Roberge et al\textsuperscript{22}) except for the absence of a small positive ridge lining the portions of the wave front that propagated across fibers. Similarly, the electrograms we recorded from the areas toward which the wave front propagated across fibers did not show the slight positive-trending hump preceding the intrinsic deflection, as described by Spach et al. We attributed these differences to different experimental conditions: (1) our measurements were taken at 200 to 300 μm from the surface of the active fibers (see “Methods”) (at distances >50 μm, in the experiments of Spach et al, the positive ridge was greatly attenuated and almost nonmeasurable); (2) in the study by Spach et al, the extracellular currents going from the positive ridge toward the resting area could reach the current sinks inside the wave front by flowing through the conducting volume above and below the elliptical wave front. These pathways were not available to the currents in our experimental conditions, because our potential distributions were measured at the insulting boundary of the preparation and the wave front was a closed, semilippoid surface. Our results are similar to those computed by Geselowitz et al\textsuperscript{23} for a semilippoid wave front, but here again, their simulated conditions were not identical with ours.

The electrograms (EGs) recorded from the epicardial electrodes at a distance of a few millimeters from the pacing needle showed initial small R waves only in those regions toward which excitation moved along fibers (Fig 3A, EGs 1 and 4) and totally negative waveforms (EGs 7 and 10) in the regions toward which excitation moved across fibers, as previously described by Corbin and Scher.\textsuperscript{4} Furthermore, we found initial R waves of increasing magnitude over a distance of several centimeters along fibers on both sides of the pacing electrode (EGs 2, 3, 5, and 6). Electrodes toward which excitation moved across fibers recorded entirely negative electrograms over distances of at least 10 mm on each side of the pacing needle (EGs 7 through 12). At a greater distance, a late positive wave appeared, but the initial portion of the electrograms was always negative-trending for as long as 30 or 40 milliseconds (EGs 13 and 14). Thus, the area surrounding the pacing electrode could be divided into four sectors, two of which showed initial R waves, while the other two showed Q waves. The magnitude of the R waves in the first two sectors increased as a function of distance from the pacing needle, finally reaching 10 mV or more near the border of the sock (EG 3). Electrograms recorded from the pacing needle at increasing intramural depths after epicardial pacing were totally negative in all experiments (Fig 3B), confirming that excitation spreading across fibers did not generate initial R waves in our experimental conditions.

**Intramural and Subendocardial Pacing**

As mentioned above, intramural pacing gave rise to well-defined potential distributions on the epicardium at 6 to 14 milliseconds after the stimulus. Thus, for deep pacing, measurable potential distributions appeared on the epicardial surface well before the arrival of excitation at the epicardium. Fig 4C through 4F depicts epicardial potentials recorded 14 milliseconds after intramural pacing at 6-, 9-, 11-, and 13-mm depth, respectively, in dog 2. The corresponding epicardial breakthrough times were 19, 29, 34, and 37 milliseconds.
Thus, these potential patterns were the epicardial expression of deep intramural events that occurred before excitation reached the epicardial surface.

To describe the potential distributions, we will consider intramural and subendocardial pacing separately. Patterns produced by intramural pacing, down to 2 or 3 mm from the endocardium, verified one of our initial predictions, that is, showed a central negative minimum located near the epicardial projection of the pacing site and two peripheral maxima that rotated CCW as a function of pacing depth (Fig 4). The amount of rotation correlated well with the rotation of fiber direction at corresponding depth, as discussed in the following section. One unexpected finding was that in all experiments, for pacing depths of ≥6 mm, the two maxima became manifestly unequal in strength. The weaker of the two maxima was consistently located on the right side of the pacing site for an observer looking at the heart from the outside. Also, the weaker maximum tended to move away from the pacing site and in some cases disappeared. This behavior was better observed on the left ventricle. A typical example is shown in Fig 4C (6-mm pacing depth). Here, the potential maximum on the left side of the panel had a magnitude of 1.81 mV, whereas the other maximum, on the right side, was only 0.36 mV (a ratio of 1 to 5) and was located at a greater distance from the pacing needle than was the left maximum (19 versus 15 mm). A similar pattern is observable in Fig 4D (9 mm), where the voltage of the two maxima was 1.42 and 0.56 mV, respectively, and the distances of the two maxima from the pacing needle were 19 and 31 mm. Total disappearance of the right maximum for a pacing depth of 8 mm is shown in Fig 5A (dog 1).

We tentatively attributed the asymmetrical behavior of the two maxima to the fact that in the thickness of the ventricular walls, the direction of myocardial fibers is not parallel to the epicardium but points slightly inward from epicardium to endocardium and from left to right (for an observer looking at the heart from the outside; see Fig 9 in Streeter9). The obliqueness of the fibers would cause deep pacing to produce an ellipsoidal wave front with one narrow end pointing slightly toward the epicardium and to the left of the observer. This would produce strong and well-defined positive formations on the epicardium on the left of the pacing needle (left maximum in Fig 4C through 4F). The opposite narrow end of the ellipsoid would point slightly toward the endocardium and to the right and therefore would project weaker potentials on the epicardium on the right of the pacing needle (right maximum in Fig 4C through 4F). This interpretation is tentative but is supported by two preliminary experiments (not shown) in which we paced the left ventricle intramurally near the AV border. In these experiments, the right maximum, not the left one, was stronger. This finding is consistent with the reversed obliqueness of the intramural fibers near the AV border (see Fig 9 in Streeter9).

When the right maximum disappeared for deep pacing (Fig 5A), it became impossible to measure the orientation of the axis joining the two maxima for these pacing depths to compare maxima rotation with fiber rotation. In these cases, we measured the rotation of the single remaining maximum, ie, the left maximum, around the pacing site as a function of pacing depth.

Unlike epicardial and intramural pacing, subendocardial pacing produced a variety of potential patterns at the epicardium. In 40% of the cases, the potential pattern was similar to that observed for epicardial or intramural pacing and showed a central minimum and one or two peripheral maxima, whose position revealed the direction of the endocardial fibers (Fig 4F). In 20% of the cases, the pattern was totally different but still showed a good correlation with fiber direction. It showed a central oblong mountain of positive poten-
Fig 4. Top left panel shows distribution of 250 electrodes on epicardial electrode array. LAD indicates left anterior descending coronary branch. Separation between electrodes was 2.5 mm in central area, 5 mm elsewhere. A thorough F. Epicardial potential distributions recorded from dog 2 at 14 milliseconds after stimulus delivery at intramural depths indicated in titles of panels. Site of insertion of pacing needle indicated by star. Other explanations as in Fig 2. Heavy dashed lines depict the axis joining the two maxima and show the counterclockwise rotation of the axis for increasing pacing depths. Top right panel summarizes the rotation of the axis. Length of lines indicates the distance between maxima for all pacing depths.

Potential, whose major axis was parallel to the direction of the subendocardial fibers (Fig 5C). At the top of the mountain, a single potential maximum indicated the epicardial projection of the pacing site. No central negative area was present, but two peripheral regions of low negativity (−0.24 mV) were observed near two opposite corners of the electrode array, at 90° from the major axis of the elongated positive lines (Fig 5C). This pattern was observed in 3 of 4 needle insertions in the right ventricle and in 2 of 21 left insertions. It lasted for 5 to 15 milliseconds and then changed into the usual distribution with one central minimum and two peripheral maxima (Fig SD). Thus, in 60% of cases of endocardial pacing, epicardial potentials indicated both the site of pacing and the direction of the subendocardial fibers. In the remaining 40% of the cases, we were unable to establish a clear correlation between the potential pattern and fiber direction. Epicardial maps exhibited a single rounded mountain of positive potential, whose position relative to the pacing needle varied in different cases, and no clear-cut minimum. Possible explanations for this behavior will be given in the “Discussion.”

A feature common to all cases of endocardial pacing was the increase in epicardial positivity relative to intramural pacing. As mentioned in the “Introduction,” we expected the voltage of the epicardial maxima to decrease monotonically with increasing pacing depth because of the increasing distance between the current sources (wave front) and the epicardium. The voltage of the maxima did indeed decrease as a function of pacing depth when the pacing site was intramural, but when the pacing site approached the endocardium, the voltage stopped decreasing and started increasing. Two examples of this behavior are shown in Fig 6A (dog 2, left ventricle, same experiment as in Fig 4) and 6B (dog 11, right ventricle). The knee of the voltage/depth function invariably occurred when the pacing depth was at 2 to 3 mm from the endocardium. In five needle insertions, the tip of the needle did not reach the subendocardial level; accordingly, the voltage of the maxima showed no increase at any pacing depth (Fig 6C).

The increase in the voltage of the maxima was just one aspect of the general increase in epicardial positivity that occurred in all cases of subendocardial pacing. When the pacing depth approached the endocardial level, the epicardial area covered by positive potentials became larger and the central negative area shrank (Fig 4F, 13 mm) or was replaced by a positive minimum or saddle (not shown) or by a positive mountain, as in Fig 5C. These findings were consistent with previously published numerical simulations (see Fig 6 in Reference 15) and can be explained by the “oblique dipole layer” model of the wave front (see “Discussion”).

Correlation Between Transmural Rotation of Fibers and Rotation of the Maxima

A total of 143 myocardial blocks from 15 hearts underwent histological study. Eleven blocks from the left ventricle and 4 blocks from the right ventricle contained pacing needles that successfully paced at all intramural depths, from epicardium to endocardium, and produced measurable rotations of the maxima for all pacing depths. In the left ventricle, total rotation of the maxima when the pacing site moved from epicardium to endocardium was 105±16.080° (SD, n=11), and total transmural rotation of the fibers was 109.918±11.864°, n=11. In the right ventricle, total rotation of the maxima was 66.500±32.306° (n=4), and total transmural rotation of the fibers was 71.750±32.325°. The correlation coefficient between total rotation of the positivity and total transmural rotation of the fibers for the same 15 myocardial blocks was .926. These data indicate a good correlation between the total rotation of the epicardial positive areas when the pacing site moved from epicardium to endocardium and the total transmural rotation of the fibers in the corresponding myocardial blocks. In all 111 left ventricular blocks, total transmural fiber rotation was 103.396±21.704°. In the right ventricular wall (32 blocks), total rotation was 74.688±23.966°. The difference between the two ventricles was highly significant (P<.0001). Our figures for fiber
Fig 5. A, Epicardial potential distribution at 15 milliseconds after pacing left ventricular wall at 8 mm intramural depth in dog 1. Same position of electrode array as in Fig 4. Site of insertion of pacing needle is indicated by star, Vertical bar intersecting the ECG at bottom of panel indicates the time instant to which the potential map is related. Comparison with Fig 4D, in which the pacing depth was 9 mm, shows that here the right maximum is missing. A relative minimum (~1.0 mV) appears near the epicardial projection of the pacing site. B, Same heart and same pacing needle as in A, but here the pacing site was epicardial and the time after the stimulus was 32 milliseconds. At 32 milliseconds, the left positive area had rotated counterclockwise (CCW) approximately 85° from its initial position near the upper end of the wave front (not shown) and was flanking the left side of the wave front. Again, the right positive area is missing. This needle insertion did not produce positive formations in the upper right quadrant of the electrode array for any pacing depth. C, Epicardial potentials at 10 milliseconds after right ventricular endocardial pacing in dog 11. Thickness of right ventricular wall at site of pacing was 4.5 mm. Position of electrode array on right ventricle is shown in Fig 1H. Instead of two peripheral maxima and a central negative area as in Fig 4F, we observed a single, elongated mound of positive potentials. Star indicates both the epicardial projection of the pacing site and the location of the potential maximum. At 16 milliseconds, the potential distribution reverted to the usual pattern, with two peripheral maxima and a central negative area (D). E, Left ventricular epicardial pacing. Electrode array position is shown in Fig 1F. Before 40 milliseconds, only the maximum facing the narrow end of the wave front was present (not shown). At 40 milliseconds, a second maximum appeared in the CCW-expanding positive area (arrow). A similar pattern is shown in F (right ventricular epicardial pacing), but here the second maximum appeared very early, at 10 milliseconds after the stimulus. Area shown is a portion of the rectangle in Fig 1D and measures 16 x 12 mm.

rotation in the left ventricular wall are smaller than those published by Streeter (about 120°, with one extreme case at 180°). Differences probably arose because our blocks were distributed over large ventricular regions, whereas Streeter’s measurements were limited to a thin, T-shaped, central area.

Fig 6. A, Left ventricular pacing. Voltage of absolute epicardial maximum as a function of pacing depth, at 14 and 16 milliseconds after the stimulus, in one dog (dog 2). Voltage increased for pacing depths >11 mm. Increase was greater at 16 milliseconds. B, On the right ventricle, in dog 11, voltage of absolute maximum increased for pacing depths >3 mm. C, In dog 18, voltage of maximum did not increase for any pacing depth. Here, the tip of the needle did not reach the subendocardial level. D, Dog 1. Total expansion-rotation of positive areas during the QRS interval as a function of pacing depth. Total counterclockwise (CCW) expansion-rotation (Rot) decreased with increasing pacing depth (a) and total clockwise (CW) expansion-rotation increased (c). Sum of CW and CCW rotations remained approximately constant for all pacing depths (a).
Evolution of Epicardial Potentials During QRS

The potential maps described in the previous sections were recorded between 6 and 14 milliseconds after the stimulus. During the subsequent stages of ventricular excitation, the wave front propagated both on the ventricular surface and intramurally. The following epicardial patterns were observed.

Epicardial pacing

Wave front. Between 10 and 40 to 50 milliseconds after the stimulus, the wave front expanded steadily until it reached the boundary of the area explored. Sequences of potential maps as displayed in Fig 7 (right ventricular pacing) and Fig 8 (left ventricular pacing) depict the epicardial expansion of the wave front. Velocity of propagation in the fast direction remained approximately constant at $67.63 \pm 10.61 \text{ cm/s}$ for 30 to 40 milliseconds. Transverse velocities measured within 10 mm of the pacing site averaged $31.09 \pm 4.93 \text{ cm/s}$, then varied as a function of distance from the pacing site, as previously shown by Colli Franzone et al., Frazier et al., and Taccardi et al. The spatial distribution of epicardial velocities for different pacing sites and depths will be addressed in a separate study.

The initial shape of the wave front was roughly elliptical, with the major axis oriented approximately along the direction of the superficial fibers (Fig 7B). From 20 to 30 milliseconds onward, the outline of the wave front definitely departed from the elliptical shape, exhibiting local bulges and a narrowing in its middle.
portion (Fig 7, 29 to 42 milliseconds). These features are also clearly visible in isochrone maps (Fig 2C, which relates to the same experiment). Simulation studies showed that the bulges and the central narrowing are due to electrotonic attraction from deeper wave fronts spreading along fibers whose direction rotates CCW relative to epicardial fibers.12,15

After 30 to 40 milliseconds on the right ventricle and 55 to 65 milliseconds on the left ventricle, the shape of the wave front became more irregular, the apparent velocity of propagation increased considerably in some areas up to 2 or 3 m/s, and one or more breakthroughs appeared, further complicating the shape of the wave front. In Fig 7, the bottom left portion of the wave front (arrow in Fig 7C) moved to the left at approximately 0.45 m/s between 29 and 42 milliseconds after the stimulus, then covered 8 mm in 3 milliseconds (Fig 7E and 7F, 42 to 45 milliseconds), a sixfold increase in apparent velocity, to 2.7 m/s. Careful inspection of the sequence of potential maps in this area showed that the abrupt apparent acceleration was due to the occurrence of an epicardial breakthrough. A breakthrough was observed in the same area also during sinus rhythm and during intramural pacing in the same experiment (see Arisi et al18).

**Negative areas.** In the negative area inside the wave front, two separate minima appeared in most cases between 10 and 20 milliseconds and persisted for 15 to 40 milliseconds. The minima were located near the narrow ends of the wave front, as previously observed by Spach et al9 in the superfused lamina (Fig 7, 18 through 45 milliseconds). Their voltage was −20 to −40 mV. The two minima were present in most experiments but could be consistently observed in potential maps only when the spatial resolution of the electrode array was 2.5 mm or better.

**Potential maxima and positive areas.** In all experiments, the two positive areas that initially faced the narrow ends of the elliptical wave front underwent a progressive expansion-rotation in a CCW direction (Figs 7 and 8). In the majority of cases, both initial maxima maintained their position near the narrow ends of the spreading wave front, while the surrounding equipotential lines progressively stretched in a CCW direction and became “comma-shaped” or “C-shaped” (Fig 7C and 7D). One or more additional maxima generally appeared in the expanding positive areas (Fig 7D, plus signs). The expansion-rotation of the positivity resulted in positive formations flanking increasingly large portions of the long, flat sides of the elliptical wave front (Fig 7C through 7F and Fig 8D and 8E).

On the right ventricle, the two positive areas expanded CCW in a relatively symmetrical way during the QRS interval (Fig 7). On the left ventricle, the upper left positive formation (as displayed in Fig 8B, arrow) expanded and rotated CCW as shown for the right ventricle and produced a strong positive ridge that flanked the left side of the wave front at 30 to 40 milliseconds after the stimulus (Fig 8D). Conversely, the lower right positive area did not produce a comparable positive formation near the right side of the wave front. The CCW expansion of the right positivity did occur but produced only low positive potentials that moved toward distant regions, away from the wave front, often beyond the boundary of the electrode array. This behavior caused the potential distribution around the wave front to become strongly asymmetrical between 20 and 50 milliseconds after the stimulus, as shown in Fig 8D and, more strikingly, in Fig 5B. In both cases, the area of low or missing positivity was located in the upper right quadrant of the electrode array. The lack of positivity, however, was not a property of a specific ventricular region: it invariably occurred on the right side of the pacing needle for all needle positions shown in Fig 1C, 1E, and 1F and for all pacing depths. Again, we tentatively attributed the weakness or absence of the late positivity near the right side of the epicardial wave front to the fact that in those areas the deep portions of the wave fronts propagated along fibers that pointed slightly toward the endocardium.

Because for all pacing depths the rotation-expansion of the right positive area produced weak positive formations that often moved out of the electrode array, we will describe more systematically the expansion-rotation of the left positive area on the left ventricular surface during the QRS interval (Figs 8 through 10).
The amount of expansion-rotation of the left positive area was estimated by measuring the angular position of the left potential maximum relative to the pacing site. The initial position of the upper left maximum (Fig 8B, arrow) was assigned the value of zero degrees. When several maxima appeared in the expanding positive area (Fig 8C, 8D, and 8E), we measured the angular position of the maximum that was closest to the leading edge of the expanding positive ridge (Fig 8D and 8E, arrows). Total observable rotation of the maximum amounted to 104±18.85° (SD, n=24) on the left ventricle. This figure reflects only part of the actual rotation because in many cases the maximum moved out of the area explored at the end of its rotation (Fig 8E and 8F). Our measurements are in good agreement with previous measurements by Watabe et al., who found a total measurable rotation of 100±15° (SD) for 108 pacing sites. On the right ventricle, rotation was 76±15.51° (n=4). The expansion-rotation process was completed in about 30 to 40 milliseconds on the right ventricle and 40 to 70 milliseconds on the left ventricle. In smaller hearts, the process was completed in a shorter time.

Intramural Pacing

Negative areas. For intramural pacing, the area surrounding the site of insertion of the needle was weakly negative before epicardial breakthrough (Fig 9B, 8 milliseconds). As excitation approached the epicardium, surface potential values near the pacing needle underwent small fluctuations until, at breakthrough time, they reached −30 to −50 mV in 2 or 3 milliseconds. (Fig 9C, 21 milliseconds). A few milliseconds after breakthrough time, an array of negative, densely packed, roughly elliptical equipotential lines appeared on the epicardium (Fig 9D). The array outlined the intersection of the expanding wave front with the epicardium. The shape of the wave front was oblong, and the orientation of its major axis was intermediate between the orientation of the fibers near the site of pacing (Fig 9A) and the orientation of the epicardial fibers (Fig 8A). This finding is in agreement with previous isochrone patterns published by Frazier et al. and also with model simulations by Colli Franzone et al. It is an expression of the helical, CW twist of the wave front as it spread from the deep pacing site toward the epicardium. The epicardial wave front propagated in all directions until it merged with other wave fronts coming from other breakthrough sites or reached the boundary of the area explored.

Positive areas. As shown in previous sections, epicardial pacing produced two epicardial positive areas that invariably expanded CCW during the first 50 to 60 milliseconds of QRS (Figs 7 and 8). When the pacing site was intramural, the positive areas expanded both CW and CCW (Fig 9). Subendocardial pacing produced a predominantly CW rotation, with a minor CCW component, as shown in a later section. For reasons discussed above, only the left positive areas are described in detail in Figs 8, 9, and 10.

Intramural pacing produced an early left maximum surrounded by low-voltage, positive equipotential lines (see Fig 9B, which relates to a pacing depth of 7 mm). The axis joining the maximum to the minimum was approximately parallel to the direction of the intramural fibers near the pacing site (Fig 9A). During the subsequent 20 to 30 milliseconds, the positive equipotential lines expanded simultaneously CW and CCW, thus assuming a “C-shaped” configuration (Fig 9C through 9F). Two distinct potential maxima developed, either simultaneously or in sequence, inside the positive C-shaped area. One maximum was invariably located in that portion of the positive ridge that expanded CW (Fig 9C, upper arrow). It was located near the left, narrow end of the emerging wave front. Later, as the wave front propagated on the surface, this maximum moved ahead of the spreading wave front, always facing a portion of the wave front that propagated along epicardial fibers (Fig 9C through 9F). The second maximum appeared in the CCW-expanding portion of the positive ridge (Fig 9E, arrow) and moved CW until it reached the end of its CCW rotation or crossed the border of the electrode array (Fig 9E and 9F). The end point of its observable CCW rotation was approximately the same for all pacing depths (Figs 8 through 10).

One or 2 milliseconds after the CW maximum assumed its position near the emerging wave front (Fig
expansion of pacing those cases. The new maximum, too, moved ahead of the expanding wave front, always facing a portion of the wave front that spread along fibers (Fig 9C through 9F).

Thus, a few milliseconds after epicardial breakthrough, a pair of positive maxima appeared on the epicardium, on opposite sides of the elliptical wave front. This pattern resembled the potential distribution observed in the same hearts shortly after epicardial pacing, i.e., one central, roughly elliptical wave front with two maxima near the two narrow ends of the wave front (Fig 8B). In both cases, the two maxima were an expression of the general rule that potential maxima face those portions of the wave front that move along fibers15 (see “Discussion”).

**Endocardial Pacing**

Describing the evolution during QRS of epicardial potentials produced by endocardial pacing poses difficult problems because of the diversity of initial patterns, shown in previous sections. We will describe first those cases (40% of all endocardial stimulations) in which the initial pattern was similar to that observed during intramural pacing (one central minimum and one or two peripheral maxima, see Fig 10B). In these cases, the negative area first shrank (Fig 10C and 10D) and then expanded again at breakthrough time (Fig 10E, 34 milliseconds). We attributed the relative predominance of positive epicardial potentials in these experiments, compared with intramural and epicardial pacing, to the fact that the wave front was widely open toward the ventricular cavity and had a large endocardial rim in contact with cavitory blood. This condition enhanced the relative strength of the transverse (as opposed to axial) current generators associated with the wave front (see “Discussion”). Because epicardial pacing generated an almost exclusively CCW expansion of the positive areas and intramural pacing produced a partly CW and partly CCW expansion, endocardial pacing was expected to produce only a CW expansion of the positivity. In fact, it gave rise to a preponderant CW expansion but also to some degree of CCW expansion (Fig 10). Endocardial pacing, like midwall pacing, also produced two antipodal maxima shortly after breakthrough time. Again, the two maxima faced opposite sides of the emerging wave front (Fig 10E and 10F, plus signs). Additional complexities resulted from the occurrence of multiple breakthroughs (Fig 10E, three arrows) and merging wave fronts, which created extensive negative areas (Fig 10F).

In the remaining 60% of the cases, a predominantly CW rotation of the positive areas was invariably present, but the potential patterns were often complex, and the amount of rotation was measurable only in half of those cases.

In all the experiments, the amount of CCW rotation-expansion of the positive areas decreased with increasing pacing depth, and the CW rotation increased. The total measurable rotation (CW plus CCW) remained approximately constant for all pacing depths. This behavior is illustrated in Figs 8 through 10 and in Fig 6D for another experiment.

The sequence of epicardial events observed during QRS for ventricular pacing at different depths did not always rigorously match the schematic description given above. For instance, in some cases, one or two additional maxima that did not fit into the pattern described appeared around the wave front, but this always happened at 50 milliseconds or later, when involvement of Purkinje fibers may have played a role in creating new wave fronts. Also, for deep pacing sites, the presence of multiple breakthroughs interfered with the regular expansion-rotation of the positive ridges.

In summary, intramural and endocardial pacing gave rise to a simultaneous CW and CCW expansion of the initial positivity that occurred in all the experiments. After epicardial breakthrough, two antipodal maxima appeared near those portions of the epicardial wave front that propagated along fibers. Pacing at increasing depths along a given needle produced varying amounts of CW and CCW expansion of the positive areas during QRS, but the sum of the CW and CCW expansion, when measurable, remained approximately constant for all pacing depths. Thus, the behavior of the positive areas during the QRS interval indicated the approximate intramural depth of the site of origin of a paced beat and also revealed whether the wave front was traveling in an epi-endocardial, endo-epicardial, or double direction.

**Correlation Between Fiber Direction and Potential Patterns Recorded During the QRS Interval**

The good correlation between fiber direction near the pacing sites and epicardial potential distributions in the early stages of a paced beat was documented in a previous section. During later stages of ventricular excitation, correlating electrical data with histological findings posed more difficult problems because the wave front spread through deep myocardial regions and we did not know the exact shape and location of those deep portions of the wave fronts. Also, the maxima often moved out of the electrode array before completing their rotation (Figs 8 through 10). In one case, the total rotation-expansion of a positive area during QRS was measurable (dog 16, right ventricle, not shown) and could be compared with the total transmural rotation of the fibers in the underlying myocardial areas. The total rotation of the left maximum during QRS was 80° (epicardial pacing), and the rotation of the fibers in the relevant areas was 90° to 100°. A qualitative agreement between rotation of maxima during QRS and rotation of fibers in the left ventricle was observed in 4 dogs (see Figs 8 through 10).

**Multiple Maxima in the Expanding Positive Areas**

We have shown that multiple maxima appeared in most experiments during the expansion of the positive areas for all pacing depths. Fragmentation of the maxima could appear as early as 10 milliseconds after an epicardial stimulus, as observed in dog 17 with a 744-lead sock (Fig 5F). In another case, fragmentation appeared as late as 40 milliseconds after epicardial pacing (Fig 5E). In other cases, no fragmentation occurred during the CCW rotation of the maxima. During intramural pacing, two separate maxima gen-

9C, upper arrow), a symmetrical maximum reached an antipodal position near the right narrow end of the wave front (Fig 9C, 21 milliseconds, lower arrow). This maximum belonged to the “right” positive area, part of which remained outside the electrode array in this experiment. The new maximum, too, moved ahead of the expanding wave front, always facing a portion of the wave front that spread along fibers (Fig 9C through 9F).

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ally appeared in the left positive area as it expanded simultaneously in a CW and CCW direction (Fig 9E). Fragmentation was never observed in previously published simulated maps.\textsuperscript{15,16} Possible mechanisms that may have produced the multiple maxima will be addressed in the “Discussion.”

**Excitation Time Maps**

Excitation time maps were obtained for all pacing depths in all the experiments. Examples relating to right and left epicardial pacing are shown in Figs 2 and 5. Further details can be found in Colli Franzone et al,\textsuperscript{12} Taccardi et al,\textsuperscript{25} and Burgess et al.\textsuperscript{26} The complex distributions of isochrone lines and epicardial velocities of propagation, as well as the temporal and spatial distribution of epicardial breakthroughs as a function of pacing depth, will be described in a separate article.

**Discussion**

The results of this study verified our initial hypothesis that epicardial potentials recorded during paced beats reflect the direction of the myocardial fibers through which excitation is spreading during both the initial and later stages of ventricular excitation. More specifically, our data enabled us to identify a number of features of the potential distributions that correlated with fiber direction. These features varied as a function of pacing site and pacing depth and also as a function of the time elapsed after the stimulus. The most significant features were the initial position of the potential maxima; their rotation during QRS; the shape of positive and negative equipotential lines; the asymmetry of the positive areas and during endocardial pacing, the shape of the positive mountain, when present; and the location of the negative areas. Correlation between fiber direction and potential patterns was detected in all cases of epicardial and endocardial pacing. Of 25 cases of endocardial pacing, epicardial potential maps showed typical features that revealed fiber direction only in 15 cases (60%). The reasons why in the remaining cases we were unable to establish a correlation may be summarized as follows: (1) Subendocardial pacing may have stimulated Purkinje fibers, thus creating multiple wave fronts spreading through fibers with variable orientation. This explanation is supported by the appearance of multiple breakthroughs (Fig 10E and 10F). (2) Subendocardial pacing created wavefronts whose rim was in contact with intracavitary blood. This enhanced the transverse, nonaxial component of the currents generated by the wave front, as discussed below. (3) The limited size of our electrode array prevented us from examining the potential distribution over the entire epicardium, where other significant features might have been present.

In addition to revealing correlations with fiber architecture, our data provided some information on epicardial and deep electrical events. Thus, epicardial potential patterns in the early stages of propagation, combined with knowledge of the distribution of fiber direction in the ventricular walls,\textsuperscript{11} enabled us to estimate the location and intramural depth of the pacing site: eg, Fig 4 shows six distinct potential patterns for six pacing depths. During later stages of QRS, two components of the epicardial potential pattern, namely, the two positive areas, rotated and expanded CCW for epicardial pacing, CW for endocardial pacing, and both ways for midwall pacing, thus revealing whether intramural propagation occurred in an epic-endocardial or endo-epicardial direction or both ways. These features provided further information about the position and intramural depth of the pacing site. In addition, epicardial potentials revealed a number of features that we had not predicted at the onset of our study. The unpredicted findings were the asymmetry of the positive areas, the increase in epicardial positivity when the pacing site approached the endocardium, the appearance of a central positive mountain for endocardial pacing, and the fragmentation of the maxima within the expanding positive areas during the QRS interval.

All the potential patterns described in this study, except the fragmentation of the maxima, can be interpreted in the light of the “oblique dipole layer,” a mathematical model of the excitation wave front first published by Colli Franzone et al\textsuperscript{28} in 1982 and recently updated by the same authors.\textsuperscript{15} This model represents the electrical generators associated with the excitation wave front as the superposition of an axial and a normal dipole layer. Both layers cover the entire wave front. The axial layer is constituted by dipoles that are parallel to the local fiber direction at all points of the wave front. The normal layer is made up of dipoles that are oriented normal to the wave front and is identical with the classic model of the wave front (uniform dipole layer). The updated model of the wave front\textsuperscript{15} maintains the essential properties of the older model but takes into consideration the structure of the myocardium as an anisotropic bidomain and avoids the simplifying assumption of a wave front having zero thickness.

When the wave front is a closed surface (early stages of an intramural stimulation) or behaves like a closed surface because its rim is epicardial and exposed to air (early stages of an epicardial stimulation),\textsuperscript{27} the normal dipole layer does not generate any potential field outside or inside the wave front. Its only electrical manifestation in the extracellular media is a potential jump of 30 to 50 mV across the entire wave front surface. In these conditions, the potential distribution in the entire heart and body (except across the wave front) is determined solely by the axial dipole layer. Conversely, when the rim of the wave front is in contact with a conducting medium (eg, cavity blood or thoracic tissues), both the axial and the normal dipole layers participate in determining the potential field in the entire heart and body.

In our experiments, the “closed surface” conditions occurred after epicardial and intramural stimulation and lasted until the wave front reached the endocardium, ie, approximately 33 milliseconds after the stimulus for epicardial pacing and progressively less for intramural pacing at increasing depths. Thus, our experiments provided a tool for selectively studying the axial component of the cardiac generators.

The model explains why, in the early stages of propagation after epicardial stimulation, potential maxima and ECG R waves occurred only in those epicardial regions toward which the wave front propagated along fibers (Figs 2 and 3). The reason is that only the axial dipoles, parallel to the fibers, affected the potential distribution outside and inside the wave front. In these conditions, the linear quadrupole model provided a reasonable approximation of the potential field at some distance from the wave front.\textsuperscript{29} Extracellular currents
flowed from the two positive poles (plus signs in Fig 2E) toward the resting tissue and then into the excited areas by crossing the wave front. Similarly, intramural pacing produced a closed, ellipsoidal wave front whose major axis was parallel to the deep fibers near the pacing site. These deep wave fronts were not actually detected in this investigation but were demonstrated by previous experimental and model studies.\textsuperscript{12,15,28} The intramural wave front generated two deep maxima aligned with the deep fibers and a central negative area whose far-field effects on the epicardium manifested themselves as a central, weak negative region and two peripheral maxima (Fig 4C through 4F); see also Fig 2 in Collin Franzzone et al\textsuperscript{15}.

Both the oblique dipole layer and the linear quadrupole models predict a progressive decrease in the voltage of the epicardial maxima and an increase in their spatial separation with increasing pacing depth.\textsuperscript{15} This behavior was in fact observed for pacing depths between 0 and 8 or 10 mm in the left ventricle (Fig 4) and is consistent with previous simulations. However, when the pacing depth approached the endocardial level, the voltage of the maxima increased (Fig 6A and 6B), the separation between maxima decreased, and the negative area shrunk (Fig 4F) or was replaced by a central positive mound (Fig 5C). The oblique dipole layer model provides the following explanation for this behavior: subendocardial pacing produced a wave front that opened at the endocardium at 5 to 10 milliseconds after the stimulus. As soon as the wave front acquired an endocardial rim that was in contact with cavitory blood, a conducting medium, the normal dipole layer started producing currents that flowed through the entire heart and body tissues. In terms of potentials, the normal dipole layer projected positive potentials into the ventricular wall, and on the epicardium, negative potentials into the cavity. These currents and potentials added themselves to those generated by the axial component. The resultant effect on the epicardium was an increase in positivity, a decrease of the negative values, and a shrinking of the negative areas. These effects are visible in Figs 4F, 6A and 6B, and 10C and 10D. In 10 of 25 cases of endocardial pacing, the normal component did not obscure the essential features produced by the axial component. In these cases, endocardial pacing produced epicardial maps that still showed a central negative area with one or two peripheral maxima (Figs 4F and 10B). In 5 cases, the effect of the normal component was preponderant in the initial stages of excitation and created a mound of positive potentials that covered a large epicardial area for 5 to 15 milliseconds (Fig 5C). Later, the axial component became predominant and reestablished the characteristic epicardial pattern with one central minimum and one or two peripheral maxima (Fig 5D). The latter behavior is consistent with model simulations (see Fig 6C in Collin Franzzone et al\textsuperscript{12}). In the 10 remaining cases, the mixture of axial and normal effects created patterns that were difficult to interpret in terms of fiber direction. The reasons why the normal component prevailed only in part of the experiments and for a variable time are still unclear. A model study of the factors that affect the ratio of the two contributions, axial and normal, and the resulting potential patterns during transmural propagation would probably elucidate this point.

Rotation-Expansion of Positive Areas

The rotation-expansion of the epicardial positive areas during the QRS interval may be interpreted as follows: Epicardial pacing created a wave front that spread both on the ventricular surface and into the depth. The superficial portion of the wave front propagated both along fibers and across fibers. The part that propagated along fibers produced two epicardial maxima that moved ahead of the wave front. The portion that spread into the depth produced positive areas only in those deep myocardial regions toward which it propagated along fibers, as shown by intramural measurements and simulations.\textsuperscript{15,28} This process generated a helical intramural positivity that expanded CCW and into the depth during the QRS interval. Part of the deep positivity was transmitted as a far-field effect to the epicardium, where an attenuated, CCW-expanding positive area appeared. Midwall pacing gave rise to a wave front that propagated both downward toward the endocardium and upward toward the epicardium. The portion that moved downward encountered fibers that rotated CCW and produced a CCW expansion of the positivity both intramurally and on the epicardium. The portion that moved upward encountered fibers that rotated CW and produced a CW expansion of the deep and epicardial positivity. This resulted in a double expansion, CW and CCW, of the epicardial positivity (Fig 9E). When the upper portion of the wave front reached the surface, the wave front acquired an epicardial rim that propagated on the epicardium and generated its own pair of epicardial maxima, facing those portions of the epicardial wave front that propagated along epicardial fibers (Fig 9C, arrows). Finally, endocardial pacing gave rise to a wave front that spread both on the endocardial surface and into the wall. The portion that propagated into the wall encountered fibers that rotated CW and produced a CW epicardial expansion of the positive areas. The small CCW component of the epicardial rotation observed during endocardial pacing was probably produced by that part of the wave front that propagated along the endocardial surface, where fiber direction often rotated further CCW at increasing distance from the pacing site, as shown by our histological studies (Fig 10A). Establishing the possible role played by involvement of Purkinje fibers in these phenomena will require a separate investigation.

The fact that the sum of the CW and CCW expansion of the epicardial positive areas was nearly constant for all pacing depths in a given experiment (Fig 6D) is consistent with the interpretation given above. For all pacing depths, the wave front propagated through the entire thickness of the wall, thus encountering fibers that underwent the same total amount of rotation. Also, intramural measurements\textsuperscript{28} and model simulations\textsuperscript{15} confirmed the presence of deep intramural potential maxima facing those deep sections of a wave front that propagated along deep fibers.

Asymmetry of Potential Distributions

A feature not reproduced by any published numerical simulation was the weakening or total disappearance of one of the two peripheral maxima, which occurred both early in QRS (Figs 4C and 5A) and during later stages of propagation (Fig 5B). As discussed in the “Results,”
the asymmetry of the positive areas was attributed to the epi-endocardial obliqueness of intramural fiber pathways.9

Multiple Maxima

Another feature not reproduced by the available numerical simulations is the presence of multiple maxima in the expanding positive areas, which we observed in most experiments for all pacing depths. We do not have a valid interpretation for the fragmentation of the maxima. Possible causes are the discontinuities of the wave fronts due to the presence of connective septa,29 undulations of fiber directions, and the presence of vessels in the wall. The opening of a wave front at the endocardium and additional wave fronts produced by involvement of Purkinje fibers may also have produced separate maxima in later stages of propagation but cannot explain the fragmentation at 10 milliseconds after an epicardial stimulus that was observed in one case (Fig 5F). Other anatomic discontinuities as described by Hort30 and Hunter et al31 might play a role in producing fragmentation of the wave front and additional maxima. However, the multiple clefts described by these authors should considerably delay intramural propagation, an effect that was not confirmed by our intramural measurements (unpublished observations).

Limitations of the Study

Our study suffers from the following important limitations.

1. Because of the limited size of the electrode arrays, many significant features, in particular the positive areas, often moved out of the region explored at 40 to 60 milliseconds after the stimulus and could not be studied. Experiments with a new sock that covers the entire heart are in progress, and part of the results have been published.35

2. Despite our attempt to create simple experimental conditions, with a single wave front spreading through fibers with known directions, interpretation of the results became complex after the wave front had reached the endocardium. At that time, many factors participated in determining intramural and epicardial potential distributions: the axial dipole layer, the normal dipole layer, the “Brody effect,”32 and the presence of additional wave fronts resulting from involvement of Purkinje fibers. Separating and quantifying the roles of these different factors will require new experimental and model studies.

3. A satisfactory interpretation of our epicardial data would require comparison with intramural electrical measurements and simulations. Such three-dimensional studies are actually in progress and the first results, partly published,12,15,28 offered valuable help for explaining our findings.

Impact of This Study on the Solution of the Forward and Inverse Problems of Electrocardiography

The ultimate purpose of electrocardiography is to provide a solution to the “inverse problem,” that is, inferring intracardiac events, such as the sequence of excitation and repolarization, from epicardiac (body surface or epicardial) measurements.33 It is well known that the inverse problem cannot be solved if we do not solve the forward problem first.34 The forward problem consists of predicting intracardiac, epicardial, and body surface ECGs from known intracardiac electric sources (eg, excitation wave fronts).

Our study contributes to the solution of the forward problem in that it describes both the wave fronts and the associated potential distributions on the epicardium for a variety of excitation sequences. Depicting both the cardiac electric sources (wave fronts) and the associated potential fields, as we did in this study, represents the only means available to us to address the forward problem experimentally. The ultimate solution to the forward problem, however, will require a mathematical model that simulates both the wave fronts and the potential distributions. Several such models are now available in the literature.15,17 These models, however, are necessarily based on simplifying assumptions: a flat ventricular wall, the constant shape of the transmembrane action potential, constant fiber direction at a given intramural depth, a simplified Purkinje network, etc. Because of these assumptions, the mathematical simulations available at present reproduce only part of the electrical features that occur in the real heart, as shown in this study. The only way to evaluate the accuracy of the forward models consists of comparing the simulations with real data of the kind we obtained in this study. The results of the present investigation are in good agreement with recent numerical simulations15 and indicate which aspects of the simulations need improvement. In future work, complete evaluation of the models will require three-dimensional, intracardiac measurements. These experiments are actually in progress, and partial results have been published.24

The contribution of this study to the solution of the inverse problem is only indirect and essentially consists of helping with the solution of the forward problem, an indispensable preliminary step. Our data show that neither the forward nor the inverse problem as defined above can be solved without a good knowledge of the distribution of fiber directions in the heart. Fortunately, complete descriptions of fiber directions in the ventricles are now available.11 Recent studies35 show that knowledge of fiber directions removes the indeterminacy of the inverse problem, which now has a unique solution in terms of intracardiac sources. In addition, by using an elementary knowledge of fiber architecture in our hearts, we were able to obtain some information on intracardiac activity from visual inspection of epicardial potential patterns. These patterns enabled us to estimate the location and intramural depth of the site of origin of a paced beat and to establish whether excitation in the area explored was spreading in an endocardial or endo-epicardial direction or both ways. Previous studies showed that abnormal intramural events, eg, the presence of a small, local necrosis36 and the site of origin of reentrant tachycardias,7,36 can also be inferred from epicardial or endocardial potential maps. These findings suggest the possible practical utility of measuring epicardial potentials.

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References

Effect of myocardial fiber direction on epicardial potentials.
B Taccardi, E Macchi, R L Lux, P R Ershler, S Spaggiari, S Baruffi and Y Vyhmeister

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