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Ventricular Tachycardia in the Infarcted, Langendorff-Perfused Human Heart: Role of the Arrangement of Surviving Cardiac Fibers

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Electrophysiologic and histologic studies were performed on Langendorff-perfused human hearts from patients who underwent heart transplantation because of extensive infarction. In nine hearts, 15 sustained ventricular tachycardias could be induced by programmed stimulation. In all hearts, mapping of epicardial and endocardial electrical activity during tachycardia was carried out. Histologic examination of the infarcted area between the site of latest activation of one cycle and the site of earliest activation of the next cycle revealed zones of viable myocardial tissue.

In two hearts in which the time gap between latest and earliest activation was small, surviving myocardial tissue constituted a continuous tract that traversed the infarct. In three other hearts in which the time gap was large, surviving tissue consisted of parallel bundles that coursed separately over a few hundred micrometers, then merged into a single bundle and finally branched again. The direction of the fibers within the bundles was perpendicular to the direction of the activation front in that area.

A similar type of inhomogeneous anisotrophy and activation delay was found in an infarcted papillary muscle removed from one of the explanted hearts and studied in a tissue bath during basic stimulation. Histologic examination of this preparation revealed that the delay was caused by a zigzag route of activation over branching and merging bundles of surviving myocytes separated by connective tissue.

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Only a small percent of patients who survive myocardial infarction develop sustained ventricular tachycardia ≥24 h after the onset of infarction (1). Sustained ventricular tachycardia can, however, be induced in 48% of patients with healed myocardial infarction but without documented arrhythmias (2). This finding suggests that in at least half of the patients who survive myocardial infarction, the substrate for sustained ventricular tachycardia is present, but in most cases, the trigger for starting a tachycardia never occurs. We therefore studied the mechanism of ventricular tachycardias associated with chronic infarction in Langendorff-perfused hearts from patients in whom extensive infarction dictated heart transplantation.

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Convincing evidence from clinical and experimental studies (3–12) shows that reentry is the underlying mechanism of these arrhythmias. In experimental models of chronic infarction, both complete occlusion of a coronary artery (6–9,12) and occlusion followed by reperfusion (13–15) have been effected. The infarcts produced in these two animal models are different, but the resulting tachycardias usually originate in a surviving epicardial zone that overlies the infarcted area, although intramural reentry has also been reported (16). In contrast, tachycardias in the infarcted human heart usually arise in a subendocardial region (17–21); however, tachycardias that originate epicardially and those in which activation revolves around the infarction scar have also been reported (22,23). Although the location of the arrhythmogenic area may differ, histologic studies (12–15,17,24,25) suggest that the arrangement of surviving cardiac fibers in and around the infarct zone plays an important role in the genesis of such tachycardias.

The purpose of our study was to investigate the role of the arrangement of surviving cardiac fibers in the infarct zone, constituting the substrate for such tachycardias. For this, we used Langendorff-perfused human hearts from patients who

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underwent heart transplantation because of extensive infarction.

Methods

Study cases. Fifteen hearts from patients who underwent heart transplantation because of congestive heart failure caused by myocardial infarction were studied in a Langendorff perfusion set-up. In six patients, the location of the infarct was restricted to the anterior wall, sometimes including the septum or lateral wall. The infarct was anterior as well as inferior in six patients, inferoposterior in two and diffuse in one. Before transplantation, the ejection fraction ranged from 13% to 27% (mean 19%). Electrophysiologic studies had not been performed before transplantation in any patient. A history of sustained ventricular tachycardia was documented in one patient; three patients were taking amiodarone.

Langendorff perfusion of the isolated heart. After removal, the heart was submerged in a cooled perfusion medium (modified Tyrode solution) containing (in mmol/liter): sodium (Na^+) 156.5, potassium (K^+) 4.7, calcium (Ca^{2+}) 1.5, phosphate ($H_2PO_4^-$) 0.5, chlorine (Cl^-) 137, bicarbonate (HCO_3^-) 28 and glucose 20. Coronary arteries were flushed with the same solution. The heart was transported to the laboratory in the cold Tyrode solution aerated with 95% oxygen (O_2) and 5% carbon dioxide (CO_2). There, the left anterior descending, circumflex and right coronary arteries were cannulated and attached to a Langendorff perfusion system. Details of this system can be found elsewhere (26). The perfusion fluid consisted of a mixture of 50% human blood and 50% of the modified Tyrode solution (total volume 2 liters). After the heart was connected, coronary flow was stabilized to approximately 200 ml/min. The ventricles were drained by rubber tubes in the apex, one into the left and the other into the right cavity. The heart started to beat spontaneously or to fibrillate within minutes of perfusion. If fibrillation occurred, the heart was defibrillated by direct current countershock after approximately 5 min. Perfusion was maintained at a temperature of 37 ± 0.5°C until either the measurements were completed or contraction noticeably decreased (after 4 to 5 h).

Induction of tachycardia. A bipolar hook electrode was used to stimulate the isolated heart with a strength of twice diastolic threshold. Up to three premature stimuli were used to induce tachycardia. The site of stimulation was epicardial and was altered if no sustained tachycardia could be evoked. In nine hearts, one or more monomorphic sustained (lasting >30 s) ventricular tachycardias could be induced. The cycle length of the induced tachycardias varied from 260 to 560 ms (mean 340). This is close to the mean cycle length of 330 ms of tachycardias that were induced in patients during antiarrhythmic surgery. One of the explanted hearts came from a patient in whom spontaneously occurring ventricular tachycardias were documented preoperatively. In four of the six hearts without sustained tachycardias, only nonsustained tachycardias, polymorphic arrhythmias or ventricular fibrillation could be induced. In two hearts, electrophysiologic recordings were of insufficient quality to compose a reliable activation pattern. In one of these two hearts, extensive endocardial resection had been performed 2 years previously because of recurrent ventricular tachycardia; in the other heart, the infarct was diffuse.

Mapping of electrical activity. Signals recorded with bipolar hook electrodes attached to the base of the left and right ventricles served as a time reference, and were used to distinguish the configurations of induced tachycardias. In the isolated heart, epicardial and endocardial mapping of electrical activity was performed during tachycardia. Only monomorphic sustained tachycardias were selected for further study. These tachycardias were stable with regard to the activation moments and the configuration of consecutive complexes. Endocardial electrical activity was recorded with use of a pear-shaped balloon electrode covered with 64 unipolar electrode terminals. The surface of the balloon was subdivided by 6 equidistant parallels and 11 equidistant meridians. Electrode terminals were placed at the intersections of these geodesic lines, yielding an almost uniform distribution of the terminals with interelectrode distances of approximately 1.2 cm. The balloon was inserted into the left ventricular cavity through the mitral valve orifice. A line on the balloon surface, running along one of the meridians, served as a spatial landmark. Sutures attached to the endocardium at the level of the topmost parallel were used to reconstruct the location of the terminals within the cavity. For recording of epicardial signals, two flexible grid electrodes, each with 64 electrode terminals, were used. In one of the grid electrodes, the terminals were arranged in an 8 by 8 matrix with interelectrode distances of 6 mm. In the other, the terminals were arranged in a 4 by 16 matrix with interelectrode distances of 10 mm. Four to eight successive positions of the grid electrode were used to scan the epicardial surface. These positions were recorded photographically.

Tissue bath recordings. The posterior papillary muscle of one heart was resected and studied in a tissue bath. In this heart, only nonsustained tachycardias could be induced. The preparation was mounted in a tissue bath in which a modified Tyrode solution circulated at a rate of 20 ml/min. The volume of the tissue bath was 75 ml. The composition of the solution was identical to that used for the isolated hearts. The solution was aerated with a mixture of 95% O_2 and 5% CO_2. Temperature was kept constant at 37 ± 0.5°C. During superfusion with an oxygenated solution, a border zone of approximately 600 μm exists in which transmembrane potential characteristics are relatively well preserved (27). The surviving subendocardial rim of the papillary muscle was approximately 400 μm thick. Stimulation was performed at a

basic cycle length of 800 ms at 1 cm from the base of the papillary muscle. Recordings were made from three sites located 0.5, 1 and 1.5 mm, respectively, from the site of stimulation, along a line perpendicular to the long axis of the papillary muscle. Additional recordings were made from six sites located along a line from the base to the top of the papillary muscle. This line ran through the 1 mm point from the site of stimulation, and the interelectrode distance was 2 or 6 mm. After electrophysiologic study, the preparation was fixed with formalin and prepared for histologic investigation.

Histologic methods. Five hearts in which monomorphic sustained ventricular tachycardias could be induced and in which the sites of earliest and latest activity were ≤2.5 cm apart were selected for detailed histologic study. After fixation with formalin, the heart was cut into seven sections: five slices with a thickness of 1.2 cm and a basal and an apical slice. The cutting planes corresponded to the six planes through the parallels. On the basis of the electrical recordings, the area between the sites of earliest and latest activity was determined and cut from the slice or slices in tissue blocks, with a length of approximately 3 cm. Sections of 10 μm thickness were produced with use of conventional histologic techniques. Both elastin-van Gieson and hematoxylin-eosin stains were employed. Elastin-van Gieson–stained sections were used to trace fibrotic cardiac tissue in the infarct zone. Hematoxylin-eosin–stained sections were used to map surviving cells. Schematic drawings, highlighting viable cardiac tissue in contrast to fibrotic tissue, were made of selected sections by using a projection microscope.

To determine whether a surviving area in one section made contact with a surviving area in the next section, transparent sheets of successive schematic drawings were made. Surviving areas that showed an overlap when stacking the sheets of adjacent sections were considered to belong to the same bundle. In this way, it was possible to demonstrate the existence of a continuous tract of surviving myocytes in subsequent sections. Natural landmarks such as the cross sections of venules and arterioles were used to orient successive sections above each other. These markers were always selected close to the site of interest in order to limit inaccurate orientation.

Results

Activation sequence during tachycardia. Fifteen monomorphic sustained ventricular tachycardias of different configurations were induced in nine isolated hearts. Cycle length of the tachycardias ranged from 260 to 560 ms (mean 340). Endocardial as well as epicardial recordings were obtained in 10 tachycardias. In seven tachycardias, earliest epicardial activation appeared ≥20 ms after earliest endocardial activation. In three tachycardias, earliest epicardial and endocardial activation was almost simultaneous (difference <20 ms). Epicardial maps usually showed a larger area of early activation (area within the 20 ms isochrone) than did endocardial maps. In all cases, the endocardial activation pattern showed a focal area of earliest activity from which activation spread more or less centrifugally and was blocked toward the infarcted zone. The site of earliest activation was always located within 2 cm of the border of the infarct. The characteristics of the tachycardias were similar to those recorded in the majority of patients during antiarrhythmic surgery (17).

Surviving myocardial tissue in the infarct. Histologic examination of the infarct area located between the site of latest activation of one cycle and earliest activation of the next cycle invariably showed that the infarct was interwoven with strands of surviving muscle fibers. The fibers within this infarcted area usually showed shifts in direction. Bundles of viable myocardial fibers surrounded by fibrous tissue ranged in diameter from that of a single cell to a few millimeters. These bundles could run individually over a few hundred micrometers or less, then merge and divide again. Bundles were located subendocardially, subepicardially or intramurally.

Tachycardias With Short Diastolic Intervals

In two tachycardias recorded in two different hearts, the distance between the latest and earliest activated site was <2.5 cm.

Activation sequence of heart 1. (Fig. 1 and 2). The endocardial activation pattern of the left ventricle is shown in the upper left panel of Figure 1. An area of damaged tissue extended from base to apex in the posterior wall. Activation started at the right border of the infarct, and main activation spread out toward the lateral wall. Activation toward the septum was blocked after 80 to 100 ms; 240 ms after the onset of endocardial activation, activity reached the septal side of the infarct (site e). The delay between activation at this site and the onset of the next cycle (at site a) was only 30 ms, suggesting reexcitation at the "origin" by means of surviving cardiac tissue between sites e and a.

In the right panel of Figure 1, endocardial electrograms recorded at sites a to f are shown. Signal f is recorded at a position between the site of latest activation of one cycle and earliest activation of the next. The signal has no sharp intrinsic deflection, but its downslope consists of several components (arrows). Comparison of the signal recorded at site f with recordings made at neighboring sites (sites e and b) reveals the origin of two of the components. The deflection indicated by the first (leftmost) of the three arrows coincides with the intrinsic deflection of the signal at site e at the border of the infarct and the surviving septum. The deflection indicated by the third (rightmost) arrow coincides with activation in the healthy lateral wall (site b). The deflection of the second (middle) arrow, however, does not coincide with documented activity anywhere else in the

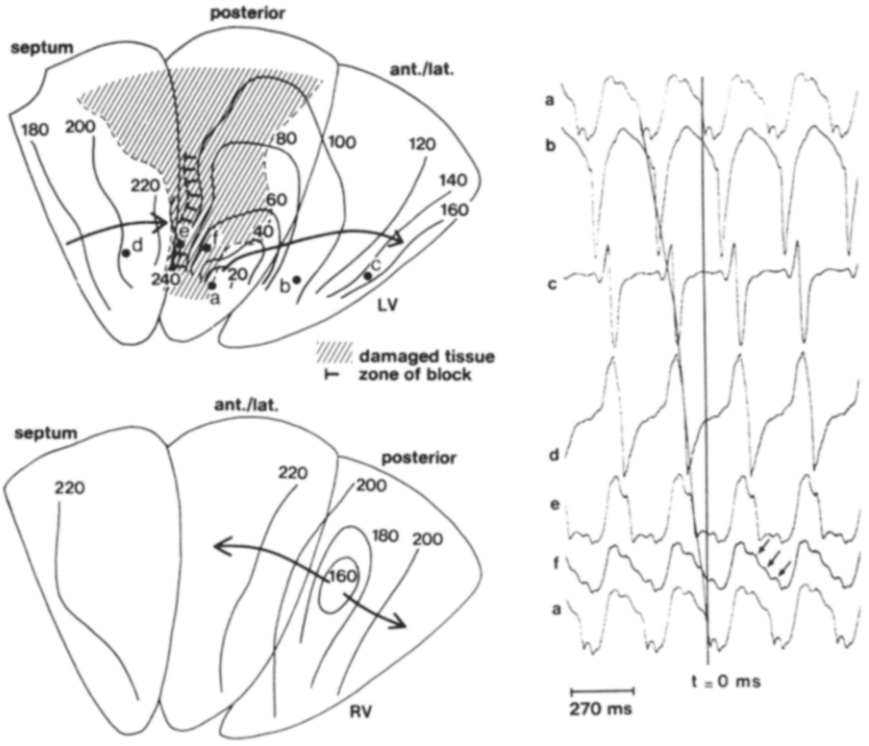
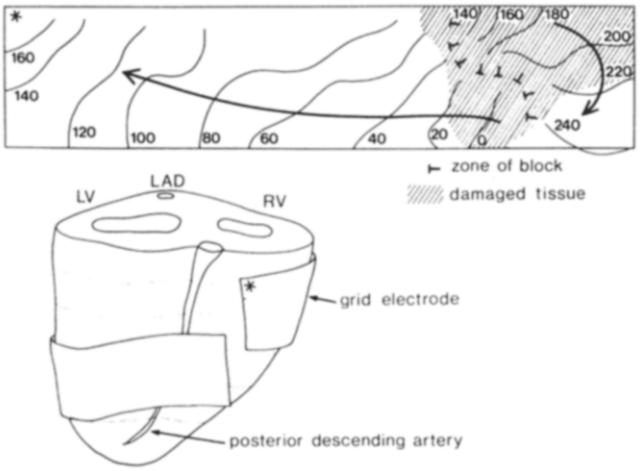


Figure 1. Endocardial activation patterns of the left (upper panel) and right (lower panel) ventricle during sustained ventricular tachycardia recorded in a Langendorff-perfused human heart with extensive posterior infarction. Isochronic maps were derived from endocardial electrograms recorded with a 64 point balloon electrode inserted into the cavity. Isochrones are in ms and timed with respect to the onset of endocardial activation of the left ventricle (LV). Arrows indicate main spread of activation. Endocardial activation started at the right side of the infarct and arrived at the left side 240 ms later. There was a time gap of 30 ms between the latest activation of one cycle and the earliest activation of the next cycle. Reentry probably occurred through surviving pathways in the infarct zone between sites e and a. Tracings are endocardial signals from the left ventricle recorded at sites indicated in the upper left panel. The area of damaged tissue, determined on the basis of the steepness of the signals, correlated well with the infarct zone. ant./lat. = anterior and lateral walls; RV = right ventricle; t = time.

tissue. This indicates that viable tissue must be present underneath the recording site. The time delay of 30 ms between activation at the sites e and a (distance approximately 1.2 cm) suggests that activation is carried back toward the "origin" with close to normal conduction velocity. The slow downstroke of the deflection indicates that surviving tissue must be located at some distance from the recording electrode.

Figure 2. Epicardial activation pattern of the same tachycardia as in Figure 1 from the position of a 4 by 16 point grid electrode shown in the lower panel. Isochrones are in ms and timed with respect to earliest endocardial activation (t = 0 ms in Fig. 1). Earliest epicardial activation arose at the lateral side of the infarct simultaneously with the endocardial onset. Arrows indicate main spread of activation. LAD = left anterior descending artery; LV = left ventricle; RV = right ventricle.



In the lower left panel of Figure 1, the endocardial activation pattern of the right ventricle indicates that earliest endocardial activation occurs in the posterior wall 160 ms after its onset in the left ventricle.

Epicardial mapping of electrical activity in the same tachycardia was performed with a 4 by 16 grid electrode (Fig. 2). The lower panel shows that in this position, the grid electrode covered the epicardial area that faced the site of earliest endocardial activity. The upper panel shows the epicardial activation pattern of the area covered by the grid electrode. The earliest epicardial activation was virtually simultaneous with the earliest endocardial activation. Epicardial activation began at the posterior wall of the left ventricle, just to the left of the posterior descending artery. As in the endocardial activation maps, there was only a small delay between latest activation in one cycle and earliest activation in the next cycle.

Surviving subendocardial tissue in heart 1 (Fig. 3 to 5). Because the sites of earliest and latest activation lay within the shaded area of slice 5 (Fig. 3, right panel), this area was removed and divided into a lateral and posterior part (Fig. 3, left panel). Figure 4 (upper panel) shows photographs of 10 μm thick histologic sections from the lateral and posterior tissue blocks. At this level, the infarct is clearly transmural. In panel b, there is a bulge of surviving tissue (arrow)

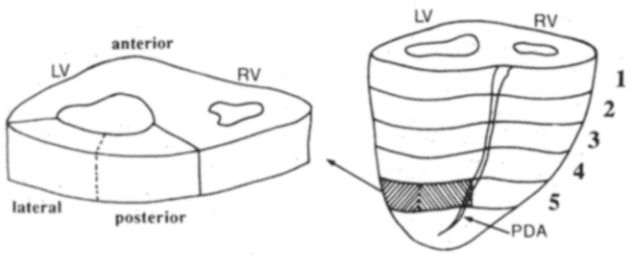


Figure 3. Right, Schematic drawing of the posterior view of the heart in Figure 1. The numbers indicate slices in which the heart was cut (basal part not shown). The upper levels of the slices correspond to the planes through the six parallels that subdivided the balloon electrode used for endocardial mapping. The **hatched area** of slice 5 is the area in which the return path for reentrant activation within the infarct was expected. **Left,** Schematic drawing of slice 5 indicating the lateral and posterior segments that were selected for detailed histologic study. PDA = posterior descending artery; other abbreviations as in Figure 1.

protruding into the infarct zone. Panel c, derived from a section 500 μm more apical in the lateral tissue block, indicates that the bulge of surviving tissue has become isolated (arrow). Finally, in panel d (1,000 μm underneath section b), the island of surviving tissue merges with the healthy lateral wall. This observation suggests that there was a surviving bundle connecting viable tissue at either side of the infarct zone and possibly forming a return path for reentry. To prove that the tract was indeed continuous, we made schematic drawings of series of sections 100 μm apart throughout the lateral tissue block of Figure 3 and compared each section with its successor. *A three-dimensional reconstruction of the tract is shown in Figure 5.* The schematic drawings of 10 successive sections (a to k), each 100 μm apart, show that the tract (gray area) fuses with remaining healthy tissue of the lateral wall at level d. From here, the tract runs down toward level k, and remains horizontal over a distance of about 6 mm in level j before it ascends and finally merges with remaining healthy tissue of the posterior wall at level a. The upper section of the reconstruction (level a) lies 100 μm beneath the lateral section in Figure 4a. Although the tract appears to be continuous, there are some narrow passages, especially in the descending and ascending parts of the tract. The smallest width of these bottlenecks was approximately 250 μm.

One might speculate that unidirectional block could occur preferentially at these sites. To demonstrate that continuity was maintained in the narrow corridors, we analyzed all the intervening sections (Fig. 5) at 10 μm intervals. At this resolution, too, the surviving tract appeared to be continuous. The tract was located at some distance from the endocardial surface, which may account for the shallowness of the endocardial signals during the presumed return of the activation wave through the tract (see Fig. 1f).

Surviving subepicardial tissue in heart 1 (Fig. 6). The subendocardial tract did not constitute the only possibility for reentry. The epicardial activation map (Fig. 2) suggested the presence of a surviving tract in the subepicardial part of the infarct. An anatomic substantiation for such a tract could be demonstrated by using the same procedure as described above. The course of the tract is schematically shown in the lower part of the middle panel (heavy line) in Figure 6. In sections a and c of the lateral wall, surviving tissue is interrupted, preventing activation from passing to the posterior wall at these levels. Section b shows continuity of surviving tissue from the left to the right, and represents the part of the tract in the lateral wall.

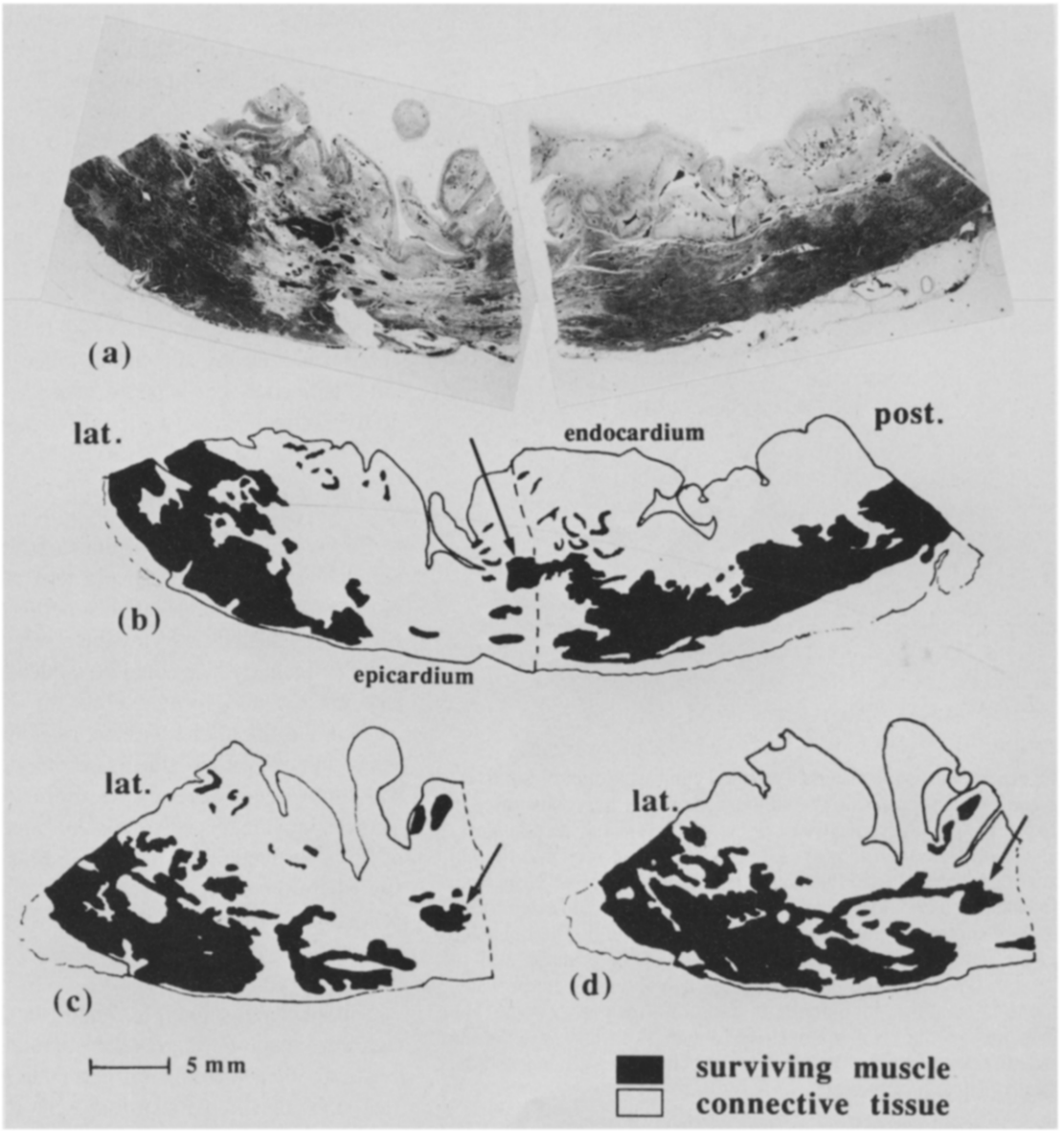
Sections d and e are taken from the posterior wall and are 100 μm apart. Each section alone is not continuous with respect to surviving tissue, but by overlapping the two, the interrupted areas in one section (ovals) are bridged by viable tissue of the other section. Continuity in this part of the tract was maintained in the intervening 10 μm thick sections. The smallest width of the tract in these areas is approximately 280 μm. The lateral and posterior parts of the tract run at different levels (middle panel) but are connected by surviving tissue at the border between the tissue blocks (the vertical part of the heavy line in the lower part of the middle panel).

Dimensions of surviving tracts in heart 1. The length of the endocardial tract within the infarct zone was approximately 13 mm. In both the endocardially and subepicardially located tracts, fiber orientation was mainly in the direction of the spread of activation. Only in the vertical part of the subepicardial tract was the fiber orientation perpendicular to the spread of activation. However, fibers in this area formed a single compact bundle and were not isolated from each other by fibrous tissue. The short length of the tracts together with a fiber orientation mainly in the direction of the tract may account for the small delay of activation in this area.

Findings in heart 2. The second heart with a small delay between earliest and latest activation exhibited similar results. A tract of surviving tissue, located 1.5 mm from the epicardial surface of the anterior wall, was traced in this heart. Its smallest width was approximately 350 μm. Two morphologically different tachycardias could be induced. In both, the area between the site of latest activation of one cycle and the site of earliest activation of the next was the same. Because we could trace only one surviving tract in this area, it is probable that this tract was used as a return path for activation in both tachycardias. The tachycardias revolved in opposite directions, indicating that unidirectional block in this area could occur in either direction.

Tachycardias With Long Diastolic Intervals

In three hearts, the sites of latest activation of one cycle of the tachycardia and earliest activation of the next were <2.5 cm apart, and the delay was >150 ms. In all three, the



direction of the surviving fibers in this area was perpendicular to the line connecting the sites of earliest and latest activation.

Endocardial activation sequence (Fig. 7). Earliest endocardial activation arose at the septal side of the infarct zone. At the base of the septum, the spread of activation toward the posterior wall was blocked. However, the wave front reached the posterior wall by way of the anterolateral wall and apex. The wave fronts merged at a mid-posterior level (160 ms isochrone) to arrive 240 ms after the onset at the base of the posterior septal border (site a). Here, a time gap of 160 ms had to be bridged to close a hypothetic reentrant circuit that reactivates the "origin" (site c). The

Figure 4. Panel a, Photograph of the sections from the two tissue blocks shown in the left panel in Figure 3 (slice 5). Sections were 10 μm thick and stained with elastin-van Gieson. **The left panel** shows the section from the lateral wall (lat.); **the right panel** shows the section from the posterior wall (post.). **Dark areas** mark surviving cardiac tissue, whereas **light areas** point to fibrotic and fatty tissue (**the sharply outlined, dense, black areas** are caused by india ink that was perfused after the experiment to trace vascular supply). **Panel b,** Schematic drawings of the sections from **panel a.** Areas comprising surviving myocytes are shaded in **black.** Note that the infarct is transmural at this level. **Panels c and d,** Schematic drawings of sections from the lateral wall 500 and 1,000 μm, respectively, beneath the level of those shown in **panel b.** Note that a bulge of viable tissue at the **left** of the surviving posterior wall (**arrow in panel b**) becomes isolated in **panel c** (**arrow**). **In panel d,** this isolated area merges with the bulk of surviving tissue in the lateral wall (**arrow**).

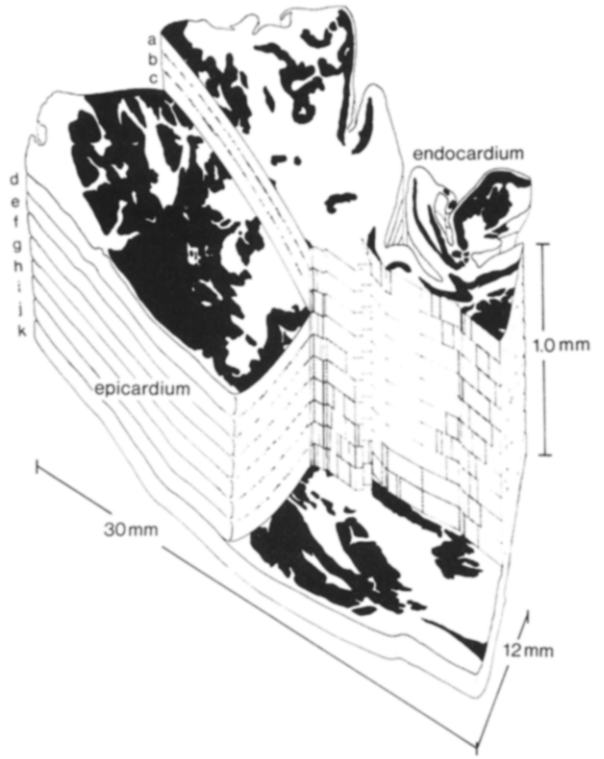


Figure 5. Three-dimensional reconstruction of a tract of surviving cardiac tissue traversing the infarct zone of the heart illustrated in Figures 1 to 4. Surviving tissue of the sections is indicated in **black**, and that of the tract in **gray**. Eleven consecutive sections, 100 μm apart and derived from the lateral tissue block in Figure 3, are used for the reconstruction. The left side of the tract is connected to the bulk of surviving tissue of the lateral wall at level d. The right side of the tract connects with surviving tissue of the posterior wall at level a. By connecting the nonaffected lateral and posterior walls, the tract creates a possible return path for a reentrant circuit. The length of the tract is approximately 13 mm. The width varies along the tract, with bottlenecks appearing in both the descending and the ascending parts of the tract.

electrographic tracings in the lower panel show that the signal recorded at the earliest activated site (site c) is initially negative, confirming the role of site c as an "origin" (the site where activation leaves a small bundle and activates remaining tissue mimicking a site of origin). The signal recorded from site b (the site between earliest and latest activated sites shows mid-diastolic activity (arrow). In about half of the tachycardias, local deflections (single complexes or fractionated activity) were recorded in the area of delayed activation. Failure to detect local activity because of a return path may be caused by 1) the isolating effect of the thickened endocardium, 2) the small diameter of the surviving bundles, and 3) the distance from the bundle to the recording site.

Histology of the area of delay (Fig. 8). The area of delayed activation consisted of a collection of surviving bundles with various diameters, separated from each other by fibrous or fatty tissue. Surviving bundles coursed separately over a few hundred micrometers and then merged into a single bundle. Fiber direction of the bundles was perpendicular to the line connecting the site of earliest and latest activation.

Similar results with regard to fiber direction were obtained from the other two hearts showing a large delay between latest activity of one cycle and earliest activity of the next. Because of the complicated architecture of branching and merging muscle bundles in the infarct, it was impossible to reconstruct a possible return path in either of these hearts.

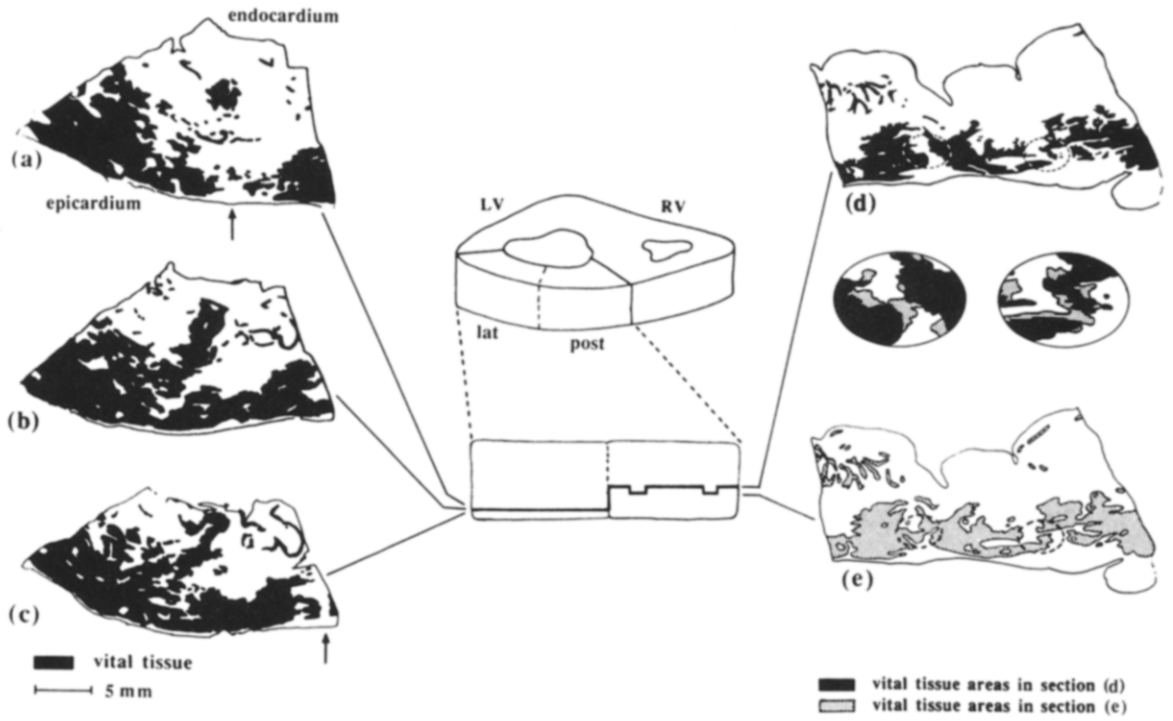
In the remaining 10 hearts with tachycardias in which the delay was >60 ms and the distance between earliest and latest activated sites was >2.5 cm, the surviving fibers had no fixed direction, but varied throughout the area of delay.

Isolated Papillary Muscle

To investigate the occurrence of large delays in areas of parallel bundles that merge and separate, we studied spread of activation in an isolated superfused papillary muscle. From one isolated heart in which only nonsustained monomorphic tachycardias could be induced, the posterior papillary muscle was located close to the earliest activated endocardial site of one of the nonsustained tachycardias. To select an area with a large activation delay, the preparation was stimulated at several sites. For each site of stimulation, a corresponding recording position was chosen at a distance of 1 mm perpendicular to the fiber direction. The stimulation site where the delay between the stimulus and the intrinsic deflection of the signal at the recording site was maximal proved to be located approximately 1 cm from the base of the papillary muscle.

Spread of activation (Fig. 9 and 10). Extracellular recordings were made during regular stimulation (at a basic cycle length of 800 ms) from sites perpendicular or parallel to the long axis of the papillary muscle (parallel to the fiber direction). Figure 9 (upper left panel) shows the histologic findings in a section perpendicular to the fiber direction at the site of stimulation. A schematic drawing of the section (lower panel) demonstrates a rim of surviving tissue along the entire endocardial surface. This rim is interrupted at several sites by fibrotic tissue. In electrographic recordings made from three sites along a line perpendicular to the fiber direction, signal C, which is recorded closest to the site of stimulation (at 500 μm distance), shows a single complex with multiple deflections. In signal B, recorded over the interruption in the rim of surviving tissue 1 mm from the site of stimulation, two complexes are present, separated by an isoelectric interval. Signal A, which is recorded 1.5 mm from the site of stimulation, is very similar to signal B, but the second complex of signal B is more pronounced.

Figure 10 (left panel) shows a schematic drawing of the papillary muscle together with six recording sites along a line parallel to the fiber direction. Electrographic signals A to E



derived from these sites show two complexes separated by an isoelectric interval. This interval becomes shorter as the recording site is closer to site F. Here, the two complexes merge, yielding a signal that consists of a single complex with multiple deflections. Although the site of stimulation was close to sites B and C, earliest depolarization is found in signal D. The first deflections in signals E and F are later in succession, indicating that activation proceeds from site D toward site F. The second deflection comes earliest in F and progressively later toward A, indicating that a second wave appears to travel somewhat later from sites F to A. The main activation at site A (second deflection) appears to reach it by a rambling route by way of site F.

Histologic correlation (Fig. 10 and 11). This observation is supported by the sections taken from the recording sites (Fig. 10). In the surviving rim of sections B to E, there is an interruption that disappears in section F. When we extended the number of sections at site F, we found that the bundles merged near site F and then divided once more.

The architecture of the papillary muscle and its spread of activation is shown schematically in Figure 11. Delay of the activation wave is due to a lengthening of the route. The apparent conduction velocity in the area around site A perpendicular to the fiber orientation would be approximately 0.03 m/s (distance 1.5 mm, delay 46 ms), but the real conduction velocity is much faster. The distance from the site of stimulation to site A by way of site F is approximately 2 cm. The delay between the stimulus and activation at site A is 46 ms, resulting in a mean conduction velocity of 0.45 m/s, a value close to normal for cardiac muscle.

Figure 6. Schematic drawings illustrating an epicardial tract of surviving tissue traversing the infarct zone of the heart described in Figures 1 to 5. In the **lower part of the middle panel**, the entire course of the tract is shown schematically (**heavy line**). On the **left**, three schematic drawings of the lateral tissue block (see **upper part of the middle panel**) are shown. Sections were 300 μm apart. **Sections a and c** show that continuity of surviving tissue is interrupted at the sites indicated by the **arrows**. In **section b**, there is continuity of surviving myocardium from the **left to right**. The surviving areas in this section constitute the lateral part of the tract. In the posterior tissue block, continuity is absent in **sections d and e (oval areas)**. Only if **sections d and e** are stacked is continuity of viable tissue present. The **enlarged ovals** between **sections d and e** show the critical areas were an interruption of the continuity in one section is overlapped by surviving tissue in the other section. The lateral and posterior parts of the tract are connected at the border between the tissue blocks. Abbreviations as in Figures 1 and 4.

Discussion

A substantial body of evidence (3–12) supports the concept that ventricular tachycardias in the chronic phase of myocardial infarction are based on reentry. Reentrant arrhythmias may be caused by abnormal membrane variables, abnormal geometric arrangement of myocardial fibers or a combination of the two. Transmembrane potentials obtained from superfused resected endocardial preparations from patients with ventricular tachycardia in the chronic phase of myocardial infarction were only mildly depressed (17). This observation indicates that action potential characteristics of

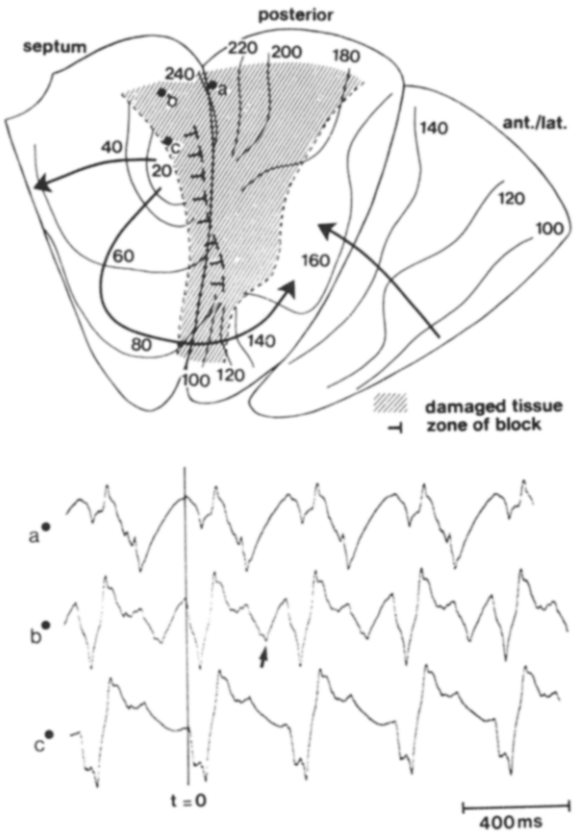


Figure 7. Endocardial activation pattern of sustained ventricular tachycardia with a large time gap between latest activation of one cycle and earliest activation of the next cycle. The distance between the site of latest and earliest activation was <2.5 cm. Isochrones are in ms and timed with respect to earliest endocardial activation. Activation starts at the left side of the infarct and arrives at the right side of the infarct 240 ms later. Electrographic tracings (**below**) are the signals recorded from the earliest activated site (**c**), the latest activated site (**a**) and an intermediate site (**b**). The signal at **site b** shows mid-diastolic activation (**arrow**). Abbreviations as in Figure 1.

surviving myocardial fibers within an infarct may be close to normal. This view is supported by findings in animal experiments (12,28), where action potentials recorded from cells in the epicardial border zone became normal with the passage of time. Therefore, in the chronic phase of myocardial infarction, reentrant tachycardias may be caused predominantly by abnormalities in the geometric arrangement of surviving fibers, and not by abnormalities in transmembrane potentials.

Recording technique. Despite certain disadvantages, unipolar recording is, in our opinion, best suited for mapping studies such as those undertaken in this study. The fast downstroke of the unipolar complex reflects the moment of activation. Areas where activation arises are characterized by an initial negative deflection, whereas recordings made from sites where activation is passing exhibit initial "R waves." Interpretation of unipolar signals remains possible in the case of polyphasic deflections. When a signal that reveals polyphasic deflections is compared with signals recorded at neighboring electrode terminals, the nature of the deflections can usually be clarified. This is usually not possible for bipolar signals with multiple components. Even the selection of that part of the signal that corresponds to the intrinsic deflection is often problematic in bipolar recordings. A disadvantage of unipolar recordings may be encountered when signals are recorded in areas of injured tissue. In that case, the intrinsic deflection is small and may be obscured by larger remote components from neighboring healthy tissue. Although in bipolar recordings, distant events are canceled, sometimes permitting better estimation of the intrinsic deflection, the steepness of unipolar complexes provides information about the vitality of underlying tissue, allowing discrimination between healthy and damaged myocardium. It is because of the facility of interpretation of unipolar complexes under different conditions that we prefer the unipolar recording mode.

The spatial resolution of the balloon electrode and one of the grid electrodes (4 by 16 matrix) was 1.4 and 1 cm^2, respectively. The spatial resolution of the other grid electrode was 0.4 cm^2. Detection of a complete reentrant circuit, in which small bundles are part of the circuit, would require the use of an electrode system with very small interelectrode distances. Even then, however, it is impossible to follow activation in all parts of the circuit because of the rambling course of the tracts. In addition, the large number of plunge electrodes that would be required, especially in the area of the tract, would certainly affect the spread of activation. Our experience (17) with intraoperative mapping during antiarrhythmic surgery has shown that the earliest activated site during tachycardia can reliably be identified. In addition, in a large number of tachycardias, presystolic or late potentials were found at several sites near the origin, permitting a tentative reconstruction of the route followed by the impulse. Thus, the resolution we used is sufficient to select areas where a possible return path for activation can be expected. Histologic examination of these areas showed that surviving bundles were present and, in some cases, the tracts were continuous, connecting remaining healthy parts of the heart on either side of the infarct. It is not possible with our methods to follow activation within the tracts.

Conduction in surviving tissue within the infarct. Bundles of viable myocardial fibers embedded in fibrous tissue are a common finding in chronic myocardial infarction (24). In the human heart, cardiac tissue preferentially survives immediately beneath the endocardium (24,29). The reason for this may be the presence of a subendocardial vascular plexus and diffusion of oxygen and substrate from the cavitary blood (30,31). The subendocardial location of surviving bundles may account for the subendocardial origin of the majority of tachycardias (18–21). The surviving subendocardial layers

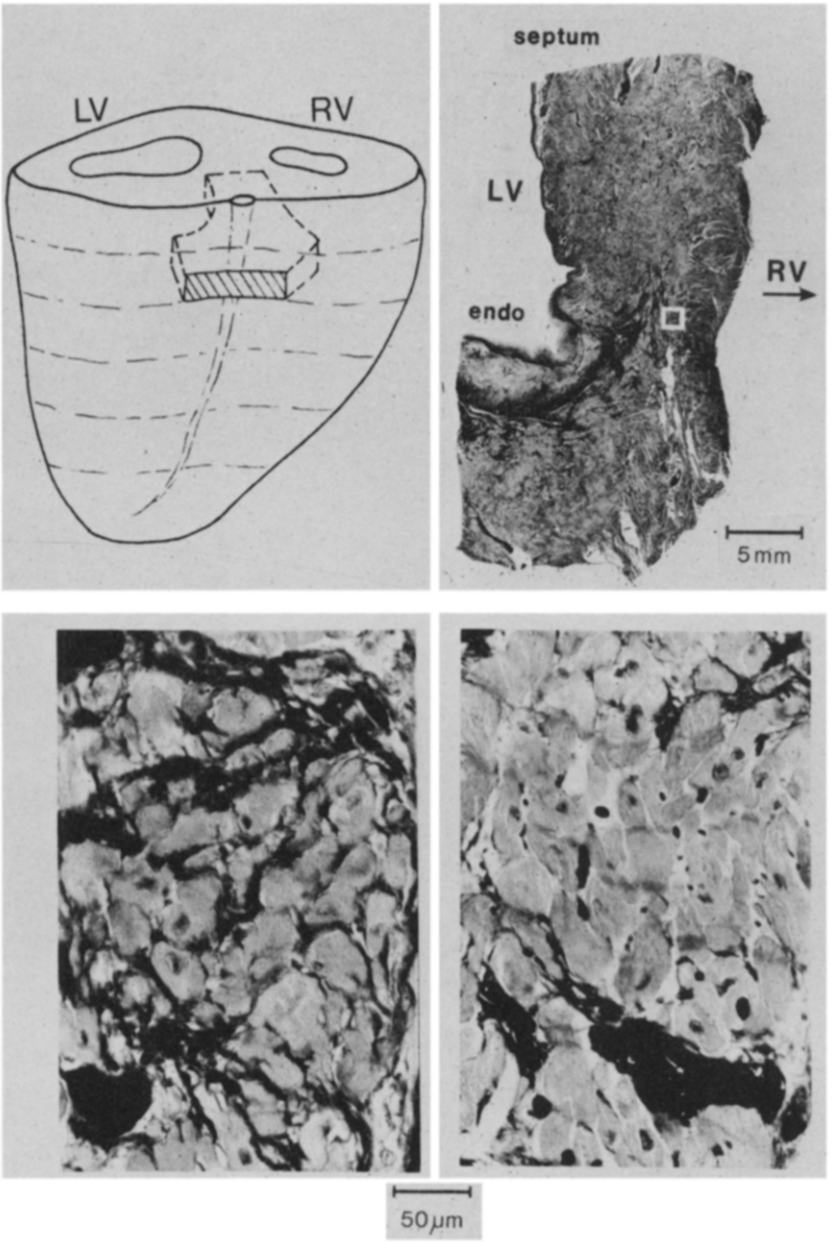


Figure 8. Upper right panel, Photograph of a section of the area between the site of earliest and latest activation in the heart in Figure 7. **Bright areas** consist of surviving myocytes; **dark areas** are mainly fibrotic. **Upper left panel,** The area from which the tissue sample was harvested. **Lower panels,** Photomicrographs of two sections 100 μm apart, showing details of the marked area in the **upper right panel.** The photomicrograph on the **left** shows that the area consists of a number of surviving bundles (**bright areas**) separated from each other by fibrous tissue (**dark areas**). The photomicrograph on the **right** shows histologic features in a section 100 μm beneath the left section. Here, the separated bundles have merged into a single bundle. Fiber direction was perpendicular to the line connecting the earliest and the latest activated site. Endo = endocardial wall; other abbreviations as in Figure 1.

resemble the surviving epicardial layers found in experimental chronic infarction after complete occlusion of a coronary artery. In these surviving epicardial sheets that overly the infarct zone, the anisotropic structure of cardiac fibers is the major determinant for reentry (11,12). Our observations showed that the surviving subendocardial layer in human infarcts is not homogeneous, but is interrupted at many sites, similar to the histologic structure of the papillary muscle in Figure 9. We also observed that surviving bundles were not confined to the subendocardial layers but were found intramurally and subepicardially as well. In cases in which the time gap between latest activation of one cycle and the earliest activation of the next cycle was small, a continuous bundle of surviving myocytes that traversed the infarct was found. This observation does not imply that we also proved the unique path followed by the activation; there are small areas of fibrous tissue within the tract that hamper the selection of this path of activation (Fig. 5).

In cases with large time gaps over short distances, clusters of surviving muscle bundles separated by fibrous tissue were present, and the repeated fusion and bifurcation of these bundles resembled the inhomogeneous anisotropy found in the papillary muscle. An important factor that determines conduction is the coupling resistance between cells. Even under normal conditions, tissue anisotropy causes a difference in coupling resistance perpendicular and parallel to the fiber direction, resulting in differences in conduction velocity along these two axes (32–35).

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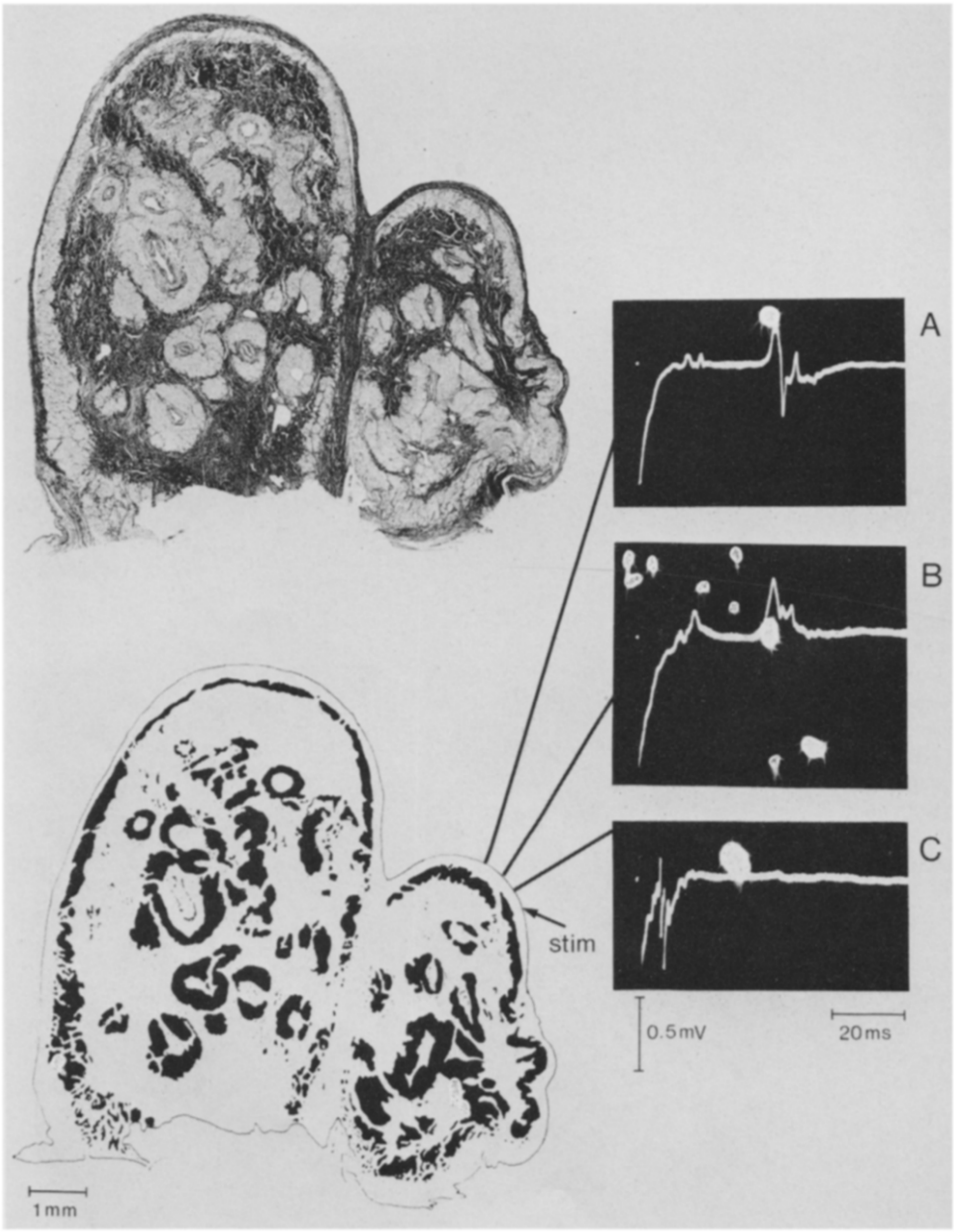

Figure 9. Upper left panel, Section of the posterior papillary muscle from the left ventricle of a heart in which only nonsustained ventricular tachycardias could be induced. **Bright areas** represent surviving cardiac tissue; **dark areas** mainly consist of fibrotic tissue. Along the entire surface, a rim of surviving tissue is present. **Lower left panel,** Schematic drawing of the section depicted in the **upper panel.** Surviving tissue is shown in **black.** Tracings on the **right** are signals recorded from sites indicated in the **lower panel.** The preparation was stimulated at the site marked by the **arrow,** using a basic cycle length of 800 ms. stim = site of stimulation.

An increase in coupling resistance may influence conduction in two ways. 1) Local delays may occur as a result of impulse transmission across a high resistance junction. The occurrence of an electrotonic foot that precedes the upstroke of the action potentials would be expected in this case. Such aberrant action potentials have been found in experimental infarction (28). 2) Proliferation of connective tissue may reduce or abolish the side to side electrical coupling between cells and increase the distance to be traveled between points (that is, a winding, circuitous route for activation may be followed). Thus, the tract is lengthened and a zigzag course of propagation results. In our example of the papillary muscle, the delay can be explained entirely by an increase in the distance to be covered, which is caused by merging and diverging bundles. A repetition of this phenomenon could cause large delays. Because the structure of the surviving bundles in the areas of large delays resembles that of the papillary muscle, delays based on a lengthening of a conduction pathway could play a role in these tachycardias.

Unidirectional block. Unidirectional block, which is necessary to initiate a reentrant arrhythmia, may result from regional differences in recovery of excitability or from the asymmetric anatomic structure of some regions. The geometry of the surviving bundles that merge and divide indicates that geometric factors may play an important role in the occurrence of unidirectional block in the hearts we studied. It could occur at sites where a thin bundle suddenly enters a larger one because current output of the small bundle is too low to drive the larger one (35,36). Conduction in the reverse direction may still be possible if the large bundle delivers enough current to depolarize the small one. Also, branching sites may give rise to a direction-dependent electrical load and, as a consequence, may cause unidirectional block (37). A three-dimensional reconstruction of a return path for

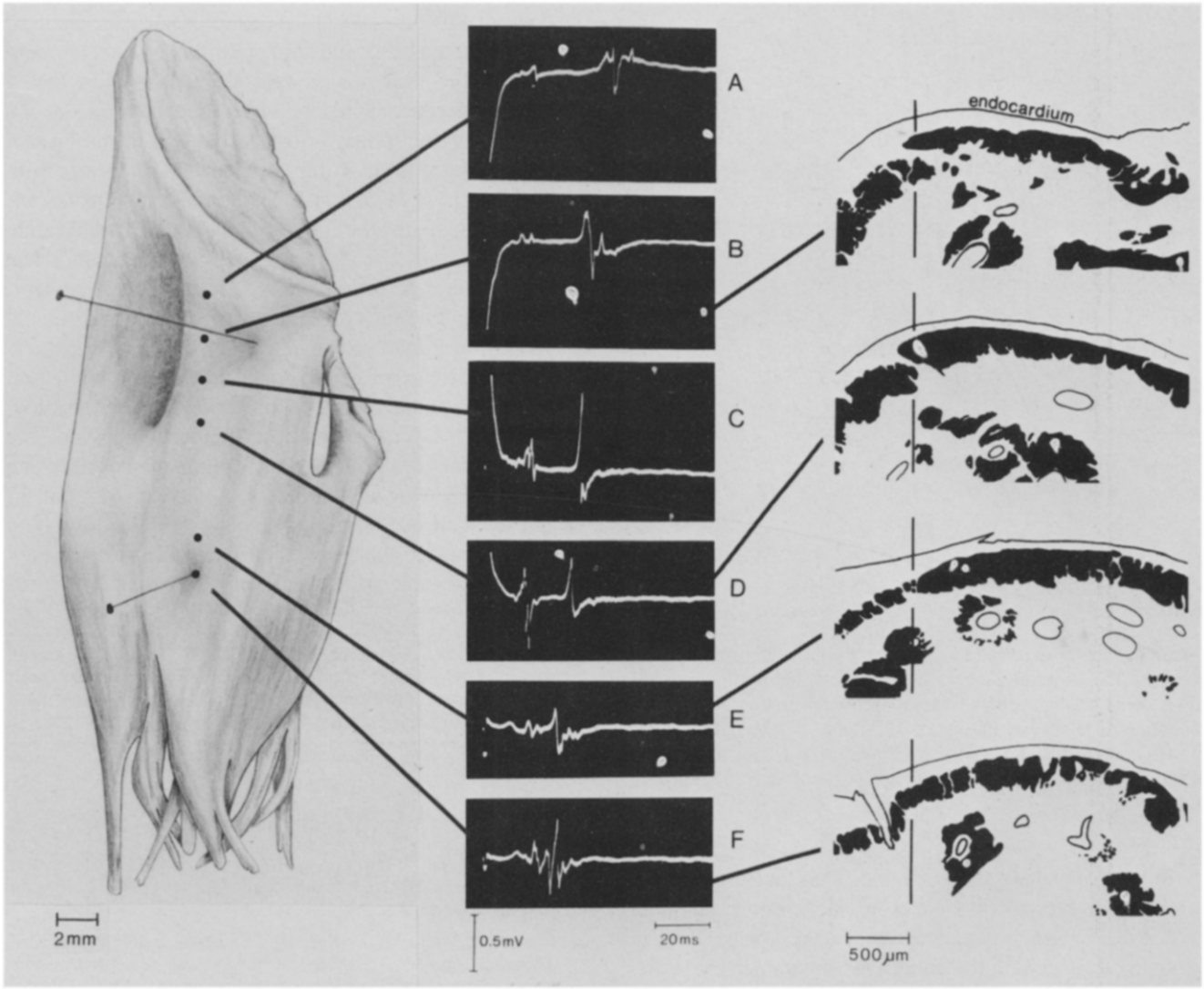

Figure 10. Left panel, Schematic drawing of the papillary muscle from the heart in Figure 9. **Black dots** indicate recording sites. The site of stimulation was located at the **upper dot.** Tracings are the signals recorded at the **black dots** during basic stimulation. **Right panel,** Schematic drawings of the histologic findings in the surviving rim at the recording sites. Sections from which these schematic drawings were obtained were cut perpendicular to the long axis of the papillary muscle. Surviving areas are shaded **black.** See text for further discussion.

activation (Fig. 5) demonstrates that there are several sites where the width of the tract changes, thus yielding possible sites for unidirectional block due to a change in diameter of a bundle. Figure 8 shows that the area of delay consists of merging and bifurcating bundles with different diameters. Thus, unidirectional block based both on an abrupt change in the diameter of a bundle and on branching sites of bundles may be expected to occur in such areas.

Macroreentry of microreentry? Surviving bundles within an infarcted area may merely constitute the return path of a macroreentrant circuit. However, it is also possible that they constitute a reentrant circuit on their own. In that case, the dimensions of the circuit can be small, depending on the conduction velocity in the circuit. In addition, the noncompromised area of the heart is not part of the circuit, and is activated by means of an exit from the tract. In the heart shown in Figure 1, two tracts were found, and it is possible that microreentry through these two pathways occurred. However, the following observations argue against this concept and support the occurrence of macroreentry. 1) A microcircuit requires an area of slow conduction, but from histologic results, it is unlikely that large delays occur in the tracts. 2) The activation pattern in Figure 1 appeared only if the delay in one of the tracts was equal to the time needed for an activation front to return to its exit from the tract through the noncompromised part of the heart. If the delay were shorter, two sites of exit would be expected. In the other heart in which we could prove that noncompromised parts of the heart were connected by surviving tissue that traversed

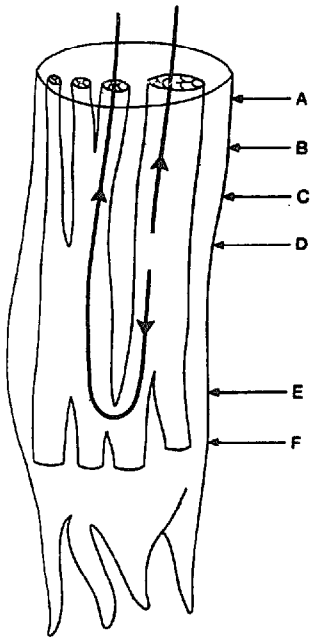

Figure 11. Possible spread of activation through the papillary muscle from the heart in Figure 10. The **heavy arrows** indicate the direction of the activation waves. **Horizontal arrows** indicate the recording sites shown in Figure 10. Delay of activation in the direction perpendicular to the long axis of the papillary muscle at **level A** occurs because of a winding route of activation through **site F.**

the infarct, only one tract was found. Thus, at least for some of the tachycardias that occur in the chronic phase of myocardial infarction, macroreentry takes place through surviving areas within the infarct and the nonaffected parts of the heart.

We are aware that tachycardias in which the time gap between earliest and latest activation is small represent only a minority of tachycardias (this observation is compatible with our findings during antiarrhythmic surgery). In cases in which the time gap is large, macroreentry through the infarct is less clear. In several tachycardias we found local activation at several sites in the zone of delay. In all these cases, spread of activation was from the last activated site toward the earliest activated site, a finding compatible with the concept that the area represents the return path of a large circuit.

Consequences for therapy. Our data show that more than one tract of surviving tissue may traverse an infarct zone, connecting the remaining healthy tissue at either side of the infarct. In addition, it appears that the location of the tracts is not confined to the subendocardial surface, but may run intramurally or even subepicardially. Both the number of tracts and their location have consequences for the mapping procedure that is usually carried out to support surgical therapy. The different locations of the tracts indicate that mapping of only the endocardial surface is not sufficient in all cases and should be extended to epicardial or even intramural areas. The presence of several tracts implies that a resection procedure should not be restricted to removal of a small area at the "origin" (that is, the exit to the bulk of surviving tissue), even if the "origin" can be located with high precision. It cannot be excluded that only one tract is preferentially involved in the maintenance of a tachycardia and that it masks the existence of other tracts. In a few mapping studies performed during antiarrhythmic surgery, we found multiple sites of "origin," suggesting that several pathways were involved in that tachycardia at the same time. The existence of several tracts may also be one reason for less than optimal results obtained with catheter ablation, even though the "origin" can be located with precision. The relatively small area destroyed by ablation may damage one circuit while leaving another intact. A second reason might be the location of the tracts. Tracts are more difficult to attack by catheter ablation if they are located intramurally and are inaccessible if their location is epicardial.

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