Cellular Electrophysiology of Human Myocardial Infarction

1. Abnormalities of Cellular Activation

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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 myo-

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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, 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-
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 μ 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>Resting potential (mV)</td>
<td>Action potential amplitude (mV)</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>-84</td>
<td>98</td>
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<tr>
<td>-80</td>
<td>100</td>
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<tr>
<td>-87</td>
<td>109</td>
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<tr>
<td>-78</td>
<td>100</td>
</tr>
<tr>
<td>-74</td>
<td>93</td>
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<tr>
<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>
<tr>
<td>-74</td>
<td>98</td>
</tr>
<tr>
<td>-72</td>
<td>90</td>
</tr>
</tbody>
</table>

*p = 0.001.
†p < 0.005.
*patient 8.
*patient 7.
*patient 10.
*patient 4.
*patient 9.

Muscle cells in three infarcted tissues were not significantly different from those of muscle cells in the two non-infarcted 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 (p < 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 (p = 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 extended 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 $M_E_2$ action potential was characterized by an initial prepotential followed by a secondary peak response. The conduction time from the peak of the $M_E_1$ action potential to the peak of the $M_E_2$ potential was 292 msec. The calculated conduction velocity between $M_E_1$ and $M_E_2$ recording sites was 0.034 M/sec. The second action potential in the $M_E_1$ 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 $M_E_2$ 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 $M_E_1$ 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 $M_E_2$ 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 $M_E_1$ and $M_E_2$ 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 $M_E_2$ 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 exhibiting 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 1 and 3 are

Figure 3. Analog records demonstrating the effect of 1 mg/l verapamil on spontaneous and paced slow response potentials. In A, $S$ indicates the commencement of pacing at a basic cycle length of 450 msec. In B the same cell impalement is shown after the addition of verapamil to the tissue bath. $S$ indicates pacing at a basic cycle length of 1000 msec.

Figure 4. The effect of proximity to surface stimulating electrodes on the action potential configuration of the variable amplitude response. The analog records in A were obtained adjacent to the surface stimulating electrodes. The records in B were obtained 2 mm from the stimulating electrode site.
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 elec-
trode. 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 
impalent 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 poten-
tial 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 in-
tensity to 3 mA returned the recording to that seen in 
6A. The amplitude changes followed the stimulus in-
tensity changes without a delay, and therefore could 
not be caused by release of endogenous catechol-
amines, which exert their effect gradually. The 
transmembrane potential recordings presented in figures 
6C and 6D were obtained 20 minutes after the addi-
tion of verapamil to the superfusate at a concentra-
tion of 0.5 mg/l. The variable amplitude responses per-
sisted; 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 stimula-
tion 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^{-3} 
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
FIGURE 6. Analog records demonstrating the effects of stimulus intensity and verapamil on the variable amplitude response. Each record is from the same cell impalement. The tissue was the same as that in figures 4 and 5. The records in A were obtained adjacent to the stimulating electrode which was being used to pace the tissue with a stimulus intensity of 3 mA. The records in B were obtained when the stimulus intensity was reduced to 2.8 mA. C and D were recorded after the addition of 0.5 mg/l verapamil to the tissue bath. The pacing stimulus intensity was 7.0 mA.

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 im- paling 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 ob- tain an implemment to observe it.

Our data indicate that in human myocardial infarction, there is survival of cells with relatively normal character-istics, 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 ac- companied 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 con- trast 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 non- infarcted 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 ac-

### Table 3. A Comparison of the Properties of the Slow Response and the Variable Amplitude Response

<table>
<thead>
<tr>
<th></th>
<th>Slow response (n = 20)</th>
<th>Variable amplitude response (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting potential (mV)</td>
<td>-37 to -66</td>
<td>-70 to -92</td>
</tr>
<tr>
<td>Action potential amplitude (mV)</td>
<td>30-66</td>
<td>8-110</td>
</tr>
<tr>
<td>Maximum rate of depolarization (V/sec)</td>
<td>0.4-7.3</td>
<td>0.1-15.3</td>
</tr>
<tr>
<td>Duration (msec)</td>
<td>151-479</td>
<td>185-384</td>
</tr>
<tr>
<td>Configuration</td>
<td>Multicomponent</td>
<td>Multicomponent</td>
</tr>
<tr>
<td>Verapamil sensitivity</td>
<td>Sensitive</td>
<td>Insensitive</td>
</tr>
<tr>
<td>Stimulus dependency</td>
<td>Weak intensity</td>
<td>Strong intensity</td>
</tr>
</tbody>
</table>

Implications for Arrhythmogenesis

The nature of our preparation would not allow us to determine the role of the electrophysiologic char-acteristics of the infarcted tissues in arrhythmia genesis in the patients. The aneurysms were resected 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.
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.

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