Use of Changes in the Epicardial QRS Complex to Assess Interventions which Modify the Extent of Myocardial Necrosis following Coronary Artery Occlusion

L. DAVID HILLIS, M.D., JOSEPH ASKENAZI, M.D., EUGENE BRAUNWALD, M.D., PAULO RADVANY, M.D., JAMES E. MULLER, M.D., MICHAEL C. FISHEIN, M.D., AND PETER R. MAROKO, M.D.

SUMMARY The goal of this study was to determine if changes in the epicardial QRS complex after coronary artery occlusion (CAO) can be used to evaluate the efficacy of interventions designed to limit infarct size. Forty-one open-chest dogs with CAO were studied: 15 were controls, 18 received hyaluronidase and eight received propranolol starting 20 minutes after CAO. Epicardial ECGs were recorded at specific time intervals to analyze ST-segment elevation and changes in Q and R waves. Transmural specimens were obtained 24 hours after CAO from the same sites at which ECGs were recorded. Q wave development (ΔQ), R wave fall (ΔR), and their combination (ΔR + ΔQ) at 24 hours correlated with the extent of necrosis, as determined by myocardial creatine phosphokinase activity depression and histologic appearance. In the control group ST-segment elevation 15 minutes after CAO (ST\textsubscript{15mm}) predicted changes in Q and R waves 24 hours later; in the treated groups, the same ST\textsubscript{15mm} prior to drug administration resulted in significantly less QRS changes. Thus, 1) Q wave development and R wave fall 24 hours after CAO accurately reflect myocardial necrosis. 2) ST\textsubscript{15mm} predicts subsequent changes in Q and R waves. 3) The efficacy of hyaluronidase and propranolol, agents previously shown to reduce myocardial necrosis, can be detected by less Q wave development and a smaller fall in R wave voltage.

LIMITATION OF THE EXTENT of myocardial infarction following coronary artery occlusion is potentially of great clinical importance, since the salvage of contractile tissue otherwise destined to undergo necrosis may reduce heart failure and, ultimately, mortality secondary to myocardial infarction. It has been shown in experimental animals that a variety of pharmacologic, metabolic, and hemodynamic interventions can reduce ischemic injury in its reversible phase and thus reduce the extent of the subsequent infarction. 1-3 Some of these interventions have now been tested in small numbers of patients with encouraging results. One of the most formidable barriers to the clinical application of the information which has been obtained in the laboratory is the lack of a suitable technique for assessing the efficacy, or lack thereof, of these interventions. Specifically, a technique is needed which can be applied at an early stage in the course of an infarction, when the injury to considerable quantities of myocardium is still in the reversible phase, to predict the ultimate amount of myocardial necrosis to be anticipated, and which can then be repeated at a later time to assess the amount of damage which has actually occurred.

An analysis of changes in the QRS complex potentially satisfies these requirements. The present report describes studies in experimental animals of: 1) The relation between alterations in the QRS complex (i.e., appearance of Q waves and fall in R waves) of the epicardial electrogram and myocardial necrosis, as determined biochemically and histologically; 2) the use of epicardial ST-segment elevation occurring soon after coronary occlusion to predict the subsequent alterations in the epicardial QRS complex; and 3) the detection, by an analysis of changes in epicardial QRS morphology, of the limitation of necrosis by hyaluronidase.

From the Departments of Medicine and Pathology, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Massachusetts.

Supported in part by Contract NOI-HV-53000 under the Cardiac Diseases Branch, Division of Heart and Vascular Diseases, NIH, and a grant from the John A. Hartford Foundation. Dr. Hillis is the recipient of a postdoctoral fellowship award (1F32-HL-05147-01) from the NHLI.

Address for reprints: D. R. Maroko, M.D., Harvard Medical School, Bldg. A, 25 Shattuck Street, Boston, Massachusetts 02115.

Received January 14, 1976; revision accepted May 18, 1976.
and propranolol, agents previously shown to reduce myocardial damage following coronary occlusion.  

**Methods**

Forty-one mongrel dogs of both sexes weighing between 20 and 34 kg were anesthetized with sodium thiamylal and placed on artificial respiration using a volume respirator (Harvard Apparatus). A left thoracotomy was performed in the fifth intercostal space, and the heart was suspended in a pericardial cradle. The left anterior descending coronary artery was dissected free from the adjacent tissue and, at the appropriate time, ligated with 00 mersilene suture material. Ten to 16 sites on the anterior surface of the left ventricle were selected for the recording of unipolar electrograms. Each site selected for electrocardiographic recording was recognized by its specific relationship to the branching of the coronary arteries and veins. Sites were chosen from within the area supplied by the occluded vessel, from distant regions (presumably normal), and from the border zone. The input impedance of the recorder amplifier was 100 megohms, and the frequency response of the system was ± 0.5 db from 0.14 to 70 Hz. The impedance of the electrode was maintained constant, as reflected in the reproducibility of the recordings. The electrode employed was a 15 mm² copper cylinder with a saline-soaked wick connected to the precordial V lead and held by a cable perpendicular to the electrode, thus minimizing mechanical stress. Because of the large area of the electrode, small variations in location did not change the configuration of the recordings. The electrograms obtained with this system are reproducible following subsequent coronary artery occlusion.  

Electrocardiographic lead aVF and systemic arterial pressure (Statham P23Db pressure transducers) were recorded continuously for the duration of the experiments on a Brush Instruments polygraph.  

In order to determine the relationship between epicardial ST-segment elevation and the subsequent development of Q waves and the effect of hyaluronidase on this relationship, the coronary artery was occluded for six hours in 17 dogs. Seven of these served as controls, and the other 10 dogs received hyaluronidase* intravenously (500 NF units/kg) 20 minutes after occlusion. In all dogs epicardial electrograms were recorded immediately prior to occlusion and 15 minutes, 2, 3, 4, 5, and 6 hours after occlusion. The ST-segment elevation 15 minutes after occlusion (ST₁₅ₐ₉) at each site was related to ΔQ, i.e., the difference in mV between the depth of a Q wave at a given time following occlusion and its depth prior to occlusion (small Q waves are normally present in epicardial leads over the interventricular septum). The relation between ST₁₅ₐ₉ and ΔQ was determined at hourly intervals for six hours.  

In a second group of 24 dogs coronary artery occlusions were maintained for 24 hours. Eight of these served as controls; eight received hyaluronidase (500 NF units/kg) intravenously 20 minutes after occlusion; and eight received propranolol, 1 mg/kg intravenously 20 minutes after occlusion, and 0.25 mg/kg every six hours thereafter. Epicardial electrograms were recorded immediately before and 15 minutes after occlusion. The thorax was then closed in layers and drained with an underwater tube. Twenty-four hours later the dogs were reanesthetized, placed on artificial respiration, and their chests reopened. Epicardial electrograms were recorded again from the same sites at which recordings had been made 15 minutes following occlusion. These 24 hour electrograms were analyzed for the development of Q waves and the loss of R wave voltage. Following the 24 hour electrograms, the animals were sacrificed, and transmural specimens weighing approximately 400 mg were obtained from each site for analysis of creatine phosphokinase (CPK) activity and for histologic examination. The changes in the QRS complex were compared with the depression of myocardial CPK activity and with the histologic findings.  

Sites at which local conduction delay occurred, as indicated by prolongation of the interval from the onset of the QRS to the intrinsic deflection exceeding 40 msec or prolongation of the entire QRS beyond 65 msec, were excluded from ST-segment analysis, since in the presence of an intraventricular conduction defect the ST segment is no longer an accurate index of ischemic injury.* In each group of eight dogs only six sites exhibited such prolongation. Sites with conduction delay at 24 hours were excluded from QRS analysis, since such delay is well known to alter QRS morphology.10 Only one site was excluded because of this criterion. Myocardial CPK analysis was carried out as previously described.9,11  

The specimens for histologic examination were fixed in formaldehyde 10% and stained with hematoxylin and eosin. They were examined by one of the investigators, who had no previous knowledge of their origins. Each section was graded according to the percentage of the section deemed necrotic: 0 (no evidence of necrosis), 1+ (1-25% necrosis), 2+ (26-50% necrosis), 3+ (51-75% necrosis), or 4+ (>75% necrosis). The following histologic features were observed in areas of myocardium considered to be necrotic: 1) increased eosinophilia of the myocardial fibers; 2) loss of cross striations with increased granularity of the cytoplasm; 3) thinning and waviness of the myocardial fibers; 4) presence of contraction bands; 5) pyknosis and disappearance of myocardial cell nuclei; and 6) interstitial infiltration of neutrophilic polymorphonuclear leukocytes.12  

All statistical analyses, except those involving the graded histologic sections, were performed using each dog as an independent statistical unit. Thus, when the relationship between two variables was analyzed, a regression line was first calculated for each individual dog. Then, the individual regression lines were averaged, and the standard error of this average was determined. The treated and untreated groups were then compared using Student's t-test.  

**Results**

1. **Correlation between Myocardial Necrosis and Epicardial QRS Changes 24 Hours following Coronary Occlusion**

In the eight control dogs in which the coronary artery was occluded for 24 hours a total of ten sites were considered to be normal, since they showed no ST-segment elevation 15 minutes after occlusion, normal myocardial CPK activity (average, 35.6 ± 0.7 IU/mg protein), and normal histologic appearance 24 hours later. None of these sites devel-

---

opera Q > 2 mV 24 hours after occlusion. In contrast, there were 54 sites with ST-segment elevation > 2 mV 15 minutes after occlusion; all of these sites had depressed myocardial CPK activity (average, 17.0 ± 0.08 IU/mg protein) and histologic signs of early myocardial infarction 24 hours later. All of these sites also developed Q waves > 4 mV (average, 13.7 ± 0.7) 24 hours after occlusion.

The relationship between myocardial CPK activity and changes in the epicardial QRS complex for the same sites is shown in figure 1 and table 1. The degree of alterations in the QRS was proportional to myocardial CPK depression. Thus, reduction in CPK activity, which is taken to represent the degree of necrosis, correlated closely with the appearance of new Q waves (ΔQ), the fall in R waves (ΔR, %R), and a combination of the two (ΔR + ΔQ).

In the dogs treated with hyaluronidase or propranolol (eight in each group) the relationship between alterations in the epicardial QRS complex which developed in 24 hours and the enzymatic changes in the subjacent myocardium was not altered from the relationship observed in the control dogs. In the control group the relationship between CPK activity and epicardial QRS changes was: CPK = (-0.57 ± 0.08) ΔR + ΔQ + (35.1 ± 0.6) (N = 8, r = -0.86 ± 0.03), and in the hyaluronidase-treated group it was: CPK = (-0.54 ± 0.27) ΔR + ΔQ + (28.8 ± 3.0) (N = 8, r = -0.51 ± 0.14); while in the propranolol-treated group it was: CPK = (-0.60 ± 0.13) ΔR + ΔQ + (35.6 ± 2.7) (N = 8, r = -0.66 ± 0.08).

There was also a good correlation between the changes in the epicardial QRS complex and the histologic appearance which developed in the 24 hours following occlusion (fig. 2). As the histologic severity of necrosis increased, a progressive elevation of (ΔR + ΔQ) was noted.

**FIGURE 1.** Left panel) The relationship between myocardial CPK activity 24 hours after coronary artery occlusion (CPK<sub>24h</sub>) and Q and R wave changes at the same time (∆R + ∆Q<sub>24h</sub>) in the eight control dogs. Each line represents one dog. The average of the eight dogs, represented by the bold line, is: CPK = (-0.57 ± 0.08)(ΔR + ΔQ<sub>24h</sub>) + (35.1 ± 0.6) (N = 8, r = -0.86 ± 0.03). Note the inverse relationship between CPK<sub>24h</sub> and (∆R + ∆Q<sub>24h</sub>) showing that a high (∆R + ∆Q<sub>24h</sub>) reflects low myocardial CPK. Right panel) An example of the individual data points in one dog. Again, note that the sites with low myocardial CPK activity have high values for (∆R + ∆Q<sub>24h</sub>).

**FIGURE 2.** The relationship between Q wave development and R wave fall 24 hours after coronary artery occlusion ([ΔR + ΔQ]<sub>24h</sub>) and the extent of necrosis demonstrated histologically at the same time in specimens from the control group and both treated groups. Histologic grade 0 = no visible necrosis; grade 1+ = 1–25% necrosis; grade 2+ = 26–50% necrosis; grade 3+ = 51–75% necrosis; and grade 4+ = >75% necrosis. Within each bar are the number of specimens from the control (C), the hyaluronidase-treated (H) and the propranolol-treated (P) dogs that are included within that histologic grade. Note that (∆R + ∆Q)<sub>24h</sub> increases progressively as necrosis becomes more pronounced. In addition, the hyaluronidase and the propranolol-treated dogs show less necrosis than the control dogs: the majority of sites from the treated dogs are 0–2+, while most of the sites from the control dogs are 3+ or 4+.

---

**TABLE 1.** Relationship between Myocardial CPK and QRS Changes 24 Hours after Occlusion

<table>
<thead>
<tr>
<th>CPK</th>
<th>(∆R + ∆Q&lt;sub&gt;24h&lt;/sub&gt;)&lt;sub&gt;24h&lt;/sub&gt; in mV</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPK = (-1.23 ± 0.16) ∆Q + (33.7 ± 1.3)</td>
<td></td>
</tr>
<tr>
<td>(N = 8, r = -0.87 ± 0.03)</td>
<td></td>
</tr>
<tr>
<td>CPK = (-0.15 ± 0.11) ∆R + (31.0 ± 1.3)</td>
<td></td>
</tr>
<tr>
<td>(N = 8, r = -0.67 ± 0.04)</td>
<td></td>
</tr>
<tr>
<td>CPK = (-0.14 ± 0.05) %R + (34.2 ± 2.7)</td>
<td></td>
</tr>
<tr>
<td>(N = 8, r = -0.64 ± 0.09)</td>
<td></td>
</tr>
<tr>
<td>CPK = (-0.57 ± 0.08)(ΔR + ΔQ&lt;sub&gt;24h&lt;/sub&gt;) + (35.1 ± 0.6)</td>
<td></td>
</tr>
<tr>
<td>(N = 8, r = -0.86 ± 0.03)</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Relationship between $ST_{15m}$ and $\Delta Q$ at Varying Time Intervals after Coronary Artery Occlusion

<table>
<thead>
<tr>
<th>Time after occlusion</th>
<th>Control</th>
<th>Hyaluronidase</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 hours</td>
<td>$\Delta Q = (0.24 \pm 0.06)ST_{15m} + (0.21 \pm 0.15)$</td>
<td>$\Delta Q = (0.12 \pm 0.06)ST_{15m} + (0.47 \pm 0.27)$</td>
</tr>
<tr>
<td></td>
<td>$(N = 7, r = 0.61 \pm 0.11)$</td>
<td>$(N = 10, r = 0.38 \pm 0.12)$</td>
</tr>
<tr>
<td>3 hours</td>
<td>$\Delta Q = (0.32 \pm 0.09)ST_{15m} + (0.34 \pm 0.15)$</td>
<td>$\Delta Q = (0.18 \pm 0.08)ST_{15m} + (0.47 \pm 0.25)$</td>
</tr>
<tr>
<td></td>
<td>$(N = 7, r = 0.60 \pm 0.06)$</td>
<td>$(N = 10, r = 0.46 \pm 0.14)$</td>
</tr>
<tr>
<td>4 hours</td>
<td>$\Delta Q = (0.52 \pm 0.15)ST_{15m} + (0.40 \pm 0.20)$</td>
<td>$\Delta Q = (0.39 \pm 0.10)ST_{15m} + (0.44 \pm 0.20)$</td>
</tr>
<tr>
<td></td>
<td>$(N = 6, r = 0.69 \pm 0.06)$</td>
<td>$(N = 10, r = 0.61 \pm 0.12)$</td>
</tr>
<tr>
<td>5 hours</td>
<td>$\Delta Q = (0.67 \pm 0.19)ST_{15m} + (0.57 \pm 0.29)$</td>
<td>$\Delta Q = (0.51 \pm 0.10)ST_{15m} + (0.60 \pm 0.27)$</td>
</tr>
<tr>
<td></td>
<td>$(N = 6, r = 0.78 \pm 0.07)$</td>
<td>$(N = 10, r = 0.71 \pm 0.07)$</td>
</tr>
<tr>
<td>6 hours</td>
<td>$\Delta Q = (0.95 \pm 0.16)ST_{15m} + (0.59 \pm 0.49)$</td>
<td>$\Delta Q = (0.63 \pm 0.14)ST_{15m} + (0.69 \pm 0.32)$</td>
</tr>
<tr>
<td></td>
<td>$(N = 6, r = 0.87 \pm 0.02)$</td>
<td>$(N = 10, r = 0.72 \pm 0.07)$</td>
</tr>
<tr>
<td>24 hours</td>
<td>$\Delta Q = (1.57 \pm 0.30)ST_{15m} + (2.2 \pm 0.6)$</td>
<td>$\Delta Q = (0.85 \pm 0.14)ST_{15m} + (1.3 \pm 0.3)$</td>
</tr>
<tr>
<td></td>
<td>$(N = 8, r = 0.83 \pm 0.02)$</td>
<td>$(N = 8, r = 0.73 \pm 0.06)$</td>
</tr>
</tbody>
</table>

*In comparison to control.

II. Use of Early ST-segment Elevation ($ST_{15m}$) to Predict Changes in the Epicardial QRS Complex

$ST_{15m}$ correlated well with the progressive development of Q waves at hourly intervals between 2 and 6 hours and at 24 hours following occlusion (fig. 3, table 2), signifying that the degree of ST-segment elevation can predict the depth of development of Q waves, even at a short time interval following coronary occlusion. Twenty-four hours after occlusion there was a good correlation between $ST_{15m}$ and changes in the epicardial QRS complex [$\Delta Q$, $\Delta R$, $\%R$, and $(\Delta R + \Delta Q)_{15m}$] (fig. 4, table 3).

III. Use of Analysis of the Epicardial QRS Complex to Assess the Efficacy of Interventions

It had been observed previously that for any level of $ST_{15m}$ both hyaluronidase and propranolol reduced the decline in CK activity at the same site 24 hours later. In the present study the dogs treated with hyaluronidase and those which received propranolol demonstrated less histologic damage for similar degrees of ST-segment elevation than did the controls. In the control dogs 54 sites had significant $ST_{15m}$ (average 7.5 ± 0.5 mV). When these sites were examined histologically 24 hours following occlusion, all ex-

Figure 3. The relationship between ST-segment elevation at 15 minutes following occlusion ($ST_{15m}$) and Q wave development ($\Delta Q$) at various time intervals after coronary artery occlusion. Note that as the time interval increases, the slope of the line increases as well, reflecting deeper Q waves. There is a statistical difference between the slopes of: 2 hrs vs 5 hrs ($P<0.05$), 2 hrs vs 6 hrs ($P<0.001$), and 2 hrs vs 24 hrs ($P<0.001$); 3 hrs vs 6 hrs ($P<0.01$), and 3 hrs vs 24 hrs ($P<0.001$); 4 hrs vs 6 hrs ($P<0.05$), and 4 hrs vs 24 hrs ($P<0.01$); 5 hrs vs 24 hrs ($P<0.01$); and 6 hrs vs 24 hrs ($P<0.01$).

Figure 4. The relationship between ST-segment elevation at 15 minutes following occlusion ($ST_{15m}$) and changes in QRS configuration at 24 hours ($\Delta R + \Delta Q_{24h}$). The regression line for all eight controls (continuous line) is: ($\Delta R + \Delta Q_{24h}$) = (3.39 ± 0.75) $ST_{15m}$ + (8.8 ± 1.9); $N = 8$, $r = 0.81 ± 0.06$. The regression line for the eight hyaluronidase-treated dogs (dotted line) is: ($\Delta R + \Delta Q_{24h}$) = (1.35 ± 0.37) $ST_{15m}$ + (5.4 ± 1.7); $N = 8$, $r = 0.60 ± 0.14$. The regression line for the eight propranolol-treated dogs (dashed line) is: ($\Delta R + \Delta Q_{24h}$) = (1.79 ± 0.41) $ST_{15m}$ + (9.0 ± 2.5); $N = 8$, $r = 0.68 ± 0.08$. Note that for any level of $ST_{15m}$, $\Delta R + \Delta Q_{24h}$ is less in the treated dogs than in the controls ($P<0.05$), reflecting less myocardial necrosis.
EPICARDIAL QRS CHANGES TO ASSESS INTERVENTIONS/Hillis et al.

Table 3. Relationship between ST<sub>ɪm</sub> and QRS Changes 24 Hours Later

<table>
<thead>
<tr>
<th></th>
<th>Hyaluronidase</th>
<th>Propranolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔQ&lt;sub&gt;ɪm&lt;/sub&gt; = aST&lt;sub&gt;ɪm&lt;/sub&gt; + b</td>
<td>(N = 8, r = 0.55, P &lt; 0.01)</td>
<td>(N = 8, r = 0.36, P &lt; 0.01)</td>
</tr>
<tr>
<td>ΔQ&lt;sub&gt;b&lt;/sub&gt; = aST&lt;sub&gt;b&lt;/sub&gt; + b</td>
<td>(N = 8, r = 0.38, P &lt; 0.01)</td>
<td>(N = 8, r = 0.60, P &lt; 0.01)</td>
</tr>
<tr>
<td>ΔR&lt;sub&gt;ɪm&lt;/sub&gt; = aRT&lt;sub&gt;ɪm&lt;/sub&gt; + b</td>
<td>(N = 8, r = 0.57, P &lt; 0.01)</td>
<td>(N = 8, r = 0.81, P &lt; 0.01)</td>
</tr>
<tr>
<td>ΔR&lt;sub&gt;b&lt;/sub&gt; = aRT&lt;sub&gt;b&lt;/sub&gt; + b</td>
<td>(N = 8, r = 0.71, P &lt; 0.01)</td>
<td>(N = 8, r = 0.68, P &lt; 0.01)</td>
</tr>
<tr>
<td>%ΔR = (ΔR&lt;sub&gt;ɪm&lt;/sub&gt; - ΔR&lt;sub&gt;b&lt;/sub&gt;)</td>
<td>(N = 8, r = 0.36, P &lt; 0.01)</td>
<td>(N = 8, r = 0.60, P &lt; 0.01)</td>
</tr>
</tbody>
</table>

The beneficial effects of hyaluronidase and propranolol, established both biochemically and histologically, were reflected in the less pronounced changes in the epicardial QRS complex. The changes in Q and R waves for the dogs given either hyaluronidase or propranolol were significantly less for any given level of ST<sub>ɪm</sub> than were those for the control dogs (figs. 4, 5, 6, 7; table 3), reflecting less myocardial necrosis.

Discussion

The ideal technique for assessing the effectiveness of interventions designed to protect injured but potentially salvageable myocardium in patients should be: 1) safe and non-invasive; 2) capable of predicting the extent of necrosis to be expected if no intervention were employed; 3) capable of assessing the extent of necrosis that actually develops; 4) capable of providing the data in items 2 and 3 accurately and in quantitative terms, i.e., in grams; 5) effective if applied immediately on the patient's admission, so that the intervention under study can be promptly applied, since delay in treatment may be expected to reduce the population of injured cells that are salvageable; 6) relatively simple, easy to apply, and inexpensive, so that its use will not be limited to specialized centers; and 7) applicable to all patients with acute myocardial infarction. Items 2 and 3 are of particular importance, since they would allow each patient to be used as his own control.

Three methods for assessing interventions in patients are currently available: analysis of washout of myocardial enzymes into the blood stream, radionuclide imaging of the heart, and precordial electrocardiographic mapping. CPK disappearance curves<sup>[18-19]</sup> can be used in two ways to assess changes in myocardial necrosis: 1) "Infarct size" can be calculated from serial CPK plasma values, and comparisons between a control and a treated group can be carried out. Since infarcts may vary in size one hundred fold, a reduction of infarct size on the order of 20% can be demonstrated only by studying an extremely large number of patients. This practical limitation has prevented the successful application of this method to the problem under con-
consideration. 2) "Infarct size" can be predicted from an analysis of the first seven hours of rise of CPK and compared to "infarct size" calculated from the CPK curve actually observed. This method has been employed in several investigations, but it has certain mathematical limitations. Actually, each patient does not serve as his own control but rather each group serves as its own control, since in individual patients the observed "infarct size" can vary markedly from that predicted. Moreover, patients can receive therapy only after completion of the predictive portion of the CPK curve, approximately 10-12 hours after the onset of the clinical event; as a consequence, several precious hours are lost. 

![Figure 5](image)

**Figure 5.** Left) A schematic representation of the heart and its arteries. The left anterior descending (LAD) was occluded at its midportion (occl). The shaded area represents the zone of ST-segment elevation 15 minutes after occlusion. Right) Examples of epicardial electrograms, myocardial CPK values (in IU/mg protein), and histologic grades from a control dog. Site A (from nonischemic myocardium) exhibited no ST-segment elevation at 15 minutes. At 24 hours it had no changes in QRS configuration and normal CPK activity, and it appeared normal histologically. Site B (border zone) showed moderate ST-segment elevation while at 24 hours there was a significant Q wave and partial loss of R wave voltage. The CPK activity was moderately depressed, and the histologic section was graded 3+ (51-75%) necrosis. Site C (center of the ischemic zone) had marked ST-segment elevation and at 24 hours demonstrated a total loss of R wave with a QS complex. The myocardial CPK activity was greatly depressed, and the histologic section was graded 4+ (>75%) necrosis.

![Figure 6](image)

**Figure 6.** The average value of $(\Delta R + \Delta Q)_{24h}$ for all sites with $ST_{15m}$ greater than 2 mV. The average $ST_{15m}$ was similar in all three groups: 7.5 ± 0.5 mV in the controls; 7.4 ± 0.5 mV in the hyaluronidase-treated group; and 7.8 ± 0.6 mV in the propranolol-treated group. Note that $(\Delta R + \Delta Q)_{24h}$ is significantly lower in the hyaluronidase-treated dogs as compared to controls ($P<0.0005$).

![Figure 7](image)

**Figure 7.** Comparison between changes in the epicardial QRS complex divided by ST-segment elevation at each site with $ST_{15m}$ greater than 2 mV. Note that the highest ratio is found in the control dogs, indicating larger $(\Delta R + \Delta Q)_{24h}$ for any given $ST_{15m}$ in the controls ($P<0.05$).
The scintigraphic techniques which use the gamma emissions of several radionuclides can be divided into those that demonstrate nonperfused areas (cold spot) and those that demonstrate the injured areas (hot spot). Although cold spot imaging is useful for some investigations, the technique is not ideally suited for the measurement of myocardial damage, since myocardial necrosis results not only from inadequate myocardial blood flow but also from an unfavorable balance between oxygen supply and demand. In addition, areas of long-standing nonperfusion cannot be distinguished from those in which the perfusion deficit is of more recent onset. The scanning of infarcts with agents that are concentrated in the injured area (hot spot) is very promising, since it provides a direct measurement of myocardial injury. Serial scintigraphy is potentially very useful in evaluating the progression of injury. At the present time, however, despite the enormous potential of these methods, they are still in the early phases of their development, and the quantitative expression of results is not yet possible.

Following initial observations on open-chest dogs using epicardial leads, we and other investigators have used precordial ST-segment mapping as a means of assessing changes in ischemic injury in patients with transmural anterior or lateral myocardial infarctions. Several studies have been performed in patients using this method, and the beneficial effects of a variety of interventions have been demonstrated. These include propranolol, intra-aortic balloon counterpulsation, hyaluronidase, nitroglycerin, and oxygen. The usefulness and limitations of these techniques have been discussed elsewhere. The advantages of this technique are its simplicity and the immediate demonstration of changes in ST-segment elevation following interventions, indicating directional changes that signify alterations in the extent and severity of ischemic injury. The disadvantages of the method are its inability to reflect the actual development of myocardial necrosis and the sensitivity of the precordial ST segment to factors other than ischemic injury, such as the development of pericarditis or alterations in electrolyte concentrations.

The approach proposed in this study appears to obviate some of these disadvantages. The changes in the epicardial QRS complex, specifically the combination of the decline of R waves and the development of Q waves during the 24 hours following coronary artery occlusion, correlate closely with the development of myocardial necrosis in the subjacent myocardium; an excellent correlation was found between these electrocardiographic changes and both the reduction of CPK activity (fig. 1) and the histologic signs of myocardial infarction (fig. 2). A corollary of this finding was the observation that epicardial ST-segment elevations 15 minutes after occlusion accurately predicted the development of the changes of the epicardial QRS complex that are indicative of necrosis 24 hours later (fig. 4), as well as of the myocardial CPK activity and the histologic signs of necrosis, as has been observed previously. Moreover, the ST-segment elevations correlated well with epicardial QRS changes at hourly intervals between two and six hours after occlusion, indicating that the ST-segment changes are predictive of QRS changes even as they are occurring (fig. 3). These findings demonstrate the close relationship between necrosis and epicardial QRS changes and are in accord with the observations of Wilson et al., who noted that transmural necrosis was present in those sites demonstrating QS complexes. Prinzmetal et al. later noted that sites demonstrating an epicardial QR complex were characterized by a mixture of living and dead myocardium.

The usefulness of analysis of the epicardial QRS in assessing the ability of interventions to reduce infarct size following coronary occlusion was studied with both hyaluronidase and propranolol, agents that had been shown previously to diminish the depression of CPK activity following coronary occlusion. First, our earlier observations demonstrating the relationship between the epicardial ST segment 15 minutes following coronary occlusion and the CPK activity and histologic appearance in the subjacent myocardium 24 hours later were verified in this study. Second, the changes in the Q and R waves, reflecting the development of necrosis, were attenuated at all time intervals following occlusion in the treated dogs. Although the magnitude of the changes in the QRS complex and CPK activity were less in the treated groups than in the control group, the relationship between these two indices of cardiac damage was similar, confirming the validity of the use of changes in the QRS complex to reflect the development of necrosis. It should be emphasized that hyaluronidase and propranolol did not reduce already existing alterations in the epicardial QRS complex; rather, these agents prevented their appearance, since these alterations reflect an irreversible phase of injury.

The two interventions employed in this study — hyaluronidase and propranolol — almost certainly exert their salutary effects on injured myocardium by different mechanisms. Although the exact mechanism of action of hyaluronidase has not been determined, it is believed that this agent may act by decreasing edema formation, thereby preserving flow to the ischemic tissue. It has been shown recently that blood flow to the ischemic area is better preserved in an animal treated with hyaluronidase than in a control. On the other hand, propranolol apparently benefits the ischemic myocardium by improving the balance between oxygen supply and demand through a decrease in myocardial oxygen consumption and not through an improvement in collateral flow. Irrespective of the intervention employed or its mechanism of action, the changes in the epicardial QRS complex reliably predict the extent of necrosis as determined by biochemical and histologic criteria.

Acknowledgment

The authors wish to acknowledge the technical assistance of Mr. Daniel White, Mr. Denis Hourihan, Mr. Joseph Gannon and Ms. Sharon Hale, as well as the secretarial help of Ms. Merriee Spence.

References

pharmacologic and hemodynamic interventions. Am J Cardiol 29: 223, 1972
31. Wilson FN, MacLeod AG, Barker PS, Johnston RD, Klostermeyer LL: The electrocardiogram in myocardial infarction with particular reference to the initial deflections of the ventricular complex Heart 16: 155, 1973
Use of changes in the epicardial QRS complex to assess interventions which modify the extent of myocardial necrosis following coronary artery occlusion.
L D Hillis, J Askenazi, E Braunwald, P Radvany, J E Muller, M C Fishbein and P R Maroko

Circulation. 1976;54:591-598
doi: 10.1161/01.CIR.54.4.591
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1976 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/54/4/591

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/