Effect of Acute Myocardial Infarction on Electrical Recovery and Transmural Temperature Gradient in Left Ventricular Wall of Dogs

By Ernest W. Reynolds, Jr., M.D., Condon R. Vander Ark, B.S., and Franklin D. Johnston, M.D.

In a previous publication, it was shown that measurements of the effective refractory period were useful in following the time course of electrical recovery. Although this study was largely concerned with the local order of transmural recovery associated with negative T waves, a few observations during the acute phase of experimental infarction confirmed the fact that recovery was accelerated, especially in the deeper myocardial layers. Wiggers studying monophasic action potentials derived from the heart surface found significant shortening of the action potential 1 minute after ligation of a coronary artery. More recent studies, using ultramicroelectrodes in special heart preparations perfused with low oxygen tension fluids, show the same finding. Since the previous studies were limited to surface measurements and to short periods of observation, it was felt some-thing more might be learned by following both the superficial and deep myocardial layers for longer periods and in regions outside the ischemic area. In addition to these studies, an attempt was made to correlate local temperature gradients and effective refractory period measurements before and after coronary artery ligation and by perfusion of warm and cold Ringer’s solution. Sayen et al. have found that an initial rise in local cardiac muscle temperature may follow coronary artery ligation and that a fall in temperature may be delayed for 30 to 60 seconds. Others have studied the effect of temperature on the polarity of the T waves or the refractory period and the T wave, but no previous attempt has been made to correlate all 3 with simultaneous measurements to study the order of local recovery associated with positive T waves.

Methods

The equipment used and manner of measuring the effective refractory period were similar to those used in a previous study, with the addition of a special circuit permitting the application of a single test stimulus at a time when the oscillograph had reached optimal paper speed. A suprathreshold stimulus was used for these measurements, but since there was a tendency for threshold to rise some hours after the ligation, it was considered essential to start with a stronger stimulus than had been employed in earlier studies. Accordingly, the 0.5 msec square wave test stimulus was raised from 2 to 5 ma. Experiments were concluded when the threshold was found to be higher than one-half the strength of the test stimulus or when ventricular fibrillation occurred.

Temperatures at the epicardium and endocardium were measured with thermistors in the arms of 2 wheatstone bridges built in this laboratory. These were carefully calibrated by plotting the un-balanced bridge voltage against known temperatures before each experiment. In use, the outputs of the 2 bridges were recorded simultaneously with the data from the refractory period measurements on a 6-channel Hathaway oscillograph. Baseline measurements were made by substituting for the thermistor a resistor that had the same resistance as the thermistor at a known temperature. The

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ACUTE MYOCARDIAL INFARCTION

thermists* used for subendocardial measurements were enclosed in polyethylene catheters and inserted tangentially to the surface through a no. 18 needle, which was then withdrawn.

Twenty mongrel dogs, weighing between 5.6 and 12.7 Kg., were anesthetized with pentobarbital, intubated, and maintained on artificial respiration. Most of these animals were studied for periods of from 2 to 7 hours with refractory period measurements, transmural temperature measurements before and after ligation of a coronary artery and vein, and in some following pericardial irrigations with warm Ringer's solution.

**Results**

Successful studies of the effective refractory period at both epicardium and endocardium following ligation of a coronary artery were made in 13 animals, of which 10 were ligations of the major anterior descending coronary artery and 3 were of small branches of this vessel. Confirmation of the presence of acute myocardial infarction at the sites at which both the epicardial and subendocardial effective refractory period and temperatures were measured was obtained by gross inspection of the sectioned heart after completion of the studies, noting the size of the hemorrhagic area and by making many microscopic sections. The latter were read independently by the Pathology Department. The hearts were also examined carefully to check the location of the endocardial thermists and bipolar stimulating and differential recording electrodes.

Accelerated recovery, as manifested by shortening of the effective refractory period following coronary artery ligation, was observed in 11 of the 13 animals† (see table 1). Of these 11, all showed accelerated subendocardial recovery and 7 out of 10 adequately tested showed accelerated epicardial recovery in addition. The mean reduction of the effective refractory period was 15.7 per cent at the epicardium and 13 per cent at the subendocardial level. With few exceptions, accelerated recovery was observed within the first 30 minutes after the ligation and was most marked some time within the first 3 hours. Figure 1 illustrates the sequence of events. In this experiment, maximum accelerated recovery occurred first at the endocardium in 1 hour and at the epicardium in approximately 3 hours, and this was shortly after the appearance of a definite Q wave in the surface lead. In all of the studies continued for longer than 2 hours and in which accelerated recovery was initially found, there was a definite terminal lengthening of the effective refractory period. In addition, there was a tendency for threshold to rise, often abruptly, as the studies proceeded. This at times prevented further measurements and was attributed to death of cardiac cells.

In 2 of the animals, studies were carried out by placing 2 sets of electrodes in the heart, one well within the infarcted area and the other slightly outside this region. This was done to see if accelerated recovery was limited to the zone of infarction or could also be demonstrated in the marginal area. These studies are recorded in table 1, experiments 177 and 176, under control site 2. In experiment 177, shown in figure 2, the control site was located at the base of the heart 1.4 cm. from the dark area of the infarcted zone, and no significant changes other than a terminal lengthening of the effective refractory period at both the epicardium and subendocardium occurred. In experiment 176, with a similar electrode placement, a 6.4 per cent acceleration of recovery was found at the subendocardial level after 3 hours and 10 minutes, and only the usual terminal lengthening of the effective refractory period at the epicardium.

**Transmural Temperature Measurements**

Since it is known that the duration of the membrane action potential and therefore the

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*Two types of thermists were used. A flat surface unit manufactured by Cole-Parmer Instrument Company with a time constant of 0.8 second and a polyethylene catheter type manufactured by Yellow-springs Instrument Company. This unit had a time constant of 0.25 second. Self-heating was negligible when the units were immersed in water. The 3 volt D.C. bridge was fed directly to the galvanometer string with an over-all sensitivity of 5.5 mm. deflection per degree.

†In experiment 170, a small infarct was accidentally produced during the control period as manifest by R5-T junction elevation and Q waves in the surface lead and by finding a small coronary artery included in the electrode suture. Since the control effective refractory period was unusually short at the epicardium and much delayed later, accelerated recovery probably occurred here, making it 12 out of 13.
**Table 1**

<table>
<thead>
<tr>
<th>Exp. no.</th>
<th>Surface</th>
<th>Control E.E.P. msec.</th>
<th>Duration of infarction</th>
<th>0 min. to 30 min.</th>
<th>30 min. to 1 hr.</th>
<th>1 hr., 30 min. to 2 hrs.</th>
<th>2 hrs., 30 min. to finish</th>
<th>% max. decrease from control</th>
</tr>
</thead>
<tbody>
<tr>
<td>177</td>
<td>Epicardium</td>
<td>148-149</td>
<td>5 hrs.</td>
<td>147-148</td>
<td>119-119</td>
<td>120-120</td>
<td>143-143</td>
<td>29.1%</td>
</tr>
<tr>
<td>Site 1.</td>
<td>Endocardium</td>
<td>148-148</td>
<td>30 min.</td>
<td>127-125</td>
<td>135-131</td>
<td>158-157</td>
<td>170-170</td>
<td>15.5%</td>
</tr>
<tr>
<td>Control site 2</td>
<td>Epicardium</td>
<td>141-140</td>
<td>Site located outside</td>
<td>139-140</td>
<td>129-139</td>
<td>142-143</td>
<td>158-159</td>
<td>0.71%</td>
</tr>
<tr>
<td></td>
<td>Endocardium</td>
<td>158-158</td>
<td>the infarcted area</td>
<td>—</td>
<td>157-157</td>
<td>168-168</td>
<td>169-169</td>
<td>0.63%</td>
</tr>
<tr>
<td>176</td>
<td>Epicardium</td>
<td>151-151</td>
<td>3 hrs.</td>
<td>High threshold</td>
<td>159-160</td>
<td>High threshold</td>
<td>162-179</td>
<td>12.2%</td>
</tr>
<tr>
<td>Site 1.</td>
<td>Endocardium</td>
<td>172-172</td>
<td>25 min.</td>
<td>153-151</td>
<td>162-172</td>
<td>167-172</td>
<td>162-179</td>
<td>No acceleration</td>
</tr>
<tr>
<td>Control site 2</td>
<td>Epicardium</td>
<td>142-140</td>
<td>Site located outside</td>
<td>150-150</td>
<td>153-153</td>
<td>167-172</td>
<td>162-179</td>
<td>6.4%</td>
</tr>
<tr>
<td></td>
<td>Endocardium</td>
<td>139-139</td>
<td>the infarcted area</td>
<td>—</td>
<td>140-141</td>
<td>140-139</td>
<td>131-130</td>
<td>18.1%</td>
</tr>
<tr>
<td>174</td>
<td>Epicardium</td>
<td>143-143</td>
<td>3 hrs.</td>
<td>117-117</td>
<td>95-94</td>
<td>120-120</td>
<td>159-157</td>
<td>20.6%</td>
</tr>
<tr>
<td>T</td>
<td>Endocardium</td>
<td>151-151</td>
<td>45 min.</td>
<td>149-147</td>
<td>150-150</td>
<td>174-174</td>
<td>182-182</td>
<td>27.0%</td>
</tr>
<tr>
<td>172</td>
<td>Epicardium</td>
<td>128-126</td>
<td>1 hr.</td>
<td>101-101</td>
<td>108-108</td>
<td>101-100</td>
<td>High threshold</td>
<td>10.6%</td>
</tr>
<tr>
<td>T</td>
<td>Endocardium</td>
<td>136-137</td>
<td>45 min.</td>
<td>100-100</td>
<td>144-143</td>
<td>164-164</td>
<td>High threshold</td>
<td>24.8%</td>
</tr>
<tr>
<td>170</td>
<td>Epicardium</td>
<td>121-121</td>
<td>5 hrs.</td>
<td>131-131</td>
<td>167-162</td>
<td>189-190</td>
<td>High threshold</td>
<td>14.2%</td>
</tr>
<tr>
<td>T</td>
<td>Endocardium</td>
<td>139-139</td>
<td>27 min.</td>
<td>138-138</td>
<td>143-142</td>
<td>150-151</td>
<td>157-156</td>
<td>16.0%</td>
</tr>
<tr>
<td>169</td>
<td>Epicardium</td>
<td>133-133</td>
<td>5 hrs.</td>
<td>155-152</td>
<td>140-139</td>
<td>158-156</td>
<td>139-140</td>
<td>No acceleration</td>
</tr>
<tr>
<td>T</td>
<td>Endocardium</td>
<td>140-140</td>
<td>10 min.</td>
<td>121-120</td>
<td>135-133</td>
<td>163-162</td>
<td>159-157</td>
<td>9.2%</td>
</tr>
<tr>
<td>165</td>
<td>Epicardium</td>
<td>132-131</td>
<td>5 hrs.</td>
<td>131-132</td>
<td>129-130</td>
<td>127-127</td>
<td>119-119</td>
<td>24.8%</td>
</tr>
<tr>
<td></td>
<td>Endocardium</td>
<td>136-137</td>
<td>49 min.</td>
<td>150-149</td>
<td>119-118</td>
<td>123-123</td>
<td>125-123</td>
<td>14.2%</td>
</tr>
<tr>
<td>164</td>
<td>Epicardium</td>
<td>148-148</td>
<td>2 hrs.</td>
<td>160-149</td>
<td>133-134</td>
<td>126-124</td>
<td>142-141</td>
<td>No acceleration</td>
</tr>
<tr>
<td></td>
<td>Endocardium</td>
<td>118-140</td>
<td>55 min.</td>
<td>—</td>
<td>139-139</td>
<td>160-160</td>
<td>180-179</td>
<td>0.71%</td>
</tr>
<tr>
<td>163</td>
<td>Epicardium</td>
<td>170-170</td>
<td>6 hrs.</td>
<td>179-179</td>
<td>181-180</td>
<td>180-180</td>
<td>178-177</td>
<td>No acceleration</td>
</tr>
<tr>
<td></td>
<td>Endocardium</td>
<td>157-157</td>
<td>47 min.</td>
<td>109-169</td>
<td>161-161</td>
<td>164-164</td>
<td>163-161</td>
<td>No acceleration</td>
</tr>
<tr>
<td>162</td>
<td>Epicardium</td>
<td>130-160</td>
<td>1 hr.</td>
<td>152-151</td>
<td>145-143</td>
<td>143-143</td>
<td>Vent. Fib.</td>
<td>6.7%</td>
</tr>
<tr>
<td></td>
<td>Endocardium</td>
<td>116-146</td>
<td>45 min.</td>
<td>141-141</td>
<td>138-139</td>
<td>138-138</td>
<td>10.6%</td>
<td></td>
</tr>
<tr>
<td>160</td>
<td>Epicardium</td>
<td>137-186</td>
<td>4 hrs.</td>
<td>182-175</td>
<td>159-158</td>
<td>170-170</td>
<td>178-177</td>
<td>5.5%</td>
</tr>
<tr>
<td></td>
<td>Endocardium</td>
<td>130-175</td>
<td>27 min.</td>
<td>179-171</td>
<td>171-169</td>
<td>162-161</td>
<td>164-163</td>
<td>15.0%</td>
</tr>
<tr>
<td>171</td>
<td>Epicardium</td>
<td>143-143</td>
<td>25 min.</td>
<td>1st Heart block, ventricular fibrillation</td>
<td>1st Heart block, ventricular fibrillation</td>
<td>13.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endocardium</td>
<td>130-160</td>
<td>14 min.</td>
<td>High threshold</td>
<td>139-140</td>
<td>12.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>173</td>
<td>Epicardium</td>
<td>127-122</td>
<td>14 min.</td>
<td>High threshold</td>
<td>120-122</td>
<td>12.8%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The first figure represents the longest interval with no response and the second figure the shortest interval with a response. In all of these experiments, the hearts were driven at a constant rate.

†Inadvertently, a small coronary artery was ligated in suturing the electrode prior to the control.

T=Concurrent temp. studies.
ACUTE MYOCARDIAL INFARCTION

Accelerated recovery, as measured by shortening of the effective refractory period following this experimental infarction, was most marked at the endocardial level in 1 hour and at the epicardial level at 3 hours, shortly after the appearance of the first definite Q wave in the epicardial lead. Above the graph are the epicardial surface leads taken over the infarcted zone. The first of these tracings was taken during the control period and the fifth tracing shows definite shortening of the Q-T interval compared with both earlier and later tracings with a constant driven heart rate of 178 beats/min.

This is the only study in which the chest remained open. In the other, the epicardium declined 1.5 C. in a 45-minute period. Five others showed no changes following coronary artery ligation.

Four special studies were done to see what effect changes in the transmural temperature gradient would have on the refractory period and shape of the T wave. The pericardial sac was irrigated with warm Ringer’s solution and the transmural temperature gradient and effective refractory period were measured at both surfaces. Figure 4 illustrates the results of one of these experiments and shows that initially the surface electrocardiogram T wave was negative and the epicardium was 0.6 C. cooler than the endocardium. The temperature gradient was then reversed with the epicardium 3.4 C. warmer than the endocardium. The T wave became positive, and the effective refractory period fell 39 per cent at the epicardium. Slightly later when the temperature gradient had fallen to zero, but both ventricular surfaces were warmer than in the control period, there was a 12 per cent fall in the endocardial effective refractory period. Because of the difficulty of maintaining the temperature gradient constant, a small vacuum aspirator was used to permit more rapid removal of warm Ringer’s solution, and the measurements were repeated. During the time that the duration of the effective refractory period are sensitive to temperature, some check on the temperature changes during the study was considered essential. Seven animals whose coronary vessels were ligated were followed intermittently with both epicardial and sub-endocardial temperature measurements. Despite careful closure of the chest wall in all but 1 experiment (see below), the epicardium was cooler than the endocardium in 6 of these animals. The transmural temperature gradient was remarkably constant in each animal and varied from 0.8 to 2.5 C., with a mean gradient of 1.4 in the 6 animals. In the seventh animal, no temperature difference of significance was observed. In 3 animals, the temperature of both ventricular surfaces declined progressively throughout the study at a rate of approximately 0.5 C. per hour. Two of the studies showed an immediate decline in temperature following coronary artery ligation. In 1 of these, shown in figure 3, the temperature declined 4.25 C. at the epicardium and 4 C. at the endocardium within 12 minutes.

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Transmural temperature measurements following acute experimental infarction. In this animal, the chest cage was left open to permit recording suction potentials (not shown), but despite the progressive decline of temperature at both the epicardium and endocardium, a precipitous fall of temperature may be seen immediately after the ligation lasting approximately 12 minutes.

T wave was positive, the effective refractory period fell 37 per cent at the epicardial surface and 7.3 per cent at the subendocardial level. Since the subendocardial temperature was essentially constant during this short period, it is reasonable to assume that if the 2 determinations could have been made simultaneously, the subendocardial effective refractory period would not have changed. When the data in this experiment were adjusted for the time required for excitation to spread from endocardium to epicardium, it was found that when the T waves in the epicardial lead were negative, recovery at the epicardium was completed 2 msec, (not a significant difference) after that of the endocardium, but when the T waves were positive, it was completed 35 msec. before recovery of the endocardium. In 1 other animal in which a similar study was done, the T waves which were initially negative became positive when the epicardium became 7.2 C. warmer than the endocardium, as is shown in figure 5. During the period when T waves were positive, the effective refractory period fell 16 per cent at the epicardium and 14 per cent at the endocardium, and if the time base of the 2 measurements were adjusted, the epicardium recovered 6 msec. in advance of the endocardium. The 2 other studies showed that the surface T waves changed from negative to positive when the epicardium was 1 and 6 C., respectively, warmer than the endocardium. These results supplement the previous study and support the concept that when the T wave is positive, recovery is slightly accelerated at the epicardial surface compared to the endocardial surface.

Discussion

There is a fair amount of evidence indicating that recovery is accelerated in severe ischemia. Wiggers, studying experimental infarction, noted a definite shortening of the A-F interval of the monophasic action potential. Trautwein et al. found shortening of the membrane action potential of the papillary muscle of the cat when perfused with oxygen deficient Tyrode's solution and, further, that this change was completely reversible. Webb and Hollander, studying rat atrial cells, pointed out that the most marked result of
anoxia was a shortening of the action potential due to a more rapid repolarization rate. Kardesch et al.3 in a perfusion preparation of dog and rabbit hearts submitted to complete anoxia, found marked shortening of the repolarization phase of the action potential. The present study confirms these observations and extends them by a study of the deeper myocardial layers and for longer periods in myocardial infarction. In the author's previous study,4 accelerated recovery was found more often at the subendocardial level of the infarced area. This was also true in the observations reported in this paper, but the epicardium was frequently found to be similarly affected. During the period of accelerated recovery the surface electrocardiogram always showed elevation of the RS-T junction, usually with some shortening of the Q-T interval, but there was nothing to indicate whether accelerated recovery was limited to the epicardial or endocardial surfaces, or was transmural.

Since the temperatures of the epicardial and subendocardial surfaces remained unchanged, or were cooler following ligation of coronary arteries, the accelerated recovery observed cannot be attributed to this factor and was most likely due to anoxia. The failure to find the initial rise in temperature reported by Sayen5 could be due to the intermittent method of determining temperature or simply to the difficulties of closing the chest satisfactorily.

All of our studies showed a significant increase in the effective refractory period as the experiments progressed, and this was true whether there was or was not initial shortening of the refractory period. This finding strongly suggests that the duration of the membrane action potentials, in heart muscle in the locations where our electrodes were placed, must have been increased at this period. As far as is known, only shortening of the duration of transmembrane action potentials has been found during ischemia of heart muscle in the relatively short term studies that have been carried out, but the long Q-T intervals with deeply inverted T waves, so commonly seen in later stages of experimental and in human myocardial infarction, strongly suggest that there must be a considerable amount of muscle with action potentials of increased duration at this time. That this may be true is suggested by figure 12 from Trautwein's work,3 showing great prolongation of the action potential duration of a Purkinje fiber after long periods of anoxia. Further studies to investigate this interesting situation are under way.

The effects of temperature on the membrane action potential and on the polarity of the T wave are well known and require no discussion here. Our studies agree with the view that warming the epicardial surface causes the T wave to become upright by slightly accelerating recovery at the epicardial surface compared with the endocardial surface. It should be emphasized that the transmural temperature gradients observed in these experiments may be quite different from those that exist in a normal intact animal where the temperature of the epicardium may be higher than that of the endocardium.18,19

Summary

Accelerated recovery, as manifested by shortening of the effective refractory period after coronary artery ligation, occurred at
either the epicardial or endocardial surface or both in 11 of 13 animals tested with a mean shortening of 15.7 per cent at the epicardial and 13 per cent at the endocardial levels. These changes are attributed to severe anoxia and are believed to be limited to the ischemic area, since studies in the periphery of an infarcted zone show no significant changes in the first 3 hours. In one instance a minor acceleration of recovery was found after 3 hours at the endocardium. All studies showed a final period of delayed recovery. It is felt that this probably reflects a prolonged duration of the membrane action potential during the later stages of myocardial infarction. This is supported by both experimental and human electrocardiographic data which show prolongation of the Q-T interval in association with deeply inverted T waves following the period of acute injury. Transmural temperature studies after coronary artery ligation showed a prompt fall in 2 studies out of 7 and no acute change in the others. Irrigating the pericardial sac with warm Ringer's solution reversed the pre-existing transmural temperature gradient, caused the T waves in epicardial leads to change from negative to positive, and reduced the duration of the effective refractory period at both the endocardial and epicardial surfaces, especially the latter. During the time that the T waves were upright, recovery was completed earlier at the epicardial than at the endocardial surface.

**Summario in Interlingua**

Un acceleramento restabilimento—manifesto in le plus eavtis effective periodo refractori post ligation del arteria coronari—occureva al superficie epicardial o al superficie endocardial o a ambas in 11 ex 13 cases testate, con un reduction del tempore de 15.7 pro cento al nivello epicardial e de 13 pro cento al nivello endocardial. Iste alterationes es attribuite al effecto de anoxia sever. Es opinate que illos es limitate al aran ischemic, proquo studios al peripheria del zona infarctate revelavala nullis significative alterationes in le curso del prime tres horas. In un caso, un leve acceleracion del restabilimento eseva trovate al endocardio post 3 horas. Omne le studios mostrava un periodo final de restabilimento retardate. Es opinate que isto reflecte probabilmente un prolongate duration del potential de action membrunal durante le studios plus tardive del infarimento myocardial. Isto es supporta per datos electrocardiographie tanto human como etiam experimental, monstrante que un prolongation del intervallo Q-T in association con profundemente invertite undas T post le periodo del valmeration acute. Studios del temperatura transmural post ligation del arteria coronari mostrava un prompte reduction in 2 ex 7 studios e nulla alteration acute in le altures. Le irrigation del sacco pericardial con calide solution de Ringer reverteva le pre-existente gradiente transmural de temperatura, rendeva positive le negative undas T in derivationes epicardial, e reduciva le duration del effective periodo refractori al superficie endocardial e, specialmente, al superficie epicardial. Durante le tempore quando le undas T eseva erecte, le restabilimento se completava plus rapidemente al superficie epicardial que al superficie endocardial.

**References**

9. Ashman, R., Ferguson, F. P., Greemillion, A. I., and Byer, E.: Effect of cycle-length changes upon the form and amplitude of the T deflec-


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