

## **Electrophysiologic and anatomic basis for fractionated electrograms recorded from healed myocardial infarcts**

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**ABSTRACT** The electrophysiologic and anatomic basis for fractionated electrograms were investigated in superfused epicardial preparations from infarcted canine hearts. Fractionated bipolar electrograms were frequently recorded in preparations from infarcts 2 weeks to 18 months old but only rarely in preparations from 5-day-old infarcts. The fractionated electrograms were not caused by movement artifacts. They were not associated with depressed transmembrane resting or action potentials (which were found in the 5-day-old infarcts), but rather transmembrane potentials recorded in the vicinity of the bipolar electrodes were normal. Despite the normal transmembrane potentials, activation time in regions where fractionated electrograms occurred was prolonged. However, prolonged activation time by itself did not cause fractionation, since fractionated electrograms were not recorded from normal preparations in which conduction was markedly slowed by a superfusate containing 16 mM potassium and epinephrine. Unipolar electrograms recorded with glass microelectrodes (tip size 1 to 5  $\mu\text{m}$ ) showed that activation in regions where fractionated electrograms were recorded was inhomogeneous. Prepotentials were found preceding the upstrokes of some action potentials in regions where double potentials were recorded, suggesting the possibility of electrotonic transmission across high resistance or inexcitable gaps, but no electrotonic potentials were seen in regions with multicomponent fractionated electrograms. Fractionated electrograms were recorded in regions where infarct healing caused wide separation of individual myocardial fibers while distorting their orientation. The anatomic changes probably caused slow and inhomogeneous activation.

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FRACTIONATED electrograms,<sup>1-11</sup> consisting of either two discrete deflections separated by an isoelectric interval (double potentials or split deflections<sup>4, 7, 8, 12</sup>) or comprised of many components<sup>1, 2, 6, 7</sup> have been recorded during mapping studies on patients with ischemic heart disease and a history of chronic ventricular tachycardia. These kinds of electrograms have been found during sinus rhythm<sup>2, 6, 7, 9-11</sup> as well as during tachycardia.<sup>1-3</sup>

It is important to determine why fractionated electrograms occur and what they mean. Their occurrence during sinus rhythm might sometimes assist in identifying patients who can develop ventricular tachycardia.<sup>6, 8</sup> The site at which these electrograms are record-

ed either during sinus rhythm or during tachycardia may indicate the site where a reentrant circuit is located.<sup>2, 6-11</sup> On the other hand, fractionated electrograms might sometimes be artifacts of recording techniques,<sup>5</sup> caused by such things as electrode movement,<sup>13, 14</sup> or distortions of the electrical signal by the filtering characteristics of the amplifiers.<sup>14</sup> Furthermore, since high amplification is often necessary to record fractionated activity in and around aneurysms, it is possible that the fractionated electrograms might sometimes represent activity originating in distant and possibly normal areas.<sup>5, 13</sup>

The studies to determine the value of fractionated electrograms for indicating those patients at risk of having ventricular tachycardia or for locating reentrant circuits must be done in humans.<sup>9, 11</sup> However, it will be difficult to determine the exact physiologic causes for such electrograms in clinical studies. To understand why fractionated electrograms occur, we have done electrophysiologic and anatomic investigations on areas where such activity is present in isolated

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superfused preparations from canine infarcts. Preliminary reports of some of our results have been presented.<sup>15, 16</sup>

## Methods

**Surgical production of myocardial infarction.** Myocardial infarction was caused in 50 mongrel dogs weighing 13 to 18 kg by a two-stage ligation of the left anterior descending coronary artery (LAD) 5 to 10 mm from its origin, with sterile techniques.<sup>17, 18</sup> Forty-five dogs survived the surgical procedure. In this report we include only data from the 36 transmural infarcts.

At various times after coronary occlusion the surviving dogs were reanesthetized with sodium pentobarbital (15 to 30 mg/kg iv) for the electrophysiologic and anatomic study. Ten animals were studied at 5 days, six at 15 days, seven at 2 months, six at 4 months, four at 8 months, two at 16 months, and one at 18 months. We chose these times because they represent periods during the subacute (5 days), healing (15 days), and healed (2 to 18 months) phases of myocardial infarction. We characterized the electrograms and the cellular electrophysiologic and microanatomic features of the muscle that survives on the epicardial surface of the transmural infarcts at each of these different stages. Five normal dogs that had not undergone coronary artery ligation served as controls.

**Electrophysiologic studies in vitro.** After induction of anesthesia, the chest was reopened and the infarcted region was visually identified by a mottled or pale appearance. A piece of myocardium approximately 20 × 20 × 3 mm was then excised rapidly with a sharp scalpel blade from the epicardial aspect of the infarcted left ventricle *in situ*. Whenever possible this piece was taken from a region devoid of large epicardial coronary arteries. It was immediately pinned to the waxed base of a 25 ml superfusion chamber, epicardial surface upward, and superfused with oxygenated Tyrode's solution (composition previously described<sup>19</sup>) at a rate of 50 ml/min. The solution was briskly bubbled with a 95% O<sub>2</sub>/5% CO<sub>2</sub> gas mixture both in the reservoir and in the bath. The pH of the Tyrode's in the tissue bath under these conditions was 7.30 to 7.35. The temperature was maintained constant at 36.5 ± 0.5°C.

The preparations of epicardial muscle were stimulated through Teflon-coated, bipolar, silver-wire electrodes at basic stimulus cycle lengths of 800 to 1000 msec.<sup>19</sup> After an initial equilibration period of 60 min, extracellular electrograms and transmembrane action potentials were recorded from subepicardial fibers at multiple sites.<sup>18, 19</sup> Extracellular electrograms were recorded through electrodes made from Teflon-coated silver wire. The diameter of the electrode surface in contact with the tissue was 0.3 mm. Bipolar electrodes had a distance between recording poles (measured from the center of one pole to the center of the other) of 0.5 to 1.0 mm. When a unipolar electrode was used, the indifferent electrode was located in the bath approximately 30 mm from the recording electrode. Extracellular signals were amplified with a Tektronix 2A61 differential amplifier. The low and high bandpasses were 0.06 and 6000 Hz. We also used 3M KCl-filled glass capillary electrodes with tip diameters estimated to be about 1 to 5 μm to record unipolar electrograms. The signal recorded with these electrodes was led into the high-input impedance negative capacitance amplifier that was used for the transmembrane potential recordings.

Membrane potentials and electrograms were displayed on a Tektronix 565 oscilloscope and photographed with a Grass C-4 oscilloscopic camera. Action potential parameters were measured by methods described in other publications.<sup>18, 19</sup>

**Histologic and morphometric analysis.** We did not usually find fractionated electrograms in preparations from noninfarcted hearts or from 5-day infarcted hearts (see Results). Because

electrograms in most regions had a similar configuration, it was not necessary to mark a specific recording site for anatomic study. Instead, the entire preparation of epicardium was fixed in 10% neutral buffered formaldehyde. After fixation, the tissue was sliced into five pieces and cut perpendicular to the LAD border and perpendicular to the plane of the epicardium. The slices were then processed for histologic study according to routine methods.<sup>20</sup> Each histologic section (5 μm thick), stained with hematoxylin-phloxine-saffron, showed the full thickness of the preparation, from the epicardial surface to the surface where the preparation was cut from the ventricular wall.

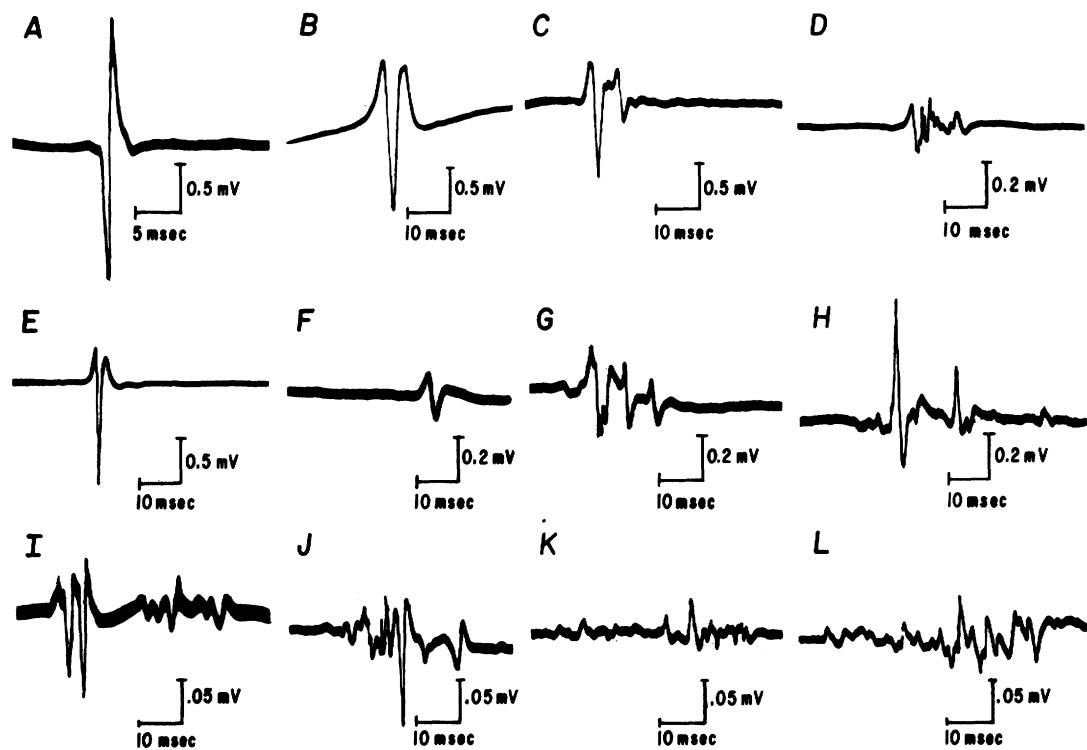
In the preparations from the healed infarcts, both fractionated and nonfractionated electrograms were found (see Results). Selected areas at which electrograms with different characteristics were recorded were marked with color-coded pins during the experiment, and then with India ink before fixation. These marked areas were then cut from the epicardial surface with a sharp razor blade and fixed in formaldehyde. The size of these pieces was approximately 2 × 4 mm and 1 to 2 mm thick. The remainder of each preparation was also fixed in the formaldehyde. The small, marked pieces were oriented in the paraffin embedding blocks so that the epicardial surface formed one margin of each section. These specimens were then serially sectioned (5 μm thick) and each section stained with hematoxylin-phloxine-saffron. The number of muscle fibers surviving at the recording sites was determined from the serial sections.

We also applied morphometric techniques to the histologic sections to determine the relative proportion of heart muscle to nonmuscular tissue in regions where different kinds of electrograms were recorded. Representative experiments from each age of infarct as well as noninfarcted hearts were selected for this analysis (two normal, four at 5 days, two at 15 days, two at 2 months, and four at 4 to 18 months). Morphometric analysis was done on blocks that were serially sectioned, yielding 50 to 150 5 μm thick sections. The sections were stained and mounted on glass slides in the usual manner. Tissue sections without folds were selected randomly (eight to 10 sections per experiment) and photographed. Each negative was enlarged and printed on 8 × 10 inch photographic paper (final magnification × 130 to 500). Morphometric analysis was confined to the region designated as the epicardial border zone.<sup>19</sup> This area extends from the layer of muscle cells immediately subjacent to the epicardium to the deepest surviving muscle layer overlying the infarct. Within the region we determined the amount of muscular tissue relative to nonmuscular tissue (including blood vessels, connective tissue, and inflammatory cells) using the point-counting method.<sup>21</sup> A grid composed of boxes no larger than the average muscle fiber diameter was superimposed on the photographs. If the tissue to be measured contained longitudinally oriented muscle fibers, the axis of the grid was placed at 19 degrees to the long axis of the fibers to counteract the bias introduced by anisotropy.<sup>22</sup> The appropriate density of points for each case was implied by the magnification of the photomicrograph.<sup>21</sup> Each cross point on the grid was evaluated to determine whether it lay over heart muscle or nonmuscular tissue. A ratio of heart muscle "hits" to nonmuscular "hits" was made. The mean and standard deviation of the ratio from all photographs from the experiments were determined.

## Results

### Characteristics of extracellular electrograms

**Dependence on infarct age.** Ventricular muscle survives on the epicardial surface of transmural canine infarcts.<sup>19, 23, 24</sup> We determined the characteristics of the extracellular waveforms recorded from this subepicar-



**FIGURE 1.** Representative bipolar electrograms recorded from superfused subepicardial preparations. Preamplifier filters were set at 0.06 to 6000 Hz. The electrogram shown in *A* was recorded from a noninfarcted preparation, the electrograms in *B* and *C* from 5-day-old infarcts, the electrograms in *D* and *G* from 2-week-old infarcts, the electrograms in *E*, *F*, *I*, and *J* from 16-month-old infarcts, and the electrograms in *H*, *K*, and *L* from 2-month-old infarcts.

dial muscle with bipolar electrodes and compared them with electrograms recorded from noninfarcted preparations. Bipolar recordings were used in much of this study because the clinical reports on fractionated electrograms have relied on this technique.<sup>1-11</sup> Thirty to 60 electrograms were recorded at approximately 2 mm intervals over the entire surface of each preparation. Extracellular waveforms recorded from subepicardial muscle in preparations from noninfarcted hearts consisted of smooth contour, biphasic, or triphasic deflections with amplitudes of 2 to 4 mV and durations of less than 5 msec (figure 1, *A*). Most of the bipolar electrograms recorded from preparations from hearts with 5-day-old infarcts had similar configurations (figure 1, *B*). The main difference between electrograms recorded from these infarct preparations and normal preparations was a decrease in the amplitude of the electrograms recorded from the infarcts (range from 500  $\mu$ V to 2 mV) and a small increase in duration (up to 10 msec). Occasionally, electrograms were recorded from some preparations from 5-day-old infarcts, which had irregular waveforms, characterized by notching or multiple components (figure 1, *C*). The total duration of these electrograms was not longer than 10 msec.

Unlike the 5-day-old infarct preparations, fractionated electrograms were frequently recorded with bipolar electrodes from the 2-week- to 18-month-old infarcts (figure 1, *D* and *G* to *L*). In three of the preparations from healed infarcts (one 2 months old, one 16 months old, one 18 months old) all electrograms were fractionated. In the remaining preparations both fractionated electrograms and electrograms with normal contours were recorded (figure 1, *E* and *F*). Some of the fractionated electrograms had two or more discrete spikes separated by isoelectric intervals (see figures 5 and 10). Other electrograms consisted of multiple spikes, separated either by slower waveforms or isoelectric segments (figure 1, *G* to *L*). The duration of the fractionated electrograms was highly variable and, in general, there was an increase with infarct age. The duration of electrograms was greater in 2- to 18-month-old infarcts (20 to 70 msec duration) (figure 1, *H* to *L*) than in 2-week-old infarcts (10 to 20 msec duration) (figure 1, *D* and *G*). We did not notice any marked differences in duration among the 2- to 18-month-old infarcts. The amplitude of the signals also decreased with infarct age so that at 2 weeks, amplitudes were consistently between 200  $\mu$ V and 1 mV (figure 1, *D* and *G*) while at 2 months and more they

were often less than 200  $\mu$ V (figure 1, I to L). In these healed infarcts electrograms that were not fractionated often had low amplitudes as well (figure 1, F).

*Is fractionation caused by recording artifacts?* It has been suggested that the fractionated nature of some electrograms might be artifactual, caused by contraction-induced electrode movement or by the filtering characteristics of the amplifier used to record them (see above). We recorded stable fractionated electrograms for 3 to 5 hr after the tissue was mounted in the superfusion chamber. Because these preparations had only a narrow surface rim of viable muscle fibers (see histologic results) there was often no visible contraction or movement of the electrodes even when the preparation was observed under the high-power optics of the dissection scope over the tissue chamber. Therefore the fractionated nature of the electrograms could not be attributed to artifacts generated by gross movement at the electrode-tissue interface. Nor was fractionation an artifact introduced by filtering out low-frequency components of a single broad electrogram. The electrograms shown in figure 1 were recorded at a bandpass of 0.06 to 6000 Hz, which permits most slow and fast components of extracellular activity to be recorded except for direct current potentials. The total duration of fractionated electrograms and number of components was influenced by changing the bandpass but we did not study these effects in detail. In general, increasing the high bandpass filter setting from 0.06 to 60 Hz decreased the amplitude of the electrograms and attenuated the slow components (compare right panels A and B in figure 2).

*Effects of electrode configuration and direction of impulse propagation.* The recording electrode configuration also influenced the characteristics of the fractionated electrograms. The electrograms shown in figure 1 were recorded with a bipolar electrode. Fractionated electrograms, however, were not caused by bipolar recording techniques per se. At all sites at which fractionated electrograms were recorded with bipolar electrodes we could also record fractionated activity with unipolar electrodes (figure 2, left). In experiments in which bipolar electrograms were first recorded and then unipolar electrograms recorded from each of the dipoles as shown in the figure, it appeared that the fractionated waveform of the bipolar electrogram resulted from summation of the fractionated unipolar waveforms (figure 2, left).

The direction of impulse propagation with relation to the orientation of the dipoles also affected the characteristics of the fractionated electrograms. Usually when the site of stimulation was changed to alter the

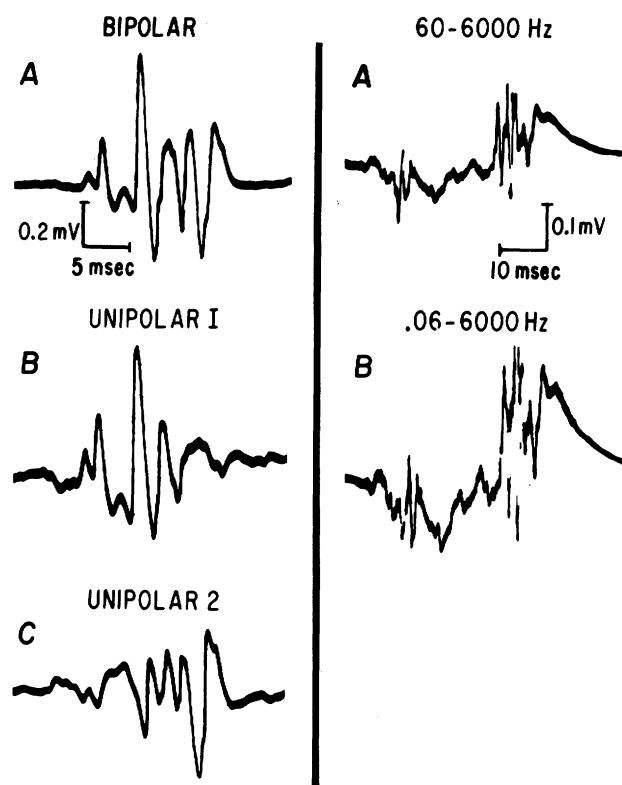


FIGURE 2. Left, Fractionated electrogram recorded with a bipolar electrode (panel A) and with each of the poles separately (panels B and C). Right, Fractionated electrogram recorded with different preamplifier filter settings.

propagation direction the number of components either increased or decreased (figure 3).

#### Electrophysiologic basis for fractionated electrograms

*Transmembrane potentials in regions of fractionation.* We have shown that fractionated electrograms appear during infarct healing. The question then arises, are there special electrophysiologic properties of the healing infarct that cause them? Spach et al.<sup>25</sup> have indicated that complex polyphasic waveforms (fractionation) could arise from a peculiar shape of the transmembrane action potentials — from membrane currents associated with a complex or multicomponent phase of depolarization of individual cells. Fractionation might also be

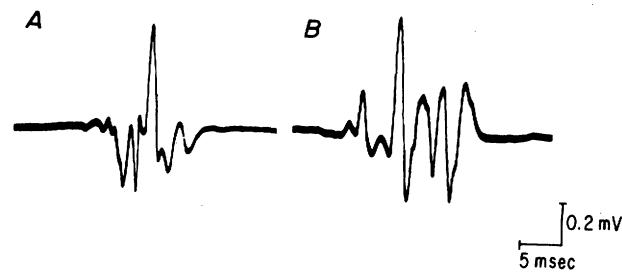
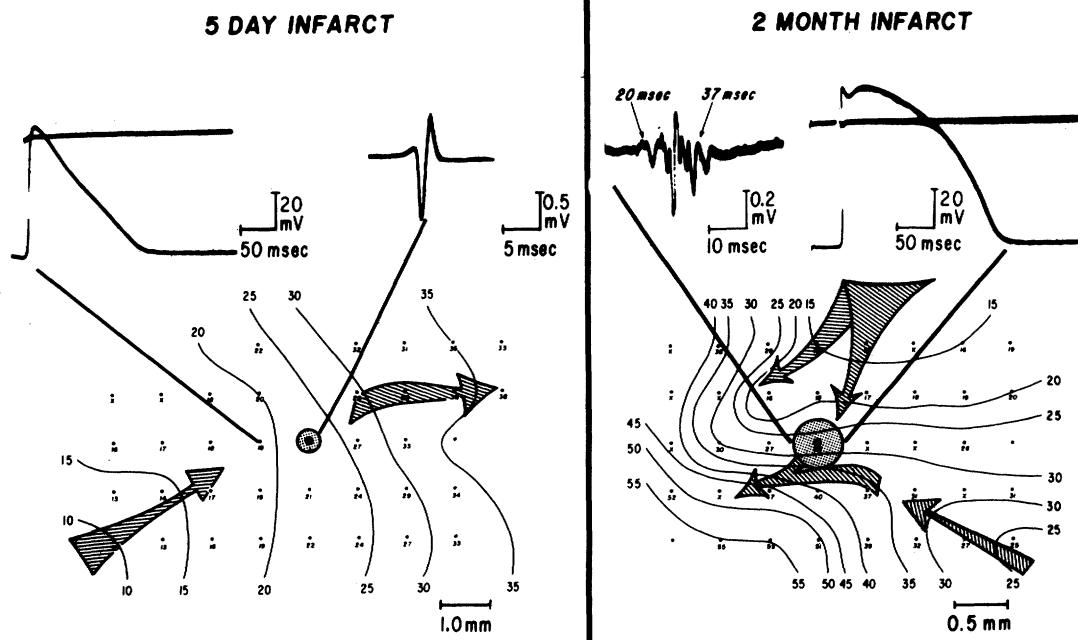


FIGURE 3. Effects of changing the direction of impulse propagation on a fractionated electrogram. Panels A and B show an electrogram recorded as the preparation was stimulated from two different sites.

the result of superposition of extracellular currents from asynchronous depolarizations in a number of functionally different cells with normally shaped action potentials.<sup>25</sup> We recorded transmembrane action potentials in regions from which fractionated electrograms were recorded and compared them with transmembrane potentials in regions where smooth, normally shaped electrograms were recorded to determine whether any particular characteristic could be correlated with the occurrence of fractionated activity. Action potentials were recorded from 10 to 30 sites within a 2 to 5 mm<sup>2</sup> area around the extracellular electrode and then from the region from which this electrode was recording after it was removed from the surface of the tissue.

In 5-day-old infarct preparations, resting potential (RMP) was  $-77 \pm 7$  mV, action potential maximum upstroke velocity ( $\dot{V}_{\text{max}}$ ) was  $73 \pm 9$  V/sec, amplitude of phase 0 (APA) was  $86 \pm 8$  mV, and action potential duration to 50% (APD<sub>50</sub>) and 90% (APD<sub>90</sub>) repolarization was  $120 \pm 10$  and  $170 \pm 15$  msec. These represent mean values  $\pm$  SE for 348 impalements at electrogram recording sites in 10 preparations. All values are significantly less ( $p < .05$ ) than values for muscle fibers in noninfarcted preparations where normal electrograms were recorded (RMP =  $-91 \pm 4$  mV,  $\dot{V}_{\text{max}} = 102 \pm 18$  V/sec, APA = 103

$\pm 6$  mV, APD<sub>50</sub> =  $175 \pm 8$  msec, APD<sub>90</sub> =  $210 \pm 15$  msec; 283 impalements in five preparations). A representative transmembrane potential recorded from a muscle fiber in a 5-day-old infarct is shown in the top left panel of figure 4. Similar results have been previously reported from other studies on transmembrane potentials of epicardial muscle surviving in infarcted regions at this period.<sup>19, 26, 27</sup> These alterations in the transmembrane potentials, however, were not associated with fractionated electrograms, which, as shown above, were not common in these preparations (figure 4, *top left*). In 2-week-old infarcts, resting potential ( $-88 \pm 9$  mV),  $\dot{V}_{\text{max}}$  ( $104 \pm 21$  v/sec), and action potential amplitude (101  $\pm 8$  mV) were not significantly different than normal, although action potential duration (APD<sub>50</sub> =  $92 \pm 8$  msec, APD<sub>90</sub> =  $115 \pm 12$  msec) was still short ( $p < .05$ ; 169 impalements in six preparations). In the healed infarcts (2 months and older) where fractionated electrograms were most prominent, the transmembrane potentials of the muscle fibers were not significantly different from normal, including the time course for repolarization (RMP =  $-86 \pm 5$  mV,  $\dot{V}_{\text{max}} = 101 \pm 15$  V/sec, APA =  $98 \pm 10$  mV; APD<sub>50</sub> =  $160 \pm 8$  msec, APD<sub>90</sub> =  $205 \pm 12$  msec; mean values for 180 impalements in seven preparations). A representative action potential recorded at a site of fractionated activity in a healed infarct is



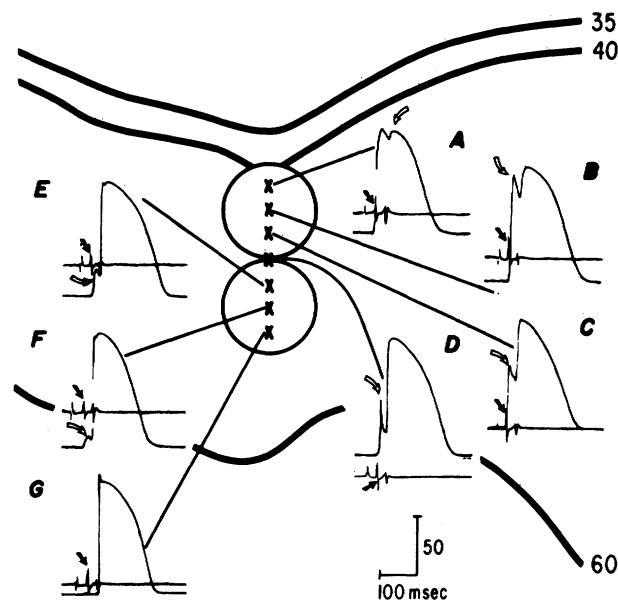
**FIGURE 4.** Activation maps of regions around bipolar electrodes in two different infarct preparations. The location and size of the electrodes are indicated by the stippled circle and the electrograms recorded in each experiment are shown above. The points at which action potentials were recorded in each panel are indicated by the dots. Representative action potentials are also shown. The arrows and isochrones show the direction of activation. The stimulus sites are not included in the maps. The distance scale for each panel is shown below; note that the scale is two times larger for the 5-day-old infarct preparation than for the 2-month-old infarct preparation.

shown in the top right panel of figure 4. In addition, in preparations from healed infarcts, transmembrane potentials recorded from regions where there were fractionated electrograms were no different from transmembrane potentials recorded from regions where electrograms had a normal contour.

In the experiments in which action potentials were recorded from regions with fractionated electrograms containing a large number of spikes (such as electrograms K and L in figure 1), the upstrokes were characterized by a normal smooth S-shaped curve. Fractionation, therefore, could not be caused by a complex action potential depolarization phase. In experiments in which action potentials were recorded from regions where "double potentials" were found, we sometimes saw low-amplitude prepotentials before the action potential upstroke (figure 5, E and F). Action potentials with two component upstrokes were also found, each component corresponding with an electrogram deflection (figure 5, C and D). For reasons described later, we do not attribute these multiple components of the upstroke to different active membrane processes but rather the evidence suggests that they are caused by electrotonic interactions among adjacent, poorly coupled fibers. Our conclusion from the data presented in this section is that fractionated electrograms are not necessarily related to depressed resting potentials or action potential upstroke velocities. Complex upstrokes of action potentials of individual muscle cells do not appear to cause multiple component fractionated electrograms, although they were sometimes found to be associated with double potentials.

*Relationship of fractionation to characteristics of local activation.* It has been suggested that fractionated electrograms recorded in acute myocardial infarction are caused by slow activation.<sup>28</sup> It was therefore surprising that the transmembrane action potentials at the sites where these electrograms were recorded in healed infarcts arose from normal resting potentials and had normal upstroke velocities, properties not usually associated with slow conduction.<sup>29</sup> To evaluate conduction characteristics in regions where electrograms were recorded, we also mapped impulse propagation. Action potentials were recorded from 20 to 50 sites within a 10 to 20 mm<sup>2</sup> area around the extracellular electrode. Activation maps were constructed for regions in which both normal and fractionated electrograms were recorded by using the beginning of the extracellular electrogram as a reference (where the potential first deviated from isoelectric) and determining the time of activation at each microelectrode recording site (measuring the time interval from the reference to the up-

stroke at 50% of its maximum amplitude). Normally shaped electrograms recorded from preparations from noninfarcted hearts and from some regions in preparations from infarcted hearts were found in areas where a broad wavefront propagated rapidly past the recording site (figure 4, left). The region around the bipolar recording electrode was activated in less than 5 msec. In the normal preparations and in these regions of preparations from healed infarcts 2 months and older, the apparent conduction velocity calculated in a direction normal to the isochrones and parallel to myocardial fiber orientation (verified by subsequent histologic study; see below) was 0.5 to 1.0 m/sec. In regions of 5-



**FIGURE 5.** Action potentials in a region where a "double" potential was recorded. The two circles in the middle of the figure indicate the bipolar electrode. The x's show where action potentials were recorded. (The microelectrode was actually adjacent to the bipoles and not beneath them.) The thick dark lines are isochrones indicating activation times and the direction of propagation at this recording site. Panels A to G show simultaneous recordings of the action potentials and the extracellular electrogram. The solid arrows in each panel indicate the first component of the "double" potential. This component is preceded by a stimulus artifact. The upstroke of the action potentials in A and B occur simultaneously with the first electrogram deflection. The unfilled arrows indicate possible electrotonic influences on the plateau phase. The upstrokes of the action potentials in C and D have two components, one corresponding to the first electrogram deflection (unfilled arrow) and one corresponding to the second electrogram deflection. The upstrokes of the action potentials in E and F are simultaneous with the second electrogram deflection but are preceded by an electrotonic prepotential (unfilled arrows) that begins with the first electrogram deflection and spans the isoelectric segment between the two deflections. The upstroke of the action potential in G occurs just after the second electrogram deflection and is not preceded by a prepotential. In this experiment, no action potential upstrokes were found to occur in the isoelectric segment between electrogram deflections. Voltage calibration is for the transmembrane potential recording.

day-old infarcts where normally shaped electrograms were recorded, apparent conduction velocity calculated in the same manner was 0.2 to 0.4 m/sec (figure 4, left).

Activation of the regions in the vicinity of the electrodes recording fractionated electrograms took a much longer period of time. The prolonged activation time was particularly pronounced in the preparations from hearts with healed infarcts (2 to 18 months) despite the normal resting potentials and action potential upstroke velocities. In figure 4, right, the fractionated electrogram had a total duration of about 17 msec. In the region from which this electrogram was recorded it took more than 12 msec for the impulse to move a distance of about 0.5 mm between the electrode poles (indicated by the stippled circle) as compared with a time of 2 msec for the same distance in the activation map of a 5-day-old infarct shown in the left panel. If it is assumed that conduction occurred in a reasonably straight line past the electrode poles (and it may not have), conduction velocity would have been approximately 0.04 m/sec. In other experiments on healed infarct preparations, activation time in the vicinity of the electrodes with which fractionated activity was recorded was also similar to the total duration of the electrogram and therefore ranged from 10 to 70 msec (apparent conduction velocities of 0.05 to 0.01 m/sec). It is also possible that some of the fractionated activity might be accounted for by slow or late activation of myocardial fibers that are too deep from the endocardial surface to be impaled with the microelectrode. Activation may be three-dimensional rather than the two-dimensional activation shown on the map.

Is the slow activation of regions where fractionated electrograms were recorded the primary cause of the fractionation? If it is, it would seem that slowing activation to a similar extent in regions where electrograms have a normal configuration should cause fractionation. We slowed conduction in these regions in both normal and 5-day-old infarct preparations by increasing the  $K^+$  concentration to 16 mM, which caused inexcitability, and then by restoring very slow conduction by adding 1  $\mu$ g/ml epinephrine to the perfusate.<sup>30, 31</sup> When this was done there was a marked decrease in electrogram amplitude, a slowing of its rate of depolarization, and an increase in its duration as shown in figure 6, A to C. At the high amplification used to display the electrogram, a second component was evident (figure 6, C), which always coincided with the repolarization phase of the action potential (figure 6, 1, 2, and 3) and was probably caused by repolarization. Similar double-component electro-

grams were recorded at all sites on the preparation where slow response action potentials were recorded. The upstroke of the action potential recorded near an extracellular electrode always coincided with the first electrogram component and repolarization always coincided with the second component, even when the microelectrode was moved to different sites around the extracellular recording electrode (see figure 6, 1, 2, and 3).

In none of these experiments in which slow conduction (conduction velocities less than 0.05 m/sec) was caused by high  $K^+$  concentration and epinephrine did multicomponent fractionated electrograms occur. Therefore, slow conduction (alone) is not the cause of fractionated activity, although it does increase the total duration of the electrogram. We also elevated  $K^+$  concentration in experiments in which fractionated electrograms were recorded from healed infarcts. When the  $K^+$  concentration in the superfusate reached 12 to 14 mM, the resting potential and upstroke velocities of the fibers in the vicinity of the fractionated electrograms were significantly depressed and activation time of these regions prolonged. The total duration of the fractionated electrogram increased, its amplitude diminished, and the rate of change of the voltage of the individual spikes comprising the electrogram diminished. However, either the number of components comprising the fractionated electrogram did not change (figure 7) or actually decreased. These results suggest further that the activation time and the action potential characteristics are not the main determinants of the fractionated nature of these electrograms.

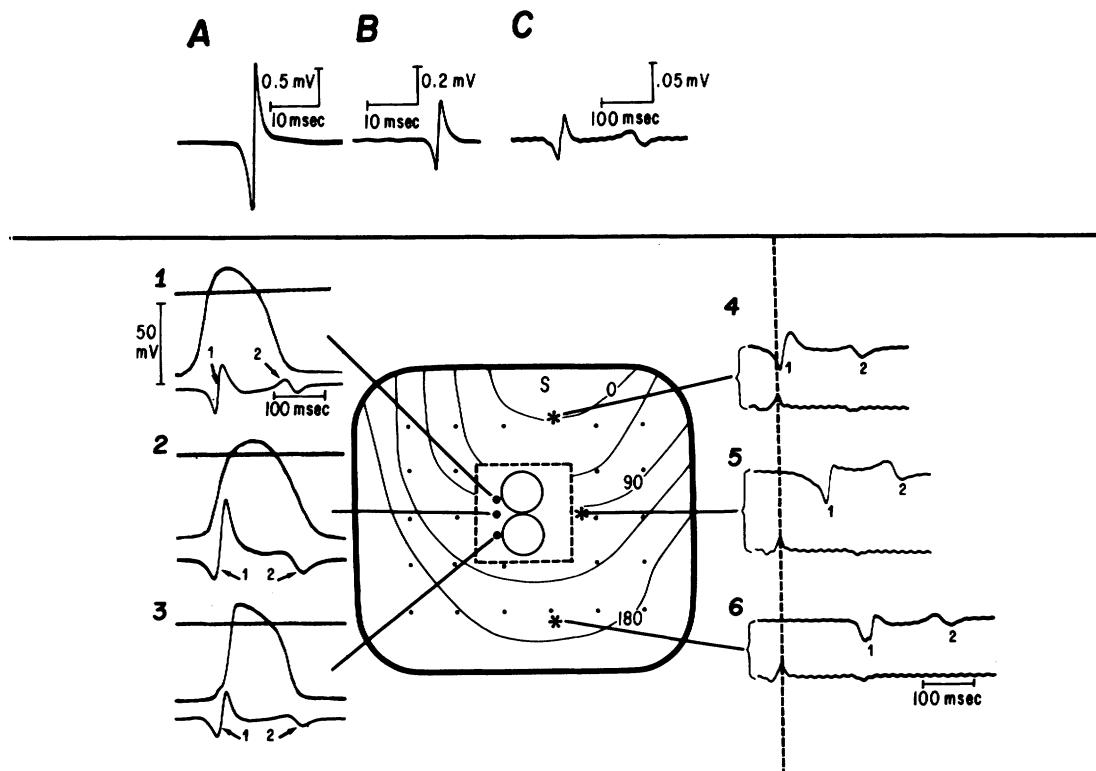
Instead of simply slow activation, fractionated electrograms might be caused by slow activation in combination with inhomogeneities in activation around the recording electrode.<sup>28</sup> Such inhomogeneities on a "micro" level would not be apparent in activation maps like the one shown in figure 4. To obtain more detailed information on characteristics of activation in the vicinity of the extracellular bipolar electrode we simultaneously recorded extracellular waveforms with glass capillary electrodes with tip diameters of about 1 to 5  $\mu$ m. The small tip size enabled us to record extracellular activity from individual muscle fibers<sup>25, 32</sup> at numerous sites within the 1 mm distance between the bipoles.

Recordings are shown in figure 8 for a representative experiment in which the fractionated electrogram had three discrete components separated by short isoelectric segments. Within a 1 mm circumference around the positive electrode pole, a single biphasic deflection was recorded by the extracellular microelec-

trode. This unipolar electrogram coincided in time with the initial deflection of the fractionated electrogram (figure 8, A). As the microelectrode was moved in steps of approximately 0.1 mm toward the negative pole, the amplitude of the waveform coinciding with the first fractionated component decreased and an extracellular potential coincident with the second deflection of the fractionated electrogram appeared (figure 8, B). This waveform became larger as the microelectrode was moved to another site (figure 8, C). Similarly, the amplitude of this waveform decreased as the extracellular electrode was moved to another site and a deflection coinciding with the third component of the fractionated electrogram appeared (figure 8, D) and increased in amplitude (figure 8, E) until only this deflection was found (figure 8, F). It is apparent from this experiment that an extracellular signal resulting

from activation could not be recorded in the vicinity of the bipolar electrode during segments between the major components of the fractionated electrogram. The results of other experiments of this kind are similar.

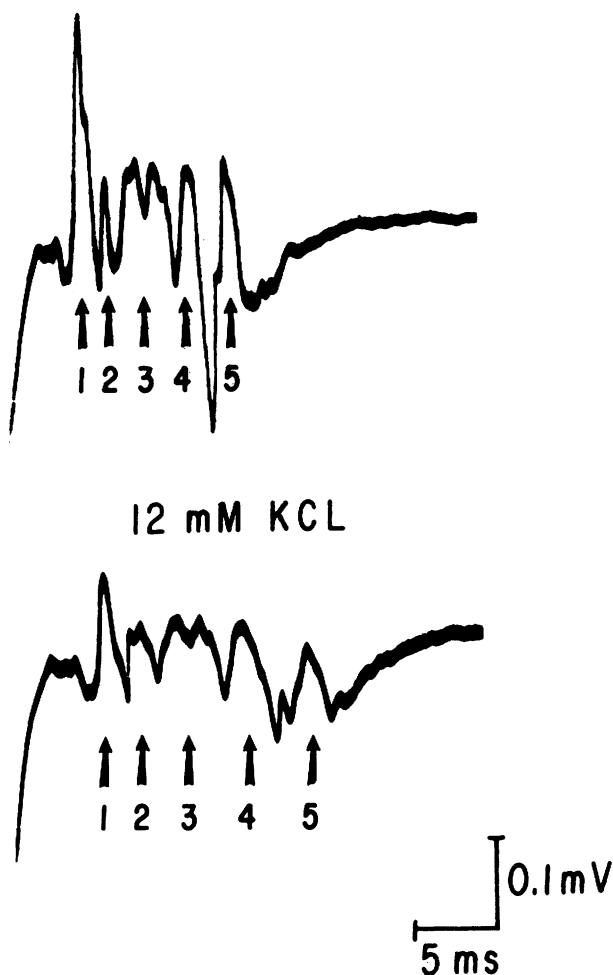
Spach et al.<sup>32</sup> have shown that a uniform biphasic waveform such as those recorded with the extracellular microelectrode is characteristic of action potentials propagating at uniform velocity in a functionally single strand or bundle of cardiac muscle. Interpreted the same way, the results of the experiment shown in figure 8 indicate the presence of three functional strands or bundles of cardiac muscle, each giving rise to a biphasic waveform. The summation of the extracellular waveforms from each of these strands causes the fractionated electrogram recorded with the bipolar electrode.<sup>25</sup> Furthermore, the results of this experiment show that activation in the area where the fractionated



**FIGURE 6.** Electograms and action potentials recorded from a normal preparation superfused with high  $K^+$  concentration Tyrode's solution containing epinephrine. At the top, panel A shows the control electrogram in normal Tyrode's solution, panel B shows the electrogram as the elevated  $K^+$  solution entered the chamber, and panel C shows the electrogram in the high- $K^+$ , catecholamine-containing solution. Note the two components to this electrogram. At the bottom center is shown a diagram of the preparation and the activation map in the high- $K^+$ , catecholamine solution. The dots and asterisks indicate sites at which extracellular electrograms were recorded with a roving electrode. They are 1 mm apart. Representative electrograms, recorded with this probe during mapping, are in the top trace of panels 4, 5, and 6. They all have two components (labeled 1 and 2). The electrogram in the bottom trace in each panel was recorded by a reference electrode near the stimulus (S). At the left, in the top traces of panels 1, 2, and 3, action potentials recorded in the vicinity of an extracellular bipolar electrode (indicated by circles) are shown. The bottom trace shows the electrogram. The depolarization phase of the action potential corresponds to the first electrogram component, and repolarization corresponds to the second component. Upstrokes coincident with the second component were not seen (see figures 5 and 10).

## 8 WEEK INFARCT

4 mM KCL



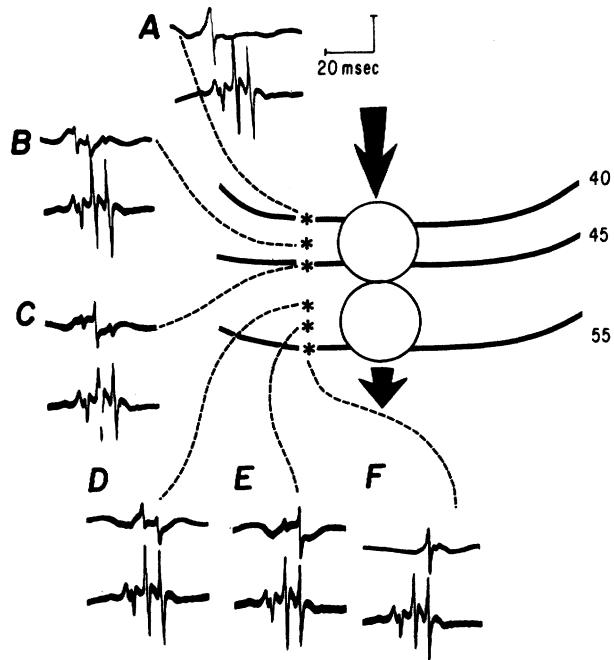
**FIGURE 7.** Effects of elevated  $K^+$  concentration on a fractionated electrogram. The electrogram shown in the top panel was recorded in a preparation from a 2-month-old infarct, superfused with Tyrode's solution containing 4 mM  $K^+$ . Some of the components of the electrogram, indicated by the arrows, are numbered. The electrogram recorded at the same site is shown in the bottom panel during superfusion of the preparation with Tyrode's solution containing 12 mM  $K$ . The elevated  $K^+$  concentration depressed the transmembrane potentials and slowed conduction. The amplitude of the electrogram decreased and the total duration increased but the same fractionated components can be identified (arrows and numbers below the electrogram trace).

electrogram was recorded occurred in steps or jumps, progressing from the 40 to 55 msec isochrones. No rapid biphasic deflections were detected at 42 to 46 msec or at 49 to 53 msec. In contrast, when similar experiments were done with extracellular microelectrodes during slow conduction caused by high  $K^+$  concentration and catecholamines, there was a smooth propagation of the waveform; upstrokes of biphasic extracellular electrograms recorded with the micro-

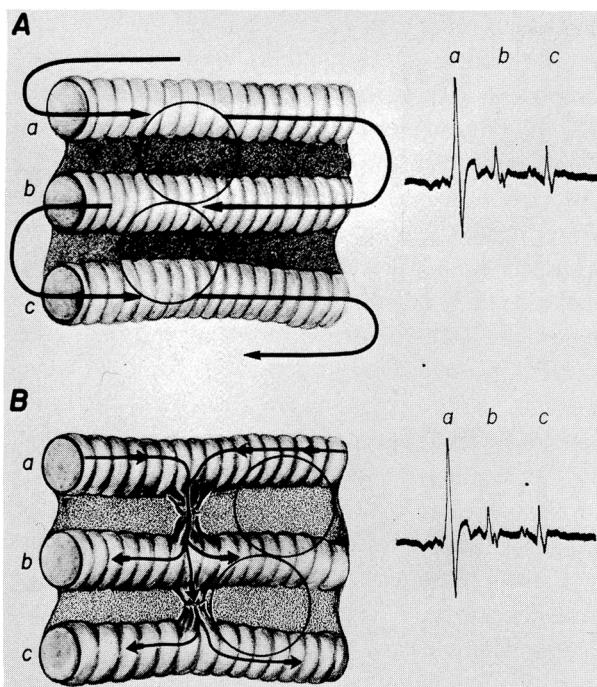
electrode occurred at all times throughout the duration of the broad bipolar electrogram and there were no time gaps without electrogram upstrokes.

Propagation with the characteristics shown in figure 8 might occur for a number of different reasons, several of which are diagrammed in figure 9. The model shown in panel A assumes circuitous conduction (indicated by the arrows) in the vicinity of the bipolar electrode. Conduction velocity in each of three functionally separate strands of muscle is normal (action potentials are normal), yet activation time in the region of the bipolar electrode would appear slow because of the circuitous pathway of propagation. Isoelectric intervals occur during the time the impulse is out of the recording field of the bipolar electrode; components of the fractionated electrogram occur when the impulse returns in one of the muscle strands. (The term "functional strand" is not meant to indicate the actual number of muscle fibers. A functional strand might be composed of a single fiber or a number of closely coupled fibers in which there is uniform propagation.)

The model shown in panel B assumes discontinuous conduction<sup>33, 34</sup> with large pauses be-



**FIGURE 8.** In each panel the top trace is the unipolar electrogram recorded with an extracellular microelectrode and the bottom trace is the fractionated electrogram recorded with the bipolar electrode (indicated by the large circles). The dashed lines and the asterisks show the sites where the unipolar electrograms were recorded, relative to the poles of the bipolar electrode. The large black arrows indicate the direction of impulse propagation and the black lines are isochrones showing activation times. The voltage calibration above is 0.2 mV for the bipolar recording and 10  $\mu$ V for the unipolar recording.



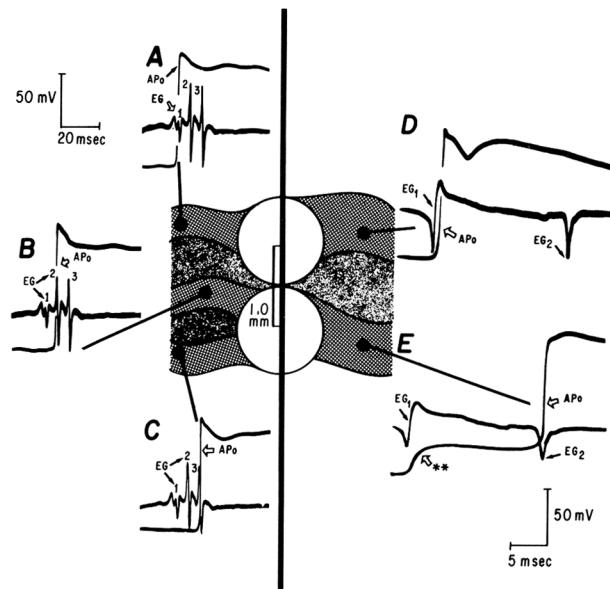
**FIGURE 9.** Two models that might explain the occurrence of the fractionated electrograms. In *A*, three cardiac fibers or bundles are indicated by the cylindrical structures. These fibers are separated by connective tissue as shown by the results of the anatomic studies and are not interconnected in the region shown by the diagram. However, interconnections do occur at a distant site. The large circles represent the location of the bipoles and the dark arrows show impulse propagation. In *B*, the three cardiac fibers are connected and impulse propagation occurs in a relatively straight line through these connections as indicated by the arrows. If it is assumed that the resistance at the connections is high, there might be a delay in conduction from one fiber to another. The model does not explain the different amplitudes of the electrogram components that may result from different diameters of the bundles or different distances of each bundle from the recording electrodes.

tween activation of each functional muscle strand; unlike the model in panel *A*, the impulse is present at all times in the vicinity of the bipolar electrode. This might occur if the resistance at intercellular contacts (intercalated discs) between myocardial fibers is high, causing slow impulse transmission across high-resistance junctions or barriers.<sup>33–37</sup> Other possible causes for such exaggerated discontinuous conduction include (1) localized increases in other components of intracellular (cytoplasmic) resistance, (2) abrupt changes in cell size or surface-to-volume ratios, (3) marked differences in the number of cells connected across the high-resistance barrier, (4) localized increases in extracellular resistance, or (5) abrupt cell branching.<sup>33–37</sup>

If abrupt increases in intercellular coupling resistance as shown in the second model (figure 9, *B*) accurately explain the multicomponent nature of the fractionated electrograms, we might expect to observe

electrotonic prepotentials occurring before the upstrokes of action potentials in regions where fractionated electrograms are recorded.<sup>36, 38–40</sup> We did observe such prepotentials before the upstrokes of action potentials recorded in some areas where “double” potentials occurred. Examples are shown in figures 5 and 10. In the experiment illustrated in figure 10, *D* and *E*, action potentials with upstrokes coinciding either with the first or second component of the “double” potential were recorded in well-defined areas indicated on the diagram. No upstrokes occurred in the segment between the two electrogram components. The upstrokes coinciding with the second electrogram component were preceded by a low-amplitude prepotential (indicated by the open arrow with asterisks in figure 10, *E*), which began during the first electrogram component and spanned the isoelectric segment.

The action potential recordings shown in figure 5 are



**FIGURE 10.** Action potentials at sites where fractionated electrograms were recorded in two different experiments, one shown in the left panels (*A* to *C*) and the other shown in the right panels (*D* and *E*). The large circles in the middle of the figure indicate the bipoles of the electrode. The electrograms in panels *A*, *B*, and *C* have three components (EG 1, 2, and 3). The upstrokes of the action potentials are indicated by AP<sub>o</sub>. Upstrokes were found corresponding to EG 1 (*A*), EG 2 (*B*), and EG 3 (*C*), but no upstrokes occurred in the segments between components. These action potentials were recorded in three areas indicated by the cross-hatching. No action potentials could be recorded from the stippled region. The electrograms in panels *D* and *E* have two components (EG<sub>1</sub> and EG<sub>2</sub>). The action potential upstrokes are indicated by AP<sub>o</sub>. Action potential upstrokes coincided either with the first component (*D*) or the second component (*E*) but never occurred in the isoelectric segment between components. Panel *E* also shows the electrotonic prepotential (indicated by asterisks) occurring before the action potential upstroke. Regions where action potentials could not be recorded were also found in this experiment (indicated schematically by shaded area).

more complex. Again, upstrokes were found that coincided either with the first or second electrogram component but not in the isoelectric segment between components. The action potentials with upstrokes occurring during the first electrogram deflection are shown in panels A and B. Also evident in these recordings are the probable electrotonic effects of distant activation on action potential repolarization: there is an exaggerated repolarization phase (unfilled arrows) before the plateau that coincides with the second electrogram deflection. As the microelectrode was moved toward sites C and D, two component upstrokes were seen, with each component coinciding with one of the electrogram deflections. At sites E and F there were only low-amplitude prepotentials before the upstrokes that coincided with the second electrogram deflection. At another site nearby (G), action potentials not preceded by electrotonic potentials were found.

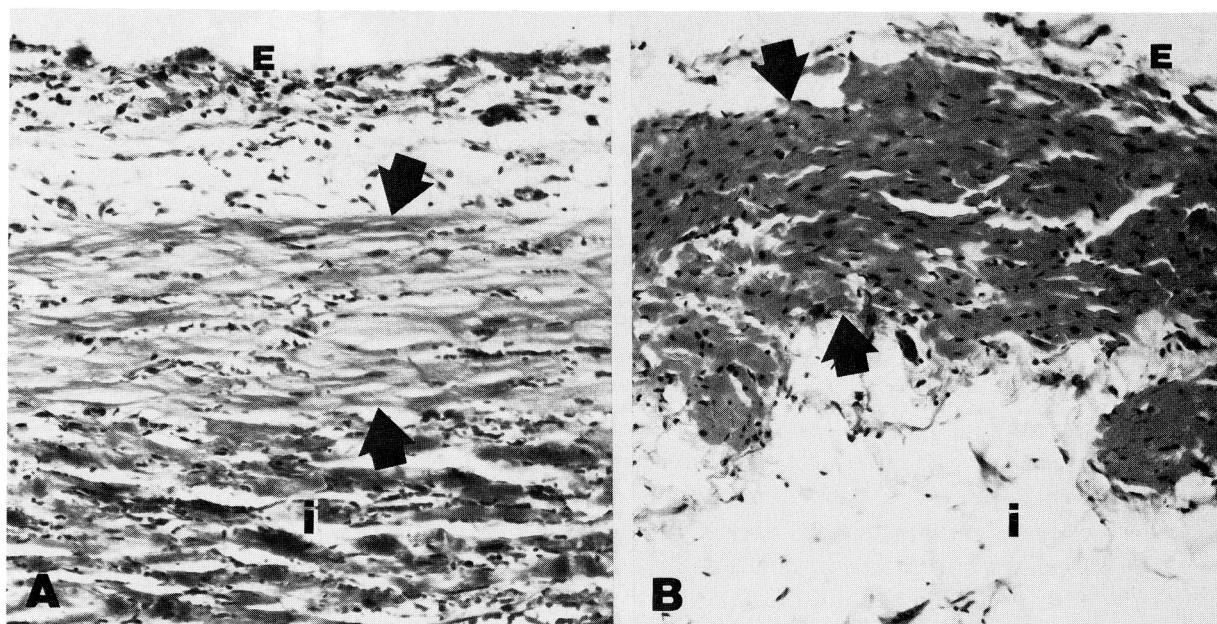
It is apparent from the recordings shown in both figures 5 and 10 that there are strong electrotonic interactions between myocardial fibers in regions where double potentials are found. However, the recordings do not completely solve the problem as to whether there is discontinuous electrotonic transmission, or circuitous conduction. Electrotonic interactions between adjacent fibers might occur even when an impulse is not conducting directly from one fiber to the other.

We did not observe electrotonic prepotentials in

most of our action potential recordings from the vicinity of fractionated electrograms with three or more components. Upstrokes of action potentials recorded near the bipolar electrode from the experiment illustrated in figure 8 are shown in figure 10, A to C. Upstrokes coincided with either the first (A), second (B), or third (C) component of the electrogram but the upstrokes are not preceded by prepotentials. This applies also to 20 other action potentials recorded in this region. In addition, action potential upstrokes were found only in well-defined regions (indicated schematically in the diagram by cross-hatching). No action potentials could be recorded in other regions (indicated by the shading). Furthermore, action potential upstrokes were not found to occur during the time between the major three components of the electrogram.

The absence of electrotonic prepotentials, however, does not eliminate the possibility that slow conduction across high-resistance barriers occurred. High-resistance barriers might change the foot of the action potential upstroke without causing the marked prepotential shown in figures 5 and 10.<sup>33, 36</sup> We did not perform the detailed analysis of the foot that would be necessary to determine whether it had been altered.

**Anatomic basis for fractionated electrograms.** There were marked differences between the microanatomy of regions where normally shaped electrograms were recorded and regions where fractionated electrograms



**FIGURE 11.** Histologic appearance of regions where electrograms without fractionation were recorded in a 5-day-old infarct preparation (A) and in a 16-month-old infarct preparation (B). Just beneath the epicardium (E), the surviving muscle fibers are indicated by the arrows. Beneath this histologically normal muscle is the infarct (i). At 5 days the infarct consists of necrotic muscle fibers, whereas at 16 months the infarct zone in this field is composed largely of fat. (Hematoxylin-phloxine-saffron; A and B  $\times$  150.)

were recorded in the infarct preparations. These differences may explain the occurrence of slow, inhomogeneous conduction and fractionated extracellular waveforms. Figure 11, A, shows the histologic appearance of the 5-day-old infarct preparation from which the normally shaped electrogram in figure 4 (*left*) was recorded. These histologic features are representative of areas in 5-day-old infarcts where smooth, biphasic electrograms were found. In these regions a thin rim of five to 30 intact ventricular muscle fibers survived the coronary occlusion and overlay the infarct (a mean value of 12 fibers in figure 11 determined from serial sections). These muscle fibers had a normal appearance and were characterized by intact cell membranes, myofibrils exhibiting cross-striations and ovoid nuclei with evenly dispersed chromatin. The muscle fibers were arranged parallel to each other, in closely packed fascicles, separated by edema and normal amounts of connective tissue. The separation of the muscle fibers is indicated by the results of the morphometric analysis. The ratio of muscular to nonmuscular elements (M/NM) at electrogram recording sites in *noninfarcted* subepicardium was  $15.9 \pm 2$  and  $12.9 \pm 1.9$  in the two experiments in which it was determined (average 14.4, which is equivalent to 93.5% muscular tissue and 6.5% nonmuscular tissue). In the experiment illustrated in figure 11, A, the M/NM ratio was  $6.4 \pm 0.8$  or 13.5% nonmuscular tissue. The mean value for the four experiments on 5-day-old infarcts that were analyzed was  $4.21 \pm 1.62$  (19.2% nonmuscular tissue). The increase in the nonmuscular component of the epicardial border zone was mainly caused by the edema.

In the 2- to 16-month-old infarcts where normally shaped electrograms such as the ones shown in figure 1 (E and F) were recorded, closely packed, parallel-oriented subepicardial muscle fibers were also found overlying the fibrotic, healed region (figure 11, B). In these areas, there were at least 10 surviving cell layers and sometimes as many as 100.

In figure 11, B, showing the site at which the electrogram in figure 1, E, was recorded, there are 14 to 18 layers of muscle cells determined from serial sections. The M/NM ratio was  $4.56 \pm 1.01$  in this experiment; nonmuscular tissue composed 17.9% of the epicardial border zone. This is similar to the results of the analysis of the 5-day-old infarcts. The fibrous tissue from the healed infarct did not penetrate into the subepicardial aspect of this rim of muscle.

In contrast, in regions where fractionated electrograms were recorded, large amounts of fibrous tissue from the adjacent healed infarct had invaded the sur-

viving subepicardial muscle layers (figure 12). This expansive growth of fibrous tissue separated the surviving muscle fibers from each other along their length to such an extent that often side-to-side contacts between bundles could not be seen. Moreover, the myocardial fibers were no longer arranged in parallel to one another. In the six experiments in which morphometric analysis was done, the M/NM ratio was  $1.35 \pm 0.71$  (42.6% nonmuscular tissue in the epicardial border zone, significantly different from 5-day-old infarcts ( $p < .05$ ).

An exact correlation between histologic and electrophysiologic results was accomplished from the serial sections of regions where electrograms were recorded. For example, from the data presented in figure 8 it was postulated that there were three functional strands of muscle giving rise to the fractionated electrogram. Figure 12, A and B, shows the histologic appearance of the area under the bipolar electrode in that experiment. Between three and 10 muscle fibers were found in each of the 120 serial sections that were examined. This epicardial border zone was 41% nonmuscular tissue. In all of the regions analyzed at which multiple component fractionated electrograms were found, the number of individual muscle fibers was usually greater than the number of electrogram components. However, as we indicated before, a functional strand might contain more than one fiber and the number of functional strands could not be determined by the anatomic study. Figure 12, C, shows the histologic appearance of the region where the "double" potential of figure 10, D and E, was recorded. In fact, only two muscle fibers were found throughout the serial sections. However, six to eight muscle fibers were found in the serial sections of another experiment in which double potentials were recorded.

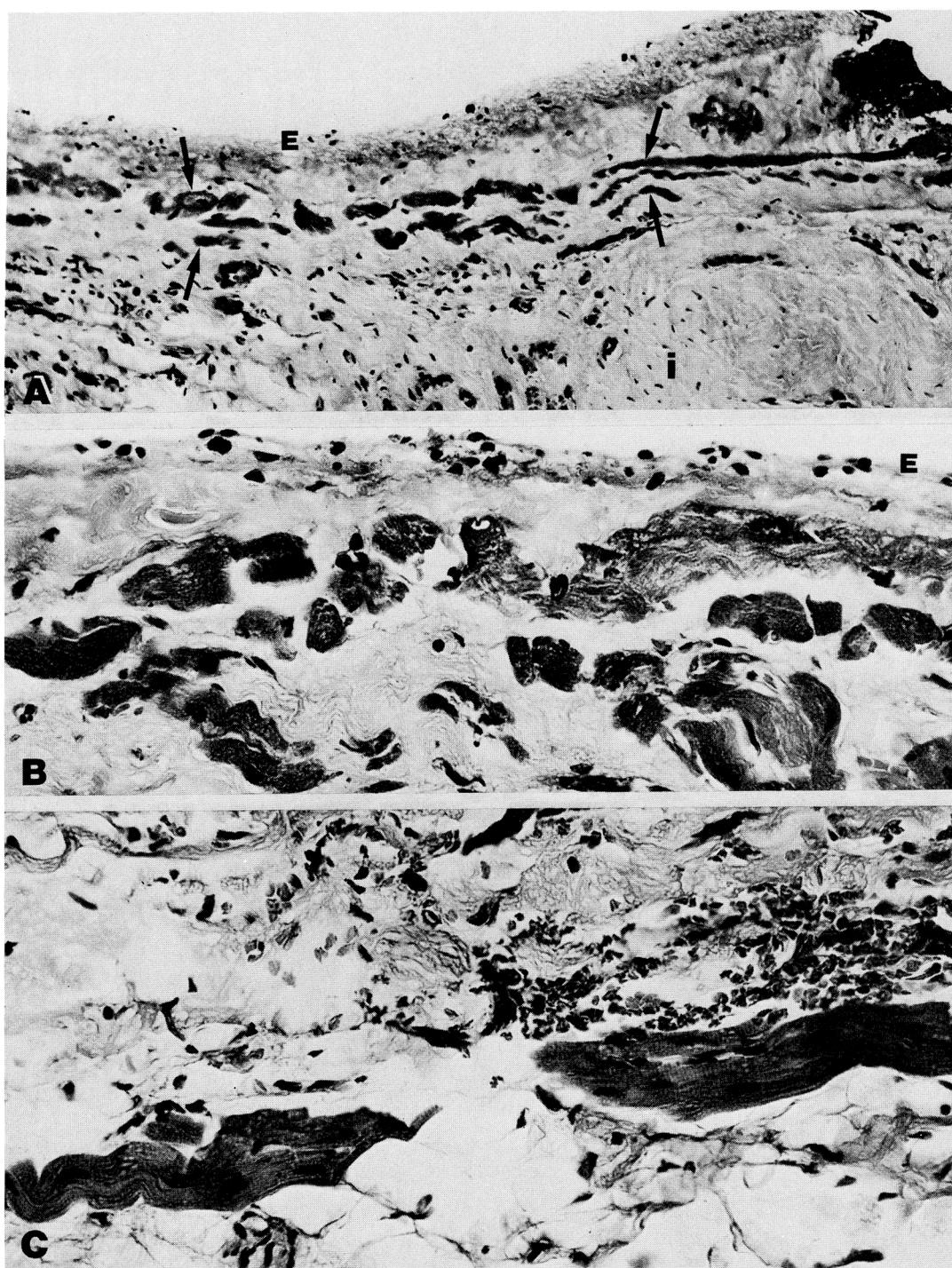
## Discussion

**Importance of fractionated electrograms.** Fractionated electrograms were first recorded with bipolar electrodes from the canine heart during experimental studies on acute ischemia and on healed myocardial infarcts.<sup>28, 41-44</sup> Similar electrograms have also been recorded from patients with ischemic heart disease with catheter electrodes and intraoperative probes, during both sinus rhythm and ventricular tachycardia.<sup>1-11</sup> Fractionated electrograms, recorded during sinus rhythm, have been found to be more numerous in the border zones of aneurysms in patients with healed infarcts and a history of tachycardias than in patients with similar cardiac pathologic status but without tachycardia.<sup>6</sup> In addition, the fractionated electro-

grams in patients with tachycardias had longer durations.<sup>6</sup> The sites from which fractionated electrograms are recorded during sinus rhythm may therefore delineate regions where reentry occurs, causing tachycar-

dia.<sup>6-8</sup> Fractionated electrograms, however, might also occur in regions other than those in which tachycardia originates.<sup>9, 11, 14, 45</sup>

Fractionated electrograms may not always correlate



**FIGURE 12.** Surviving muscle fibers in healed infarcts from which fractionated electrograms were recorded. Beneath the epicardium (E) a few layers of viable muscle, indicated by the arrows, remain at 16 months (A). Directly subjacent is the healed infarct (i). Black ink at the upper right marks the position of the microelectrode used to record extracellular potentials in figure 8. At high magnification (B) the entrapped muscle fibers can be readily seen to be separated and distorted by connective tissue. In panel C, two isolated muscle fibers, in a different preparation, course between the thickened epicardium and the fat of the subjacent healed infarct. (Hematoxylin-phloxine-saffron; original magnification A  $\times 150$ , B  $\times 350$ , C  $\times 400$ .)

with the occurrence of arrhythmias in canine preparations of ventricular tachycardia. After complete occlusion of the left anterior descending coronary artery, ventricular tachycardia is often inducible during the first week (at a time fractionated electrograms were not usually found in the isolated preparations) but may become more difficult to induce later on (when fractionated electrograms were often found in isolated preparations).<sup>23, 46</sup> We do not have any data explaining this discrepancy. One possibility is that during infarct healing in the canine heart, the area of infarction shrinks markedly. If reentrant tachycardia at 3 to 5 days in this canine preparation requires relatively large circuits,<sup>47, 48</sup> the infarcted area after healing may be too small for reentry despite the persistent slow conduction.

**Characteristics of fractionated electrograms.** The electrograms recorded in our experiments are not entirely comparable to those in the clinical studies. The bipolar electrograms that we recorded from normal muscle had durations of 5 msec or less and amplitudes of 2 to 4 mV, whereas fractionated electrograms had prolonged durations of 10 to 70 msec and reduced amplitudes that were often less than 1 mV. The durations of both normal and fractionated electrograms were shorter than those of electrograms recorded with a catheter electrode, recently reported by Cassidy et al.<sup>11, 49</sup> (mean duration of 54 msec for normal electrograms and durations of more than 133 msec for fractionated electrograms) or the duration of electrograms recorded intraoperatively by Weiner et al.<sup>6</sup> (mean duration of fractionated electrograms was  $97 \pm 17$  msec). These differences in the absolute values of normal and abnormal electrogram durations may be related to the size of the recording electrodes and the distance between poles. The catheter electrodes used in the studies of Cassidy et al.<sup>11, 49</sup> had a 10 mm distance between dipoles, whereas the electrodes themselves consisted of relatively wide rings. They are therefore expected to record electrical activity from a larger area than our electrodes, which had tip diameters of 0.3 mm and interelectrode-pole distances of 0.5 to 1.0 mm. The bipolar electrodes generally used for intraoperative mapping are also larger than the ones we used.<sup>6</sup> Our data are comparable to the clinical data if electrogram characteristics are expressed as the ratio of amplitude to duration, as suggested by Cassidy et al.<sup>11</sup> Because of the reduced amplitudes and increased durations, fractionated electrograms have significantly decreased ratios compared with normal in both the clinical studies and our experimental study.

#### Electrophysiologic and anatomic causes of fractionated

electrograms. Fractionated electrograms became more apparent as the infarcts healed. Healing was associated with a return in resting potential and action potential characteristics to normal. A similar improvement in action potentials with infarct healing has also been shown in the studies of Myerburg et al.<sup>50</sup> These data show that fractionated electrograms in the healed infarcts are not caused by abnormal or depressed action potentials (although they might be caused by depressed transmembrane potentials in the instances where fractionation has been recorded during acute ischemia).<sup>28, 44</sup> Despite the normal transmembrane potentials in the healed infarcts, activation in the vicinity of the extracellular recording electrodes was much slower than that in the subacute (5-day-old) infarcts; it sometimes took as long as 70 msec for the wavefront to pass by the electrode. We were also sometimes able to show marked inhomogeneities in activation with closely adjacent areas around the electrode activated at very different times. Different components of the fractionated electrograms coincided with activation of the different adjacent regions. It is therefore apparent that the slow and inhomogeneous conduction and the summation of extracellular currents occurring at disparate times cause fractionation. This possibility had been proposed in earlier studies demonstrating fractionated electrograms.<sup>28</sup>

Why is conduction slow and inhomogeneous in healed infarcts when transmembrane action potentials are normal? The answer to this question may be found in the structural changes that occur during infarct healing. Connective tissue from the necrotic region invades the bordering (subepicardial) areas where there is surviving muscle. These muscle fibers become widely separated and their orientation distorted. These structural changes might lead to an increase in the effective axial resistance, a term used by Spach et al.<sup>33</sup> to describe the resistance to current flow in the direction of propagation. The effective axial resistance depends on the intracellular and extracellular resistivities, the size and shape of the cells, cellular packing, and the resistance, extent, and distribution of cell-to-cell couplings.<sup>33</sup> Distortion of the cells by the connective tissue with a resulting decrease in intercellular connections might increase resistance to current flow and thereby slow conduction.<sup>34</sup>

A reduced space constant has been found in regions of chronically infarcted canine myocardium by Spear et al.<sup>51</sup> and supports this suggestion. It is possible that slow electrotonic transmission across high-resistance or inexcitable gaps sometimes caused the marked conduction delays. Models of this kind of propagation

have been studied by Wennemark *et al.*,<sup>52</sup> who used direct current to cause the area of conduction block, and by Antzelevitch *et al.*<sup>39</sup> and Jalife *et al.*,<sup>40</sup> who used a sucrose gap. In our study, intervals between deflections comprising the fractionated electrograms ranged from 5 to 20 msec, similar to the delays that can be caused by either a high intracellular resistance<sup>53</sup> or electrotonic transmission across inexcitable areas.<sup>52</sup> However, we never observed delays on the order of 100 or 200 msec that sometimes occurred in the sucrose gap experiments.<sup>40</sup>

Action potentials in regions where we recorded double potentials sometimes showed prepotentials before the upstroke, similar to the prepotentials recorded from regions just distal to an area of block in other experiments in which slow, electrotonic transmission has been demonstrated.<sup>38-40, 52</sup> On occasion we also saw two distinct components during the depolarization phase of the action potential in these regions (figure 5, *A* to *D*), previously shown during electrotonic transmission by Wennemark *et al.*<sup>52</sup> There is also the possibility that a change in extracellular resistance related to the increased connective tissue alters current flow and conduction velocity. Additional experiments are required to determine whether effective axial resistance is increased or whether electrotonic transmission across inexcitable gaps is occurring in the healed infarcts. The slowed and inhomogeneous activation we observed might also be caused by conduction at normal velocities over circuitous pathways caused by the structural changes (diagrammed in figure 9).

**Relevance of experimental data to clinical observations.** The pathologic anatomy of endocardial regions where fractionated electrograms are recorded in humans is very similar to that of the epicardial regions of healed infarcts that we studied. Bundles of muscle fibers are widely separated during infarct healing by the ingrowth of large amounts of connective tissue.<sup>54</sup> This anatomic phenomenon and the action potential characteristics we found in our experimental study may explain some of the features of fractionated electrograms. First, fractionated electrograms are sometimes comprised of rapid spikes (no quantification of rapidity is available) called "high frequency" components,<sup>11</sup> although they may also consist of slowly rising deflections. Electrograms with rapid components would not be expected if action potential upstrokes were depressed, since slow upstrokes cause slow rates of extracellular voltage change.<sup>32</sup> On the other hand, rapid spikes might be generated by action potentials with rapid upstrokes. Second, fractionated electrograms have very low amplitudes. Our data suggest that such

low amplitudes are not caused by a reduction in the rate of rise or amplitude of the action potential<sup>32</sup> but may be a result of the sparsity of viable muscle fibers surviving in the ischemic region. This would be expected to decrease the density of extracellular current. Low-amplitude electrograms may also be caused by propagation in nonuniformly anisotropic tissue.<sup>34</sup> Third, the very nature of fractionated electrograms — asynchronous or repetitive spikes — appears to be caused by asynchronous excitation of different poorly interconnected muscle bundles or by delay in conduction from one region of a fiber to another region of the same fiber across high-resistance intercellular connections. If, in fact, these areas of fractionated electrograms delineate reentrant circuits in healed infarcts, the role of slow conduction caused by changes in passive properties of cardiac fibers must be given consideration as a cause of reentrant tachycardia.

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