Cellular Electrophysiology of Human Myocardial Infarction

1. Abnormalities of Cellular Activation

JOSEPH F. SPEAR, PH.D., LEONARD N. HOROWITZ, M.D., ARTHUR B. HODESS, M.D., HORACE MACVAUGH, III, M.D., AND E. NEIL MOORE, D.V.M., PH.D.

SUMMARY Ventricular tissues were obtained at the time of operation from 12 patients who underwent aneurysmectomy or mitral valve replacement. The electrophysiologic characteristics of these tissues were determined in a tissue bath using microelectrodes. Normal-appearing action potentials were recorded from surviving Purkinje fibers and ventricular muscle cells within infarcted ventricular tissues. Normal muscle action potential recordings from infarcted tissues were similar to action potentials from noninfarcted papillary muscles, except that the duration of the action potential was significantly longer in the former. In other areas slow response potentials were recorded. These action potentials conducted slowly and were eliminated by verapamil. We observed verapamil-sensitive slow response automaticity, but this did not correlate with ventricular tachycardias, present in three patients. Variable amplitude responses arising from normal resting potentials and characterized by stimulus intensity-dependent changes in action potential amplitude were recorded in tissues from two patients. These potentials had many characteristics similar to the slow response, but were not eliminated by verapamil. We also saw inexcitable cells with both normal and abnormal resting potentials. The heterogeneous electrophysiologic characteristics of these tissues provide a likely substrate for arrhythmias and may be the source of the ectopic ventricular rhythms observed in these patients.

SEVERAL INVESTIGATORS have reported the survival of cells on the endocardial surface of healed transmural myocardial infarction observed 24 hours–6 months after experimental infarction. In the canine model, little ventricular muscle survives within the infarct zone, while Purkinje fibers do survive and retain relatively normal electrophysiologic properties. In the feline model, both muscle and Purkinje tissues survive within infarcted tissue up to 6 months after acute coronary occlusion. These surviving cells show both normal and abnormal electrophysiologic properties which may have arrhythmogenic potential. In human myocardial infarction, histologic and electrophysiologic studies indicate that both Purkinje fibers and muscle cells survive. One study suggests that pathologic changes may persist in these tissues long after an acute myocardial infarction.

In this report we evaluate the electrophysiologic properties of infarcted human ventricular myocardium 1–60 months after acute myocardial infarction. The observations indicate that both Purkinje fibers and muscle cells survive. We also document persistent electrophysiologic abnormalities in surviving cells of tissues obtained as late as 60 months after infarction.

Methods

Specimens of human ventricular tissue were obtained from 12 patients at the time of cardiac surgery. The patients ranged in age from 37–68 years. Aneurysmectomy was performed for intractable heart failure or ventricular tachycardia. Mitral valve replacement was performed for severe mitral regurgitation. Before surgery, all patients had some degree of chronic congestive heart failure (table 1). Three of the 12 patients had chronic sustained ventricular tachycardia. No patients had evidence of digitalis toxicity. Cardioactive drugs were discontinued at least 24 hours before operation in nine of 12 patients without ventricular tachycardia, but were continued in the three patients with arrhythmia to the time of surgery. Morphine and halothane were used as anesthetics.

The tissues were resected promptly at the initiation of cardiopulmonary bypass and were placed in continuously oxygenated, cooled (20–21°C) Tyrode's solution and transported to the electrophysiologic laboratory. Transit time was less than 8 minutes in each case. The tissues were placed in a tissue bath and superfused with Tyrode's solution, which was maintained at 37°C and gassed with 5% CO₂ and 95% O₂. The composition of the Tyrode's solution in mmol/l was: NaCl 137; NaHCO₃ 12; dextrose 5.5; NaH₂PO₄ 0.9; MgCl₂ 0.5; KCl 2.7; CaCl₂ 1.2.

Close silver bipolar electrodes 0.01 inch in diameter...
were used to pace the tissue and record surface electrograms. Tissues were paced by a custom designed digital device with a constant current stimulus isolation unit (Bloom Associates, Ltd., Narberth, Penn) with an output range of 0–10 mA. The stimuli were square wave pulses 2 msec long. Transmembrane potentials were recorded with standard 3 M potassium chloride-filled glass micropipettes. Data were recorded on analog tape and 35 mm film. The time from resection of the tissue until electrophysiologic recordings ranged from 10–30 minutes. After electrophysiologic studies, the preparations were fixed in 10% neutral buffered formalin, Bouin’s solution, or Carnoy’s solution and imbedded in paraffin and sectioned at a thickness of 2–5 μ. The tissues were mounted on glass slides and stained with either trichrome stain, hematoxylin and eosin, or para-aminosalicyclic acid, before and after diastase.

Aneurysmal tissues used in our studies varied from 3–8 mm thick. Microelectrode impalements were made only on the endocardial surface at depths of approximately 100 and 200 μ. Since angiographic findings indicate that these tissues were not perfused in situ, and were probably oxygenated solely via cavitary blood, we felt that superfusion by oxygen saturated Tyrode’s solution would be sufficient to maintain the surviving subendocardial cells to be studied. To verify that the tissue isolation was not responsible for the abnormal electrophysiologic responses, in one study the tissues obtained included both noninfarcted and infarcted papillary muscle (patient 7). They were studied simultaneously in the same manner and were mounted together in the tissue bath. The noninfarcted papillary muscle showed only normal cells, while the infarcted muscle had abnormal electrophysiologic characteristics.

### Results

The characteristics of the ventricular tissues we examined are presented in table 1. Nine were ventricular aneurysms and four were left ventricular papillary muscles. Two of the four papillary muscles were obtained from noninfarcted regions and did not show histologic or electrophysiologic evidence of infarction. The infarcted tissues were resected 1–60 months after acute myocardial infarction.

The extensive fibrosis in the resected aneurysms made impalements of surviving cells very difficult. In the 13 tissues studied, we obtained 54 separate impalements of excitable cells. The electrophysiologic properties which we describe are based on observations of these impalements. The impalements showed cells with relatively normal action potential characteristics as well as a broad range of abnormal electrophysiologic responses. We defined normal cells in infarcted tissues based on their contrasting characteristics with the depressed action potentials and their similarity to potentials recorded in the noninfarcted human tissues. Four of the 13 tissues were spontaneously automatic.

### “Normal” Cells

Three of the infarcted tissues had normal action potentials (patients 4, 9 and 10). These included action potentials with characteristics resembling both Purkinje fibers and ventricular muscle cells. These recordings were verified histologically to be from areas of Purkinje tissue or muscle (fig. 1). In the two noninfarcted tissues (patients 7 and 8), only normal-appearing action potentials were recorded. Using the t test to compare means, the resting potential, action potential amplitude and rate of depolarization of mus-

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**Table 1. Characteristics of the Ventricular Tissues**

<table>
<thead>
<tr>
<th>Pt no.</th>
<th>ECG</th>
<th>Months post-infarct</th>
<th>CHF</th>
<th>VT</th>
<th>Tissue</th>
<th>Spontaneous basic cycle length (sec)</th>
<th>Normal cells</th>
<th>Slow response</th>
<th>Variable amplitude response</th>
<th>Inexcitable normal resting potentials</th>
<th>Inexcitable abnormal resting potentials</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AMI</td>
<td>9</td>
<td>+</td>
<td>+</td>
<td>AN</td>
<td>1.39–1.48</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>ALMI</td>
<td>60</td>
<td>+</td>
<td>+</td>
<td>AN</td>
<td>1.25–1.40</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>ASMI</td>
<td>6</td>
<td>+</td>
<td>+</td>
<td>AN</td>
<td>1.11–1.92</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>ASMI</td>
<td>25</td>
<td>+++</td>
<td>+</td>
<td>AN</td>
<td>1.17–2.93</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>IMI</td>
<td>6</td>
<td>+</td>
<td>+</td>
<td>AN</td>
<td>1.11–1.92</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>AMI</td>
<td>9</td>
<td>+++</td>
<td>+</td>
<td>AN</td>
<td>1.25–1.40</td>
<td>+</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>7</td>
<td>IMI</td>
<td>12</td>
<td>+++</td>
<td>+</td>
<td>PM</td>
<td>1.11–1.92</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>8</td>
<td>MVP</td>
<td>−</td>
<td>+++</td>
<td>+</td>
<td>PM</td>
<td>1.11–1.92</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>AMI</td>
<td>1</td>
<td>+++</td>
<td>+</td>
<td>PM</td>
<td>1.11–1.92</td>
<td>+</td>
<td></td>
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</tr>
<tr>
<td>10</td>
<td>AMI</td>
<td>18</td>
<td>+++</td>
<td>+</td>
<td>AN</td>
<td>1.11–1.92</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>11</td>
<td>AMI</td>
<td>24</td>
<td>+++</td>
<td>+</td>
<td>AN</td>
<td>1.78–2.93</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>12</td>
<td>AMI</td>
<td>54</td>
<td>+</td>
<td>+</td>
<td>AN</td>
<td>1.11–1.92</td>
<td>+</td>
<td></td>
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</tr>
</tbody>
</table>

*Noninfarcted tissue.

Abbreviations: AMI = anterior myocardial infarction; ALMI = anterolateral myocardial infarction; ASMI = anteroseptal myocardial infarction; IMI = inferior myocardial infarction; MVP = mitral valve prolapse; CHF = chronic heart failure; VT = ventricular tachycardia; AN = aneurysm; PM = papillary muscle.
Figure 1. Histologic sections showing surviving Purkinje fibers and ventricular muscle cells. The sections were stained with trichrome stain. Fibrous tissue is stained dark gray, ventricular muscle is stained light gray and Purkinje fibers are pale. Fifty and 500 μm calibration bars are shown below each section. In A, below a superficial layer of fibrous tissue is a broad band of pale-staining Purkinje fibers. Section B was taken through a free-running ventricular trabeculum. Surviving ventricular muscle cells can be observed below the superficial layer of fibrous tissue. A central core of fibrous tissue is also apparent. The tissues were obtained from patient 4.
Table 2. Characteristics of Normal Action Potentials

<table>
<thead>
<tr>
<th>Normal muscle</th>
<th>Infarcted tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resting potential (mV)</strong></td>
<td><strong>Action potential amplitude (mV)</strong></td>
</tr>
<tr>
<td>-90</td>
<td>110</td>
</tr>
<tr>
<td>-74</td>
<td>90</td>
</tr>
<tr>
<td>-85</td>
<td>101</td>
</tr>
<tr>
<td>-77</td>
<td>95</td>
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<td>-78</td>
<td>100</td>
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<td>-74</td>
<td>93</td>
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<td>-75</td>
<td>94</td>
</tr>
<tr>
<td>-74</td>
<td>95</td>
</tr>
<tr>
<td>-85</td>
<td>103</td>
</tr>
<tr>
<td>-80.2 ± 5.7</td>
<td>99.0 ± 6.2</td>
</tr>
</tbody>
</table>

*<i>p = 0.001.</i>  
*<i>p = 0.005.</i>  
*<i>patient 8.</i>  
*<i>patient 7.</i>  
*<i>patient 10.</i>  
*<i>patient 4.</i>  
*<i>patient 9.</i>

muscle cells in three infarcted tissues were not significantly different from those of muscle cells in the two noninfarcted tissues (Table 2). However, the action potential duration of 90% repolarization was 300.8 ± 73.9 msec (SD) in the noninfarcted muscle and 427.4 ± 46.4 msec in the infarcted muscle (<i>p</i> < 0.005). In the infarcted tissues, resting potential, action potential amplitude and maximum rate of depolarization were not significantly different between Purkinje fibers and muscle cells. The duration of the Purkinje fiber action potentials at 90% repolarization, however, was significantly longer than that of muscle cells (<i>p</i> = 0.001).

To verify that both Purkinje fibers and muscle cells survive in non-perfused aneurysmal tissues, histologic sections were made in areas in which transmembrane potentials were also recorded. In figure 1A the endocardial surface is at the top. Fibrotic tissue extends from the surface to a depth of 50 μ as indicated by the dense, dark stain. An area of pale staining Purkinje fibers 100–125 μ thick appear below the fibrotic tissue. Microelectrode recordings from this area showed normal Purkinje-type action potentials. Deeper lying surviving muscle cells (stained gray) can also be seen in this section. Figure 1B shows a section through a ventricular trabeculum. Fibrotic tissue extends from the surface to a depth of 40–130 μ. Below the fibrotic tissue, a thin layer of muscle cells 180–280 μ thick surrounds a central core of fibrous tissue. In all specimens in this study, tissue sections revealed surviving subendocardial muscle and Purkinje tissue with fibrous tissue and fatty infiltrates extending transmurally throughout the aneurysm.

The Slow Response

In six of the tissues, action potentials were recorded resembling "slow response" potentials.9, 10 The action potentials recorded in a ventricular aneurysm (patient 4) during surface bipolar pacing presented in figure 2 are representative. The stimulation and recording arrangement is shown schematically in figure 2A. Transmembrane potentials were recorded along a ridge of viable ventricular muscle (microelectrode [ME1 and ME2). The ridge was overlying fibrotic aneurysmal tissue approximately 5 mm thick and was 7 mm from the cut edge. The ME1 recording was obtained 1 cm from the site of stimulation. The analog records in 2B show relatively normal-appearing ventricular muscle cell action potentials at this recording site. One centimeter distal to ME1, we obtained transmembrane potential recording ME2. The recording in figure 2B showed abnormal resting potential as well as low-amplitude and multicomponent action potentials. The first stimulated action potential in the sequence conducted from ME1 to the ME2 recording site with a
significant delay. The ME₂ action potential was characterized by an initial prepotential followed by a secondary peak response. The conduction time from the peak of the ME₁ action potential to the peak of the ME₂ potential was 292 msec. The calculated conduction velocity between ME₁ and ME₂ recording sites was 0.034 m/sec. The second action potential in the ME₁ recording site was evoked by a premature stimulus with coupling interval of 550 msec. In this case, the action potential did not engage the distal recording site, although it can be seen from the ME₂ recording that the transmembrane potential had returned to its resting value at this time. Thus, the membrane refractoriness outlasted the action potential duration in the conducting pathway. The third action potential in the ME₁ record was evoked by stimulation at a coupling interval of 500 msec after the second action potential. In this case, the activity conducted to the ME₂ recording site. However, the configuration of the action potential and its duration are quite different from the initial conducted response. The prepotential is longer and the action potential peak is depressed. The peak-to-peak conduction time between ME₁ and ME₂ recording sites for the third response was 0.02 m/sec. The fourth action potential evoked at a coupling interval of 850 msec after the third response engaged the distal ME₂ recording site with only a small response which appears to consist of only the prepotential component of the other responses.

In four of the tissues, spontaneous diastolic depolarization was recorded. In each of these cases, the spontaneous automaticity arose from cells which exhibited a slow response. The spontaneous basic cycle length of the automaticity recorded in the four tissues was slow, ranging from 1.25–11.92 sec (table 1). In addition, the spontaneous automaticity occurred in tissues obtained from patients who did not exhibit paroxysmal ventricular tachycardia before surgery. In two cases (patients 6 and 7), the tissue giving rise to the automaticity was verified by histologic techniques to be ventricular muscle. Figure 3 shows transmembrane potential recordings in an aneurysm from patient 6, in a region which histologically was ventricular muscle. The first two action potentials in panel A were unpaced and occurred at a spontaneous coupling interval of 1.25 sec. The maximum diastolic potential was −40 mV, and slow diastolic depolarization was apparent. At the time indicated by S, pacing at a cycle length of 450 msec was commenced. The multicomponent and variable configuration responses to this pacing are displayed in the right hand portion of the records of A. Fifteen minutes after the addition of verapamil to the superfusate at a concentration of 1 mg/l, spontaneous automaticity was eliminated. Pacing at a cycle length of 1000 msec failed to evoke an action potential. These data support the conclusion that the transmembrane action potentials were of the slow response type and were probably mediated by the slow inward current. Verapamil at concentrations of 0.5 and 1 mg/l were also applied to the tissues obtained from patients 3 and 11, and eliminated all slow response activity, including spontaneous automaticity in the tissue from patient 11.

The Variable Amplitude Response

In two of the tissues (from patients 3 and 9), we observed a different phenomenon with characteristics similar to the previously described slow responses.
These action potentials, however, arose from more polarized resting potentials and were dependent on stimulation parameters. Action potentials representative of this activity are presented in figure 4. Recordings were made during pacing through surface electrodes at a basic cycle length of 800 msec. The recordings in figure 4A were obtained adjacent to the surface stimulating electrodes. The resting potential was $-92$ mV, and the action potential amplitude was 110 mV. The recording in 4B was made 2 mm from the stimulating electrodes. In this impalement the resting potential was also $-92$ mV. However, the depolarization phase of this action potential showed a prominent inflection or notch. The initial rapid spike preceding the depolarization in the record is the stimulus artifact. There was a significant latency of 30 msec between the stimulus artifact and the foot of the action potential (a conduction velocity of 0.07 M/sec) associated with an alternation in the configuration of the action potential. Action potentials I and 3 are
shorter than 2 and 4 in the figure. In this preparation, the amplitude, duration and depolarization phase of the action potential with a given impalement could also be modified by changing the location or polarity of the surface stimulating electrode. The effect of changing the polarity of stimulation on the action potential configuration is shown in figure 5.

The action potential configuration also depends on the intensity of stimulation through the surface electrode. This phenomenon is demonstrated in figure 6. The transmembrane potential recordings in figure 6A were made adjacent to the point of stimulation. The intensity of the bipolar stimulation was 3 mA. The resting potential of this cell was -86 mV and the amplitude of the initial action potential in figure 6A was 104 mV. There were complex-to-complex variations in the action potential amplitude and duration. In 6B, action potentials from the same cell impalement are shown at a time when the surface stimulation intensity was reduced to 2.8 mA. In this case, there was a significant variation in action potential amplitude, configuration and duration. While the resting potential remained at -86 mV, the action potential amplitude varied from 42-60 mV. The low amplitude and multicomponent nature of this response is similar to the slow current-dependent slow response in figures 2 and 3. Return of the stimulus intensity to 3 mA returned the recording to that seen in 6A. The amplitude changes followed the stimulus intensity changes without a delay, and therefore could not be caused by release of endogenous catecholamines, which exert their effect gradually. The transmembrane potential recordings presented in figures 6C and 6D were obtained 20 minutes after the addition of verapamil to the superfusate at a concentration of 0.5 mg/l. The variable amplitude responses persisted; however, surface stimulation with higher current intensity (7 mA) was required to produce responses comparable to those described in figure 6B. In addition, the duration of the action potentials tended to be longer, and there was a greater separation in the components of the multicomponent responses. The stimulus dependency, the persistence of the action potential activity in the presence of verapamil, and the relatively normal resting potentials for these cells suggest this phenomenon is different from the slow current-dependent slow response.

The properties of the slow response and variable amplitude response recorded in our preparations are shown in table 3. In our experiments on human tissues the configuration of the slow response could be modified by the coupling interval of the stimulation, but was independent of the intensity of stimulation. In some other experimental preparations the amplitude of the slow response potential has been shown to be stimulus intensity-dependent. However, these graded responses do not approach normal with increased stimulus intensity. The variable amplitude response, in contrast, showed prominent stimulus intensity dependence, with amplitudes ranging from depressed to normal.

In four tissues, only resting potentials could be recorded. These resting potentials ranged from very abnormal (less than -20 mV) to normal (-90 mV). We could not, however, in these impalements, evoke an action potential with either direct surface stimulation of 10 mA, or stimulation of 4 mA through the microelectrode impaling these cells. Furthermore, the addition of epinephrine to the superfusate (5 x 10^{-4} mg/ml) did not make the cells excitable. It is not known whether these cells were in fact inexcitable or whether our stimulation intensity was insufficient to
bring them to threshold. Three of these tissues were obtained from the patients receiving high-dose antiarrhythmic agents (procainamide or bretylium) at the time of operation in an attempt to control intractable ventricular arrhythmias.

**Discussion**

In these studies we report for the first time electrophysiologic evidence of persistent abnormal cellular activity in human ventricular tissues as late as 60 months after acute myocardial infarction. In addition, these experiments demonstrate that slow response automaticity occurs in ventricular muscle in spontaneous human disease. We have verified the existence of normal Purkinje fiber and ventricular muscle action potentials surviving within the fibrous scar of ventricular aneurysms up to 25 months after myocardial infarction.

**Electrophysiologic Heterogeneity of Chronic Myocardial Infarction**

The characteristics of the ventricular tissues summarized in table 1 show the large degree of variability in electrical activity observed in these tissues. In individual tissues characteristics ranged from relatively normal action potentials to abnormal electrical responses (patients 4 and 9). The tissue from patient 3 showed slow response potentials, variable amplitude responses and inexcitable cells, with both normal resting potentials and abnormal resting potentials. Myerburg et al.4 have also described heterogenous electrophysiologic properties in chronic experimental...
myocardial infarction. Because of the difficulty in impaling the cells in the matrix of dense fibrous tissue, the absence of records of a type of electrical activity in a given tissue does not indicate that it was not present. It may have been present, but we were unable to obtain an implemation to observe it.

Our data indicate that in human myocardial infarction, there is survival of cells with relatively normal characteristics, both electrophysiologic and histologic. The histologic sections suggest that one explanation for this survival might be diffusion between the tissue and chamber blood. The degree of normality of these cells cannot be established from our electrophysiologic recordings, since both the noninfarcted tissue and the infarcted tissues were from patients who had varying degrees of chronic heart failure. Studies in animals indicate that hypertrophy and failure are accompanied by changes in the electrophysiologic properties of cells. Therefore, the action potential recorded even in the noninfarcted tissue may not be truly normal. Our data do allow us, however, to contrast the electrophysiologic properties of the infarcted and noninfarcted tissues, and indicate that the electrophysiologic changes in the infarcted tissues are not due only to chronic heart failure in these patients. The action potential durations of the relatively normal cells in the infarcted tissue are longer than in the noninfarcted papillary muscle, and this may also be a late characteristic of infarcted tissue.

Abnormalities of Cellular Activation

The slow response activity which we observed in human ventricle is similar to that previously reported in human diseased atrial muscle. The verapamil-sensitive muscle automaticity resembles the calcium and sodium-dependent automaticity described in depolarized guinea pig papillary muscle. The mechanism of slow response activity which persists in tissues as long as 25 months after myocardial infarction is unknown. In normal tissue, slow response activity can be induced during depolarization of the membrane with voltage clamp techniques, high potassium solutions in the presence of elevated catecholamine levels, or reduction of the pH. While potassium concentration and pH were normal in the tissue bath, we cannot be sure they were within the intercellular spaces of the tissue itself.

We also observed variable amplitude responses originating in cells with normal resting potentials. Some of their characteristics were very similar to the slow response activity. Areas with variable amplitude responses show very slow conduction velocities, with evidence of dissociated conduction of wavefronts (figs. 4, 5 and 6). The mechanism for the variable amplitude response is not entirely clear. Certainly, the presence of local block and inexcitability contributes to the variable amplitude response. We do not know whether a defect in the sodium conductance system in these tissues plays a role. The basis for the local block and inexcitability may have a purely morphologic substrate. The extensive fibrosis of these tissues may insulate islands of excitable tissue. A phenomenon similar to the variable amplitude response was described by our laboratory in isolated rat papillary muscles subjected to stretch, and also by others in tissue-cultured myocardial cells. In these preparations, disruption of cell-to-cell activation causing local slowing of conduction and block produced responses similar to those of figures 4, 5 and 6. Studies of conduction across the Purkinje fiber papillary muscle junction and in atrioventricular node indicate that in the cases of local conduction block the inactivated cells have a strong electrotonic repolarizing influence on the action potentials of active cells proximal to the block. The variable amplitude response in the tissues therefore may reflect the electrotonic depression of the action potentials of active cells by adjacent inactive cells. The stimulus-dependent characteristics of the variable amplitude response support this hypothesis.

The observation that variable amplitude response activity may exist in tissues simultaneously exhibiting slow response activity (patient 3) presents the possibility of mixing of the properties of the slow response and variable amplitude response. In such tissues, part of the characteristics of slow response may be due to the electrotonic interactions in the asynchronously activated tissue.

Implications for Arrhythmogenesis

The nature of our preparation would not allow us to determine the role of the electrophysiologic characteristics of the infarcted tissues in arrhythmia genesis in the patients. The aneurysms were excised from the ventricles without the inclusion of normal, noninfarcted myocardium. Consequently, we could not study the conduction of activity between the infarcted tissue and the normal myocardium in our tissue bath. However, studies using catheter mapping in patients with ventricular aneurysms do indicate that electrical activity within the aneurysm contributes to arrhythmia production in these patients.22
The spontaneous automaticity that we observed in four of the 13 tissues occurred in both Purkinje tissue and ventricular muscle. The presence of automaticity in ventricular muscle in two of the tissues suggests that in myocardial infarction, the focus for ectopic depolarizations may be in ventricular muscle and not exclusively in surviving Purkinje fibers. In all cases, the automaticity was slow response automaticity. The spontaneous rate of this automaticity was relatively slow and occurred in tissues from patients without ventricular tachycardia. While in vitro, this abnormal automaticity was not sufficient to be responsible for the ventricular tachycardias observed. In vivo autonomic and other factors may have modified this automaticity. Although we did not observe triggered automaticity or overdrive acceleration of these pacemakers, these phenomena are characteristic of slow current-dependent automaticity and could have been responsible for clinical arrhythmias. The abnormal electrophysiologic characteristics of the tissues, such as very slow conduction and local areas of block, provide a likely substrate for reentry, a cause of ventricular arrhythmias in these patients.

Acknowledgment

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References

3. Friedman PL, Fenoglio JJ Jr, Wit AL: Time course for reversal of electrophysiologic and ultrastructural abnormalities in subendocardial Purkinje fibers surviving extensive myocardial infarction in dogs. Circ Res 36: 127, 1975
10. Aronson RS, Cranefield PF: The electrical activity of canine cardiac Purkinje fibers in sodium-free, calcium-rich solutions. J Gen Physiol 61: 786, 1973
16. Aronson RS, Cranefield PF: The effect of resting potential on the electrical activity of canine cardiac Purkinje fibers exposed to sodium-free solution or to ouabain. Pflugers Arch 347: 101, 1974
17. Davis LD, Helmer PR, Ballantyne F III: Production of slow responses in canine cardiac Purkinje fibers exposed to reduced pH. J Mol Cell Cardiol 8: 61, 1976
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