LABORATORY INVESTIGATION

MYOCARDIAL ISCHEMIA

Effect of graded coronary flow reduction on ionic, electrical, and mechanical indexes of ischemia in the pig

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ABSTRACT This study was performed to determine the relative sensitivities of ionic, electrical, and mechanical indexes of myocardial ischemia. We used ion-selective and bipolar plunge electrodes, epicardial unipolar electrodes, a suction electrode, and ultrasonic crystals to determine the changes in intramyocardial extracellular potassium ([K⁺]ₑ) and extracellular pH (pHₑ), local activation, epicardial TQ-ST segment, monophasic action potential duration (MAPD), and regional contractility during graded coronary flow reduction in open-chest pigs. A carotid-to-coronary shunt was created to perfuse the left anterior descending coronary artery via a roller pump. The shunted coronary flow was reduced in a stepwise fashion at 5-min intervals. In 25 pigs, the approximate myocardial flow associated with the initial changes in each variable was as follows: midmyocardial [K⁺]ₑ, pHₑ, and TQ-ST segment, 0.7 to 0.8 ml/min/g; subepicardial [K⁺]ₑ and TQ-ST segment, 0.6 to 0.7 ml/min/g; segmental shortening, 0.5 to 0.6 ml/min/g; local activation and epicardial TQ-ST segment, 0.3 to 0.4 ml/min/g; epicardial MAPD, 0.15 to 0.2 ml/min/g. Our results indicate that changes in [K⁺]ₑ, pHₑ, and TQ-ST segment provide the most sensitive means of detecting myocardial ischemia and of determining the effect of interventions capable of influencing the ischemic process.


ACUTE MYOCARDIAL ISCHEMIA includes a variety of ionic, electrical, and mechanical alterations. These include (1) a decrease in energy-rich substrates, (2) a rise in extracellular potassium, (3) a fall in extracellular and intracellular pH, (4) a decrease in resting membrane potential and a shortening of action potential duration, (5) a slowing of conduction, (6) a deviation of TQ-ST segment, and (7) a decrease in the rate and magnitude of muscle fiber shortening. The endocardium is more sensitive than the epicardium to the effects of a decrease in coronary blood flow. This effect has been attributed to two factors: (1) greater metabolic activity in the subendocardium and (2) transmyocardial redistribution of nutrient blood flow favoring the epicardium. In the pig, such redistribution occurs with partial, but not with complete, reduction of blood flow. Thus it is reasonable to expect that the progressive reduction in coronary flow will cause changes in deeper levels of the myocardium to occur before changes in the epicardium. Although this concept is supported by the results of studies exploring the effects of a partial reduction in flow, most of the studies used large reductions in flow, which precluded the precise determination of the flow at which the variable of interest first changed.

This study was performed to determine the relative sensitivities of changes in extracellular myocardial potassium ([K⁺]ₑ), extracellular pH (pHₑ), local activation, intramural and epicardial TQ and ST segments, monophasic action potential duration (MAPD), and myocardial fiber shortening to graded reductions of flow in the left anterior descending coronary artery (LAD) in the pig and the precise flow at which these changes first occurred. We chose the pig as our experimental model because of its low collateral flow in the coronary circulation.

Methods

Experimental procedures. Twenty-five domestic pigs weighing 22 to 34 kg were immobilized with ketamine (10
mg/kg) and anesthetized with thiamylal sodium (25 mg/kg). Anesthesia was maintained with α-chloralose (30 to 50 mg/kg) as needed. The animals were ventilated through an endotracheal tube by a Harvard respirator with a mixture of air and oxygen to maintain arterial oxygen saturation greater than 95%, carbon dioxide tension at 35 to 45 mm Hg, and pH at 7.35 to 7.45. A catheter was placed in the descending aorta for monitoring of arterial blood pressure and sampling for blood gas determinations and in the femoral vein for intravenous infusions of saline and anesthetics.

After midsternal thoracotomy, the heart was suspended in the pericardium and the right atrium was paced to maintain a constant rate that was slightly faster than the spontaneous rate, ranging from 1.5 to 2.0 Hz. A tapered Teflon catheter was inserted into the LAD below the first diagonal branch and connected to a catheter placed in the right carotid artery. This carotid coronary shunt was routed through a constant-flow roller pump (Cole Palmer), which permitted the controlled reduction in flow from a control value of 1.2 to 1.5 ml/kg body weight/min (30 to 50 ml/min) to zero. Heparin (initial 3000 U bolus followed by 7000 U/hr) was administered to ensure cannula patency. Epicardial temperature was monitored by a Yellow Springs temperature probe sutured to the left ventricular epicardium and was maintained at 35° to 38°C by using a heating pad and covering the thoracotomy incision with a polyethylene sheet.

Preparation and placement of electrodes and crystals. Miniature K+-sensitive and H+-sensitive electrodes were fashioned and calibrated by the method described previously from our laboratory.6 In 17 experiments, six K+ and six H+ sensitive electrodes were placed in the midmyocardium (i.e., at 4 to 6 mm below the epicardial surface) at various locations within the ischemic zone. The precise positions of the electrodes were determined after each experiment by careful dissection of the electrode from the muscle. In nine of the 17 experiments (group A), bipolar electrograms, a monophasic action potential, and an epicardial unipolar electrogram were also recorded from the center of the ischemic zone. The bipolar electrograms were recorded by five Teflon-coated stainless-steel bipolar electrodes and filtered between 50 and 500 Hz. One electrode was placed in the nonischemic zone and four in the ischemic zone, each within 5 mm of a K+-sensitive electrode. Epicardial monophasic action potential (MAP) recordings were obtained by a suction electrode39 placed on the center of the ischemic zone 5 min before reduction of coronary flow. The epicardial unipolar electrogram was recorded by connecting the reference barrel of the suction electrode to the positive input of the direct current–coupled amplifier. The reference electrode was placed in the neck.

In eight of the 17 experiments (group B), myocardial segment length was recorded in addition to the changes in midmyocardial [K+]i and pHi. In these experiments, two pairs of ultrasonic crystals, 8 to 15 mm apart, were placed 6 ± 2 mm below the epicardial surface of the left ventricular wall. One pair was placed in the nonischemic area and the second was placed in the center of the ischemic zone.

In eight additional experiments (group C), we recorded the changes in [K+]i and unipolar electrograms from four K+-sensitive electrodes placed in the midmyocardium (4 to 6 mm from the epicardium) and four K+-sensitive electrodes placed in the subepicardium (1 to 2 mm from the epicardium). The unipolar electrograms were recorded from the reference barrel of the K+-sensitive electrodes. In addition, three epicardial unipolar electrodes were placed on the epicardium in the center of the ischemic zone. The reference electrode for all unipolar electrograms was located in the neck.

Experimental protocol. The preparation was allowed to stabilize for at least 60 min after placement of the various electrodes. Coronary blood flow through the roller pump then was reduced in a stepwise fashion at 5 min intervals as follows: 50, 40, 30, 20, 15, 10, 5, 2.5, and 0 ml/min, followed by return to control flow. In 15 experiments, mononuclear (1 ml/kg body weight) was injected intravenously, with the shunt flow stopped, 15 sec before the animal was killed. The unstained tissue perfused by the shunt blood was dissected and weighed to determine the mass of tissue supplied by the shunt.

Data recording and analysis. Hemodynamic data, myocardial shortening, and the amplified signals from six of the ion-selective electrodes were continuously recorded on a 12-channel Graphite Linear recorder. Bipolar electrograms, MAP, and unipolar electrograms were continuously displayed with a lead II ECG on a Honeywell 1858 Visicorder and recorded at the end of each level of coronary flow on paper moving at speeds of 200 and 400 mm/sec.

The amplified signals from all ion-sensitive electrodes were sampled at 30 sec intervals by a DEC PDP-11/03 minicomputer at a rate of 150 samples/sec. Millivolt readings during the TQ segment were converted to changes in local K+ and H+ activity by means of the Nernst equation and epicardial temperature as previously described.6 Absolute values of myocardial K+ activity and pH were determined by relating the measured changes in these variables to the value of arterial [K+]i and pH obtained just prior to coronary flow reduction. Changes in pH were referenced to arterial pH because interstitial pH and arterial pH have been shown to differ only minimally despite differences in PCO2.40 The K+ activity was converted to [K+]i by an activity coefficient of 0.746.40 The integrity of the electrode in vivo was determined before and after coronary flow reduction by the rapid injection of a solution containing 3 mg KCl and by a 60 sec period of respiratory acidosis. Data were accepted only from electrodes that demonstrated reproducible responses to each bolus of KCl or to each period of acidosis and that maintained a stable baseline throughout the study. In each experiment, the number of functioning K+-sensitive electrodes varied from three to five and that of H+-sensitive electrodes varied from two to four.

Local activation time was measured from the onset of the QRS complex in the ECG to the peak of the intrinsic deflection in each local electrogram. The millivolt difference between the T-Q potential and the S-T potential measured 100 msec after the peak of the R wave of the unipolar electrogram was taken as the TQ-ST segment deviation (ΔTQ-ST). The [K+]i, pH, local activation, and TQ-ST segment data from the electrode showing earliest changes were used to determine the threshold flow in that variable. The criteria for acceptance of the MAP and the method of measuring MAPD were as described by Autenrieth et al.39 End-diastolic length (EDL) and end-systolic length (ESL) were measured according to the method of Theroux et al.,22 and percent shortening was calculated as (EDL - ESL) × 100/EDL. Percent shortening was then normalized to the fraction of the control (%ΔL) period. Our criteria for threshold changes in the indexes were (1) an increase in [K+]i greater than 0.3 mM, (2) a decrease in pH greater than 0.03, (3) a prolongation of local activation time of more than 2 msec, (4) a change in TQ-ST segment greater than 1 mV, (5) a shortening of the MAPD of more than 15 msec, and (6) a decrease in relative myocardial fiber shortening greater than 10%.

Statistics. We calculated mean ± SE and tested the significance of difference by the Student’s t test for paired and unpaired data. Differences were considered significant when p < .05.

Results

A total of 25 experiments, nine in group A, eight in group B, and eight in group C, were performed. The
mean value of arterial $[K^+]_e$, arterial pH$_e$, heart rate, and mean arterial pressure were similar in the three groups (table 1). The threshold flows for the change in midmyocardial $[K^+]_e$ and pH$_e$ determined from the 17 experiments in groups A and B in which they were measured simultaneously were similar and averaged 16.4 ± 0.7 ml/min (figure 1). In this representative experiment, $[K^+]_e$ recorded in the midmyocardium began to rise, and pH$_e$ recorded from the same location began to fall 3 min after decreasing flow through the carotid-coronary shunt to 20 ml/min. Each decrement of flow thereafter resulted in a further increase in $[K^+]_e$ and a decrease in pH$_e$. These values tended to plateau by the end of the fourth minute at each flow step.

The threshold flow for changes in subepicardial $[K^+]_e$ (within 2 mm of the epicardial surface) was lower than the threshold flow for changes in the midmyocardial $[K^+]_e$ (more than 4 mm below the epicardial surface). Figure 2 shows the results of a representative experiment from group C in which this comparison was made and shows that the threshold flow for the change in midmyocardial $[K^+]_e$ was 20 ml/min, and the threshold for change in subepicardial $[K^+]_e$ was 15 ml/min. The figure also shows that at each level of flow below 15 ml/min, midmyocardial $[K^+]_e$ is greater than subepicardial $[K^+]_e$.

At each myocardial level, the threshold flow for changes in the TQ-ST segment of the locally recorded unipolar electrogram was the same as the threshold flow for changes in $[K^+]_e$ at that level. Figure 3 shows the unipolar electrograms from the experiment illustrated in figure 2. The first change in midmyocardial TQ-ST segment occurred at a flow rate of 20 ml/min, and the first change in subepicardial TQ-ST segment occurred at a flow rate of 15 ml/min. These are the same flows at which the changes in $[K^+]_e$ occurred. Changes in the TQ-ST segment of the electrogram recorded on the epicardial surface did not occur until the flow was reduced to 10 ml/min. The results from the eight experiments in which these comparisons were made are shown in figure 4. The mean threshold flow for changes in midmyocardial $[K^+]_e$ was 18.8 ± 0.8 ml/min, and that for changes in TQ-ST segment was

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### TABLE 1

Mean values (± SE) of heart rate, mean arterial pressure, arterial $[K^+]_e$, and arterial pH$_e$.

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>MAP (mm Hg)</th>
<th>$[K^+]_e$ (mM)</th>
<th>pH$_e$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>131 ± 5</td>
<td>94 ± 5</td>
<td>4.1 ± 0.1</td>
<td>7.38 ± 0.01</td>
</tr>
<tr>
<td>Group B</td>
<td>123 ± 5</td>
<td>90 ± 6</td>
<td>4.0 ± 0.1</td>
<td>7.40 ± 0.01</td>
</tr>
<tr>
<td>Group C</td>
<td>131 ± 6</td>
<td>92 ± 7</td>
<td>4.1 ± 0.2</td>
<td>7.40 ± 0.01</td>
</tr>
</tbody>
</table>

n = 9 in group A, 8 in group B, and 8 in group C. There are no statistically significant differences (by Student's unpaired t test) among the groups.

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FIGURE 1. Midmyocardial $[K^+]_e$ and pH$_e$ recorded from the center of the ischemic zone. The interval between each reduction of coronary flow, displayed on the horizontal axis, represents 5 min. The return to 40 ml/min was maintained for 17 minutes. Note that the changes in $[K^+]_e$ and pH$_e$ occur simultaneously 3 min after reducing coronary flow to 20 ml/min.

FIGURE 2. Midmyocardial (Mid) and subepicardial (Subepi) changes in $[K^+]_e$. As in figure 1, the interval between each reduction in coronary flow displayed on the horizontal axis represents 5 min. Note that midmyocardial $[K^+]_e$ begins to rise when coronary flow is reduced to 20 ml/min, whereas a rise in subepicardial $[K^+]_e$ requires a reduction in coronary flow to 15 ml/min.
FIGURE 3. Local unipolar electrograms recorded from the midmyocardium, subepicardium, and epicardium in the same experiment shown in figure 2. The midmyocardial and subepicardial recordings were obtained from the reference pole of the [K+]e electrode. Note that T-Q depression occurs in the midmyocardium and subepicardium at the same flows associated with the first rise in [K+]e, shown in figure 2 (20 and 15 ml/min, respectively). These changes occur in the absence of any changes in the epicardial electrogram, which does not change until coronary flow is reduced to 10 ml/min.

16.9 ± 1.3 ml/min. This difference was not statistically significant. The threshold flow for the changes in subepicardial [K+]e and TQ-ST segment averaged 14.4 ± 1.1 and 13.8 ± 1.8 ml/min, respectively. These values were significantly less than the threshold flows in the midmyocardium. The threshold flow for changes in the TQ-ST segment on the epicardial surface was 8.4 ± 1.4 ml/min. This flow was significantly less than the threshold flow for changes recorded in the subepicardium.

Changes in midmyocardial [K+]e and pH_e occurred before changes in relative myocardial segment length. Figure 5 shows the averaged results from the eight experiments in which these relationships were compared. The threshold flow for changes in midmyocardial [K+]e and pH_e was 17.1 ± 1.0 ml/min, whereas the first change in relative segment length required a decrease in flow to 12.1 ± 1.0 ml/min. This difference was statistically significant at the p < .01 level.

The changes in midmyocardial [K+]e and pH_e also occurred before prolongation of activation and before shortening of the epicardial MAP. Figure 6 shows the averaged results from the nine experiments in which these relationships were compared. The threshold flow for changes in midmyocardial [K+]e was 15.9 ± 0.9 ml/min, and that in midmyocardial pH_e was 15.9 ± 1.3 ml/min. The threshold flow for changes in activation was 7.3 ± 0.8 ml/min. Shortening of the epicardial

FIGURE 4. Mean ± SE of the threshold flow for changes in midmyocardial and subepicardial [K+]e and TQ-ST segment and in epicardial TQ-ST segment. These data were obtained from the group C animals, in which these variables were measured simultaneously.

FIGURE 5. Mean ± SE of the threshold flow for changes in midmyocardial [K+]e, pH_e, and segment length (%ΔL). These data were obtained from the group B animals, in which these variables were measured simultaneously.
MAP required a further reduction in flow, occurring at 3.8 ± 0.4 ml/min. The threshold flow for changes in the TQ-ST potential recorded on the epicardium in this series of experiments was 7.5 ± 0.8 ml/min. This value is not statistically different from the threshold flow of 8.4 ± 1.4 ml/min recorded in the group C experiments shown in figure 5.

We determined the mass of tissue perfused by the carotid-coronary shunt in 15 of the 25 experiments. In these experiments, the perfused tissues averaged 22.3 ± 0.9 g. The weight of the 10 animals in which muscle mass was not determined was the same as the weight of the 15 animals in which the perfused muscle mass was determined (31.4 ± 1.2 kg vs 29.8 ± 1.4 kg; p = NS) and the carotid-coronary shunt was inserted at the same location in each experiment. Therefore we assumed that the mass of perfused tissue was the same through all experiments. Applying this assumption, we then determined the threshold flow (expressed as ml/min/g ventricular muscle) for the variables measured in the three series of experiments. These results are shown in figure 7. The threshold flow ranged from 0.77 ml/min/g tissue for the initial changes in midmyocardial [K+]e, pH, and TQ-ST segments, to 0.55 ml/min/g tissue for segment length shortening, and on to 0.17 ml/min/g tissue for the initial shortening of the MAP recorded on the epicardial surface in the center of the zone supplied by the carotid-coronary shunt.

Discussion

The purpose of our experiments was to determine the relative sensitivities of the ionic, electrical, and contractile markers of ischemia by reducing coronary flow in a series of graded steps. The previous studies, summarized in table 2, used a variety of techniques for reducing coronary flow and usually measured only two of the three variables referred to above. They did not determine the flow at which these changes first occurred. The new information provided by our study is the comparison of the precise flow at which the first change occurs in ionic, electrical, and mechanical variables in the same preparation under the same set of experimental conditions. We have accomplished this by shunting blood from the carotid artery through a roller pump to the LAD and by reducing coronary blood flow in a series of predetermined steps. We have labeled the coronary flow associated with the first change in each variable as the ischemic threshold for that variable.

Our study indicates that changes in midmyocardial [K+]e, pH, and TQ-ST segments are coupled and precede a decrease in contractility, prolongation of activation, or shortening of the epicardial MAP. The measured changes in [K+]e and pH represent the balance between K+ or H+ efflux from the cells and their washout from the extracellular space. However, our data do not permit analysis of the precise contributions of these two factors to the ionic changes in the extracellular space we have recorded. Myocardial blood flow in the pig and the dog has been shown to be in the range of 1.0 to 1.5 ml/min/g.28,38 The threshold flow for changes in midmyocardial [K+]e, pH, and TQ-ST potential which we observed was approximately 0.8 ml/min/g. This is consistent with other data showing that changes in midmyocardial pH and PCO2 occur when coronary flow is reduced by 20% to 25%, i.e., between 0.75 and 1.2 ml/min/g.10,20,21

It has been shown that changes in the TQ-ST potential occur simultaneously with changes in PCO2.20,21 Ischemia-induced changes in the TQ-ST potential are caused by changes in resting membrane potential that are thought to be caused primarily,
TABLE 2
Relative sensitivities of various indexes of myocardial ischemia in the setting of low-flow ischemia

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Coronary flow reduction steps</th>
<th>Ionic</th>
<th>Electrical</th>
<th>Metabolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maekawa et al. 21</td>
<td>8</td>
<td></td>
<td>Local TQ-ST</td>
<td>Pmo₂</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pmco₂</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[K+]e</td>
<td>Lead II ECG</td>
<td>Lactate (cs)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PO₄</td>
</tr>
<tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pm₀₂</td>
</tr>
<tr>
<td>Case et al. 48</td>
<td>6–8</td>
<td>[K+]e</td>
<td>Local TQ-ST</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>Khuri et al. 20</td>
<td>5</td>
<td></td>
<td>Local TQ-ST</td>
<td></td>
</tr>
<tr>
<td>Hoper et al. 32</td>
<td>1</td>
<td>[K+]e</td>
<td>Local TQ-ST</td>
<td></td>
</tr>
<tr>
<td>Smith et al. 35</td>
<td>3</td>
<td></td>
<td>Local TQ-ST</td>
<td></td>
</tr>
<tr>
<td>Battler et al. 36</td>
<td>3</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Mori et al. 37</td>
<td>4</td>
<td></td>
<td>ATP</td>
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<td>Yamaguchi et al. 33</td>
<td>3</td>
<td>Local activation</td>
<td>McFee VCG</td>
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</table>

CS = coronary sinus; Pm₀₂ = intramyocardial oxygen; Pmco₂ = intramyocardial carbon dioxide; PO₄ = inorganic phosphate.

Although perhaps not entirely, by the increase in [K+]e, 40–42 our study provides the link between these results by showing that the changes in [K+]e, pHₑ, and TQ-ST potentials recorded at the same location occur simultaneously.

The threshold flow for changes in [K+]e and TQ-ST segments was greater in the midmyocardium than in subepicardium as anticipated by the transmural redistribution of flow that occurs in the pig during the partial reduction of coronary flow. 28 The difference in [K+]e in these myocardial regions became progressively greater as coronary flow was decreased (see figure 2). These results indicate that significant transmural gradients in [K+]e and the associated electrical changes exist during low-flow as well as no-flow ischemia. 3, 43 Several other groups have reported that changes in the TQ-ST segment at endocardial and midmyocardial electrograms occur at higher flows than such changes in the epicardial electrogram. 3, 20, 21 Maekawa et al. 21 reported that changes in endocardial TQ-ST segment first occurred when coronary flow was reduced by 20% from the control flow of 1.2 to 1.4 ml/min/g, that changes in midmyocardial TQ-ST segment occurred when coronary flow was reduced by approximately 40%, and that epicardial TQ-ST segment changes did not occur until coronary flow was reduced by more than 60%, i.e., the flow reduction associated with a 90% constriction of the coronary artery. Our results are consistent with these reports and can be attributed to the transmyocardial distribution of nutrient flow that occurs when coronary flow is reduced. 28 Although midmyocardial [K+]e and TQ-ST segment changes were noted to occur when coronary flow was approximately 0.8 ml/min/g, changes in subepicardial [K+]e and TQ-ST segments occurred at flows of 0.6 ml/min/g and changes in the epicardial TQ-ST segment did not occur until coronary flow was reduced to approximately 0.35 ml/min/g. At this flow rate, we noted that midmyocardial [K+]e had approximately doubled, reaching levels in excess of 6 mM, and that as much as a 6 mV change in the TQ-ST segment occurred in the midmyocardial electrogram.

Holland and Brooks 44 have emphasized that the TQ-ST segment deflection on the body surface or epicardial electrogram recorded during ischemia is influenced by a variety of spatial and nonspatial factors. These included the location of the electrodes, the area, location, and shape of the ischemic zone, the magnitude of the transmembrane voltage differences between ischemic and nonischemic areas, and the solid angle subtended by the recording electrodes and the lateral margins of the ischemic zone. In our experiments, the absence of TQ depression (or ST elevation) on the epicardial surface at a time when a significant TQ depression or ST elevation occurs at deeper layers might be attributed to an epicardial layer of nonischemic tissues. However, it is more difficult to explain the absence of any change in the TQ-ST segment on the epicardial surface when significant TQ and ST segment shifts are occurring in the midmyocardium and subepicardium. It is possible that a border zone similar to that recently reported to exist between the subendocardium and endocardium during no-flow ischemia 45 might cause voltage gradients opposite in direction to
those existing between the epicardium and the subepicardium. It is also possible that inhomogeneities in $[K^+]_e$ at the same level of myocardium in the center of the ischemic zone similar to those reported during no-flow ischemia$^3, 43$ might produce voltage gradients that will oppose the gradients between the normal epicardium and deeper ischemic levels. Whether such a subendocardial border zone or inhomogeneities exist during low-flow ischemia remains to be shown. Further studies are required to address these and other possible explanations. Nonetheless, the recognition that ischemic changes can extend to the subepicardium without causing TQ-ST segment changes on the epicardial surface has important clinical implications.

We found that changes in midmyocardial $[K^+]_e$ and $pH_e$ occur at significantly greater flows than the decrease in contractility. This result differs from that of Hoper et al.$^32$ and Battler et al.$^36$ who reported that changes in contractility preceded or occurred simultaneously with changes in ionic or electrical variables. However, Hoper et al.$^32$ compared midmyocardial contractile changes to changes in epicardial $[K^+]_e$, whereas Battler et al.$^36$ reduced coronary flow to achieve a predetermined change in wall thickness. Thus they did not evaluate the threshold flow for either the change in contractility or the change in TQ-ST segments. Our results are more consistent with those of Smith et al.$^35$. They observed that endocardial ST segment changes were more sensitive than changes in wall motion, whereas epicardial TQ-ST segment changes were less sensitive. Since the changes in TQ-ST segment have been shown to correlate with changes in $[K^+]_e$ and $PCO_2$, it is reasonable to assume that the subendocardial TQ-ST changes observed by Smith et al.$^35$ were associated with changes in subendocardial $[K^+]_e$.

The relationship between changes in extracellular K$^+$ and myocardial activation has been studied by others. Morena et al.$^36$ showed that an increase in $[K^+]_e$ to 10 mM in the absence of a change in pH, $Po_2$, or glucose did not alter activation in the isolated, perfused pig heart, whereas the simultaneous lowering of pH and $Po_2$ caused changes in activation similar to those induced by coronary ligation. However, these investigators did not study the effects of lower concentrations of potassium in the presence of a reduced $pH_e$ or $Po_2$. Kagiyma et al.$^47$ have shown that at all levels of $[K^+]_e$ lowering pH slowed conduction. Thus, it is likely that in the setting of low pH and $Po_2$, $[K^+]_e$ levels below 10 mM might have caused activation slowing. Kleber et al.$^18$ studied the effects of a progressive increase in $[K^+]_e$ on conduction and reported that slowing of conduction in the longitudinal direction did not occur until $[K^+]_e$ was raised above 8 mM. However, again, neither $pH_e$ nor $Po_2$ were altered.

In our study, prolongation of activation occurred when midmyocardial $[K^+]_e$ was 6.9 ± 0.4 and $pH_e$ was 7.20 ± 0.03. These values were associated with a decrease in coronary flow to 0.3 to 0.4 ml/min/g. This value is consistent with the results of others who reported that the changes in activation require a 50% to 75% reduction of flow.$^{29, 30, 33, 36}$ In our earlier studies of no-flow ischemia,$^3, 6, 41$ significant activation delay occurred when midmyocardial $[K^+]_e$ levels were less than 5.0 mM. We postulated$^42$ that the inhomogeneity of the $[K^+]_e$ changes, the rate of the $[K^+]_e$ changes, and changes in cellular coupling induced by simultaneous changes in $pH_e$ and $Po_2$ might be responsible for these early changes in activation. The results of the present study suggest that those early changes in activation are dependent on the rapidly occurring changes associated with no-flow ischemia and do not occur with the more gradual changes that characterize low-flow ischemia.

Shortening of the MAP recorded from the epicardial surface was the least sensitive of the various markers of ischemia evaluated in this study. A reduction of coronary flow to less than 0.2 ml/min/g was required to shorten the MAPD by 15 msec.

In summary, our results have shown that the spread of ischemia from subendocardium to epicardium, and the onset of ischemia at any level, is monitored most sensitively by the changes in $[K^+]_e$, $pH_e$, and the TQ-ST segment of the locally recorded electrogram. Changes in these variables at the midmyocardial level occur before changes in relative midmyocardial segment length or activation time and before changes in the TQ-ST segments of the epicardial electrogram or in MAPD recorded on the epicardial surface. The sensitivity of the change in $[K^+]_e$ and $pH_e$ to subtle reductions in coronary flow suggests that these variables may provide a sensitive means of detecting the effects of physiologic and pharmacologic interventions believed to influence the ischemic process.

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