Effect of serial brief ischemic episodes on extracellular K⁺, pH, and activation in the pig

WILLIAM F. FLEET, TIMOTHY A. JOHNSON, CHRIS A. GRAEBNER, AND LEONARD S. GETTES

ABSTRACT This study was performed to determine the reproducibility of the ionic and electrical changes associated with serial ischemic episodes. We used ion-selective and bipolar plunge electrodes to determine the changes in left ventricular extracellular potassium ([K⁺]e), extracellular pH (pHe), and local activation during sequential 10 min occlusions of the left anterior descending coronary artery separated by 50 min of reperfusion in open-chest anesthetized pigs. We found that uniformly during the initial occlusion, and in approximately 50% of animals during the second occlusion, [K⁺]e rose more rapidly but to a lower level than in subsequent occlusions. By the third occlusion the changes in [K⁺]e were reproducible. Extracellular acidosis was greatest in the first occlusion and decreased progressively with each subsequent occlusion. Local activation was characterized by a decrease in spontaneous improvement and increase in block with each successive occlusion. The occurrence of ventricular fibrillation could not be directly attributed to the magnitude of the change in [K⁺]e or pHe. Moreover, the occurrence of ventricular fibrillation in one occlusion did not necessarily predict its occurrence thereafter. Our results indicate that serial episodes of ischemia are associated with different but predictable changes in ionic and electrical events that may be clinically relevant and that must be appreciated before the results from similar protocols with serial ischemic episodes can be interpreted meaningfully.

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ACUTE MYOCARDIAL ISCHEMIA causes a rapid depletion of energy-rich substrates,13 a rise in the extracellular concentration of K⁺ ([K⁺]e),49 a fall in extracellular and intracellular pH,10-13 and slowing of conduction through the ischemic area.15-17 Acute coronary occlusion of more than 20 min duration causes irreversible cellular injury.19 Shorter periods of ischemia cause ionic and electrical changes that are rapidly reversed by reperfusion,6 although mechanical20-22 and metabolic23,24 changes may persist for long periods after reperfusion.

If the ionic and electrical changes induced by brief episodes of ischemia were reproducible or predictable as well as reversible, they could then be used to study the effects of interventions designed to influence the ischemic process. Prior work from our laboratory6 and from the laboratories of others7,8 suggests that the rise in [K⁺]e induced by serial 10 min occlusions may be reproducible. However, these studies were not designed to address this issue specifically and did not measure the associated changes in pH or electrical activity. Changes in myocardial blood flow, ventricular activation, electrocardiographic waveform, and arrhythmias are reproducible when two 5 min periods of ischemia are separated by 40 min of reperfusion25 but are not reproducible when the occlusions are separated by only 3 min. Occlusions greater than 5 min in duration have not been studied in this manner. Moreover, no studies have tested the reproducibility of the changes in extracellular pH (pHe) during serial brief episodes of ischemia, nor has the reproducibility of the electrical and ionic changes been studied concomitantly.

We have studied the simultaneous changes in myocardial [K⁺]e, pHe, and local activation, as well as the incidence of ventricular fibrillation, during serial 10 min occlusions of the left anterior descending coronary artery (LAD) in open-chest swine. Our results provide a basis for the interpretation of experiments that use serial ischemic episodes to test the effects of physiologic and pharmacologic interventions and may apply to clinically occurring repetitive episodes of myocardial ischemia in man.
Methods

Electrodes. Miniature K⁺-sensitive plunge electrodes, modified from designs described earlier, were fashioned from Teflon-coated silver wire 0.005 inch in diameter. The cut end of each wire was chloridized in sodium hypochlorite (NaOCl), covered with a mixture of cellulose acetate and titanium dioxide, soaked in 3 mM KCl solution, and covered with a polyvinyl chloride–based membrane containing the K⁺ ionophore valinomycin. The pH-sensitive electrodes were constructed in an analogous manner with the H⁺ ionophore p-octadecyloxy mchlorophenylhydrazone. The response characteristics and time constants of these electrodes in vitro and in vivo were similar to those of previously described design. Reference electrodes, similarly constructed, lacked only an ion-selective membrane. A K⁺-sensitive, pH-sensitive, and common reference electrode were placed into a 20 gauge short-beval needle for insertion into the midmyocardium. Each electrode was bent back on itself just beyond the tip so that the needle could be withdrawn, leaving the electrode embedded in the myocardial tissue. The K⁺–sensitive electrodes were calibrated in solutions of 3, 10, and 20 mM KCl before and again after each experiment, and the pH-sensitive electrodes were calibrated in solutions of pH 6 and 8. Data were accepted only from those electrodes that demonstrated a 57 to 61 mV shift per decade change in K⁺ or H⁺ activity both before and after each experiment.

Millivolt readings from the K⁺- and pH-sensitive electrodes were amplified by a high-impedance instrumentation amplifier and serially connected to a low pass filter (1 kHz). The amplified signals from all ion-selective electrodes were sampled every 15 sec by a DEC PDP-11/03 minicomputer during the S-T segment of the cardiac cycle, thus avoiding interference from the electrocardiographic signal. Epicardial temperature was monitored with a Yellow Springs temperature probe sutured onto the left ventricular epicardium. Millivolt readings from ion-selective electrodes were converted to changes in local K⁺ and H⁺ activity with the Nernst equation and epicardial temperature. Absolute values of myocardial K⁺ activity and pH were determined by relating the measured changes in these variables to the values of arterial [K⁺] and pH obtained just before each occlusion. 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. The results are expressed as millimolar K⁺ concentration ([K⁺]), calculated from K⁺ activity with an activity coefficient of 0.746.

Local midmyocardial bipolar ventricular electrograms were recorded by Teflon-coated stainless steel bipolar plunge electrodes. One electrode was placed in the nonischemic area, one or two electrodes were placed along the lateral margin, and two or three electrodes were placed in the center of the ischemic zone. These bipolar electrograms were filtered between 50 and 500 Hz and continuously displayed with a lead I electrocardiogram on the oscilloscope of a Honeywell visicorder. Recordings were made every minute during occlusions at paper speeds of 200 and 400 mm/sec. Local activation was determined from the onset of the QRS complex in the electrocardiogram to the peak of the high-frequency deflection in each local electrogram. Activation delay was determined by subtracting the starting activation time from the activation time at each minute of ischemia. Activation block was said to occur when no high-frequency deflection was discernible.

Experimental protocol. Domestic pigs of either sex weighing 20 to 25 kg were immobilized with ketamine (10 mg/kg) and anesthetized with thiamylal sodium (25 mg/kg). Anesthesia was then maintained with α-chloralose in polyethylene glycol (mol wt = 400) as needed in doses ranging from 30 to 50 mg/kg/hr. No anesthetic was given within 20 min of an occlusion. The animals were ventilated through an endotracheal tube on a positive-pressure respirator (Harvard Apparatus) with a minute volume and oxygen mixture sufficient to maintain arterial oxygen saturation greater than 95%, arterial PCO₂ at 35 to 45 mm Hg, and arterial pH at 7.35 to 7.45. A femoral venous catheter was used to infuse drugs and 0.9% saline solution. Systemic arterial pressure was measured by a Millar pressure transducer placed in the descending aorta via the femoral artery. Arterial blood samples were obtained before each occlusion for determination of pH, PCO₂, and Po₂ and for the independent determination of serum [K⁺].

After a midsternal thoracotomy, the LAD was dissected distal to the second diagonal branch, and a polyethylene snare was placed around the LAD. Two methods were used to position as many as nine electrode groups along the lateral border and in the center of the ischemic zone (figure 1). In six animals the artery was occluded for 30 sec to demarcate the border of the ischemic zone (group A). During this period, one or two electrodes were placed along the lateral margin. The snare was then released, and the remaining electrodes were inserted. In nine animals (group B) the artery was occluded for 10 min, during which all electrodes were inserted. The integrity of K⁺ and pH electrodes

![FIGURE 1. Schematic representation of the different protocols used in this study.](image-url)
in vivo was determined 30 min after placement by the response to a bolus injection of 1.5 meq KCl in 3 ml of normal saline or to 45 sec of respiratory acidosis, respectively. Data were accepted only from electrodes that responded promptly to each KCl bolus or period of acidosis.

A series of five or six occlusions of the LAD was initiated 50 min after placement of the electrodes (see figure 1). Each occlusion was 10 min in duration, and episodes were separated by 50 min of reperfusion. Right atrial pacing was used to maintain a constant heart rate of 90 beats/min in all experiments in which the spontaneous rate was slower than this, or at the rate of the initial occlusion when the spontaneous rate was faster than 90 beats/min. Release of each occlusion was performed slowly over 30 to 60 sec to reduce the incidence of reperfusion arrhythmias. Animals that fibrillated were quickly defibrillated by 10 to 20 W-sec applied directly to the heart. Integrity of electrodes was retested after defibrillation by a second KCl bolus and period of respiratory acidosis. After termination of each experiment, either by spontaneous ventricular fibrillation or by the injection of a large KCl bolus, the hearts were removed and the electrodes were dissected free of myocardial tissue for recalibration. All electrodes included in the study were located in the midmyocardium (±3 mm from endocardium and epicardium).

Electrodes were categorized as being in the center of the ischemic zone when they were more than 5 mm from the visible cytanotic border and at the margin of the ischemic zone when they were within 5 mm of the border.29-31 The number of functioning K+-sensitive electrodes in each experiment varied from four to eight, and the number of functioning pH-sensitive electrodes varied from three to six. To minimize the impact of these differences in the number of working electrodes, when mean values were determined, results from all electrodes in a given location (center or margin) from each animal were pooled to compute mean changes in [K+]e and pH, at each location at each minute of ischemia. Thus each experiment was weighted equally. Statistical evaluation was performed with Student’s t test for paired and unpaired data.

The occlusions are identified as C1 to C6. In group A the electrodes were inserted without the benefit of a 10 min occlusion and thus C1 was the first experimental occlusion. In group B the electrodes were inserted during C1 and the experimental occlusions commenced with C2 (figure 1).

Results

A total of 15 animals were studied; six were in group A and nine were in group B. Eight animals completed the series of occlusions without an episode of ventricular fibrillation. Of these, four were in group A and four were in group B. Seven animals had at least one episode of ventricular fibrillation. Two of these were in group A and five were in group B (not statistically significant). [K+]e was measured in all 15 animals; pH, was measured in eight, six in group A (two of which fibrillated) and two in group B (both without ventricular fibrillation). The mean heart rates, starting [K+]e, and starting pH, for each occlusion are shown in table 1. There were no significant differences between occlusions in these variables.

Extracellular K+. Figure 2 shows two representative experiments in which the electrodes were placed 50 min before the first occlusion (group A). For each experiment, the changes in [K+]e recorded by a single K+-selective electrode located in the center of the ischemic zone during successive occlusions are superimposed. In the experiment shown in figure 2, A, [K+]e during C1 rose slightly more rapidly in the early minutes of ischemia than during C2. However, [K+]e during C1 reached a plateau after 5 min of ischemia, whereas in C2 [K+]e continued to rise and attained a higher peak. The [K+]e changes during C2 to C5 were then reproducible. In the experiment shown in figure 2, B, the change in [K+]e was again more rapid during C1 than during C2 and reached a greater peak value in C2. However, unlike the experiment shown in figure 2, A, peak [K+]e was slightly greater in C3 than in C2. The [K+]e change was then reproducible in C3 to C6.

Figure 3 shows two representative experiments in which the electrodes were placed during the first occlusion, C1 (group B). In the experiment shown in figure 3, A, the change in [K+]e during C2 (the first experimental occlusion) predicted the [K+]e changes during subsequent occlusions. In the experiment shown in figure 3, B, the peak [K+]e in C3 was greater than in C2, but thereafter the changes in [K+]e were reproducible. Thus the changes observed in [K+]e during C2 to C5 were similar in groups A and B.

These experiments are representative of the patterns consistently observed in the center of the ischemic zone. The occurrence of ventricular fibrillation during one occlusion did not affect the reproducibility of subsequent occlusions. In all experiments, release of occlusion caused a return of [K+]e to preischemic values within 5 min. The changes in [K+]e during C2 predicted the changes during C3 to C5 in 54% of all experiments. In the remaining 46%, reproducibility of [K+]e

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Mean values (± SEM) of heart rate, [K+]e, and pH, just before the start of each of five sequential occlusions (C1 to C5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C1</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>125 ± 4</td>
</tr>
<tr>
<td>[K+]e (mM)</td>
<td>4.1 ± 0.1</td>
</tr>
<tr>
<td>pH,</td>
<td>7.39 ± 0.03</td>
</tr>
</tbody>
</table>

HR = heart rate.

n = 8 animals. Differences were not statistically significant.
was not attained until C₃. As previously described,⁶ [K⁺]ₑ rose more slowly and to a lower peak value at the margin than in the center. However, the pattern of reproducibility was the same in both regions.

Our results indicate that once two occlusions produce similar changes in [K⁺]ₑ, i.e., C₃ = C₂ or C₄ = C₃, the changes in [K⁺]ₑ during two subsequent occlusions will be similar. This is illustrated in figure 4, which shows the mean value of [K⁺]ₑ at each minute of ischemia during the second of the two matching occlusions (labeled M) and during two subsequent occlusions, M + 1 and M + 2. The changes in [K⁺]ₑ during these three occlusions did not differ significantly either in the center (figure 4, A) or at the margin (figure 4, B).

**Extracellular pH.** Occlusion of the LAD caused a fall in pHₑ from a preischemic value of 7.39 + 0.02, which began within 30 to 45 sec of occlusion and returned to preischemic values within 6 min of release. The fall in pHₑ did not have a plateau phase during C₁. The pattern of change in pHₑ recorded by single electrodes in the center (panel A) and margin (panel B) of the ischemic zone during sequential occlusions differed from that of changes in [K⁺]ₑ. This is illustrated in figure 5, which shows the changes in pHₑ during five sequential occlusions from a single representative experiment in a group A animal. The figure demonstrates that acidosis was greatest during the initial experimental occlusion (C₁ in this instance) and decreased progressively with each occlusion. The progressive decrease in acidosis with successive occlusions was consistently observed in all experiments in both groups A and B. Figure 6 shows the mean value of pHₑ at each minute of ischemia during each of five sequential occlusions. The data in this figure are taken from the four animals in group A that did not fibrillate during any occlusion.

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**FIGURE 2.** [K⁺]ₑ measured by single K⁺-selective electrodes in the center of the ischemic zone during two separate experiments (panels A and B) from group A. In each experiment, [K⁺]ₑ was measured during serial 10 min occlusions of the LAD separated by 50 min of reperfusion.

**FIGURE 3.** [K⁺]ₑ measured by single K⁺-selective electrodes in the center of the ischemic zone during two separate experiments (panels A and B) from group B. In each experiment, [K⁺]ₑ was measured during serial 10 min occlusions of the LAD separated by 50 min of reperfusion.
Although the changes in pH were not reproducible during sequential occlusions, the differences in pH from one occlusion to the next were predictable. Figure 7 shows the mean pH at each minute of ischemia during the second of two occlusions that yielded matching changes in [K⁺] and the two subsequent occlusions (M+1, M+2). Figure 8 shows that the mean differences in pH between M and M+1 increased throughout the occlusion and were approximately 0.1 pH units at the center and 0.05 pH units at the margin after 10 min of ischemia.

Activation delay. The patterns of the changes in activation delay were assessed in the eight animals that did not have ventricular fibrillation. In this group, a total of 22 electrodes were placed in the center of the ischemic zone. At 13 electrode sites (59%) a discrete activation spike could be identified throughout all occlusions. At the remaining nine sites (41%) activation block occurred in the course of one or more of the occlusions. Figure 9, A, showing data from a group A animal, illustrates the characteristic activation pattern at sites with perceived activation during all occlusions. C resulted in an initial delay in activation within 1 min of the occlusion. This was followed by a phase of spontaneous improvement that lasted approximately 3 min. Thereafter local activation again became increasingly delayed. The spontaneous improvement in activation occurred later and was less marked in C and
FIGURE 6. Mean pH (± SEM) in the center and at the margin of the ischemic zone at each minute of ischemia during five successive occlusions (C1 to C5). *p < .05 compared with the subsequent occlusion; n = 4 animals without ventricular fibrillation (group A).

C3. Spontaneous improvement did not occur at all in C4 or C5. Figure 9, B, shows the declining incidence of spontaneous improvement in each occlusion at the 13 electrode sites with preserved activation in the eight animals without ventricular fibrillation. The panel demonstrates that spontaneous improvement was never observed after C3.

Figure 10, A, also showing data from a group A animal, illustrates the characteristic pattern observed at the nine electrode sites demonstrating activation block during one or more of the occlusions. During C1, the changes in activation were similar to that shown in figure 9, A. In C2, activation block occurred after 3 min of ischemia but activation was restored before the end of the occlusion. In C3 and in all subsequent occlusions, activation block persisted throughout the occlusion. Figure 10, B, shows the combined data from the nine electrode sites and illustrates that activation block occurred with increasing frequency with each occlusion. Furthermore, once activation block occurred at a particular location, it was observed in all subsequent occlusions at that location. The time to onset of block was either the same or shorter in each subsequent occlusion.

We often observed both patterns of activation changes (loss of spontaneous improvement and the development of block) in the same heart. Moreover, since only two or three centrally placed electrodes were used in each animal, it is possible that both patterns were present in all hearts. The changes in local activation in the center of the ischemic zone were rapidly reversed by reperfusion. Activation delay was
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FIGURE 8. Mean differences (± SEM) in pH_e at alternate minutes of ischemia between M and M + 1 at the center and at the margin; n = 6 animals without ventricular fibrillation (groups A and B).

minimal or did not occur at the lateral margin of the ischemic zone. The animals with ventricular fibrillation were excluded from the analysis shown in figures 9 and 10 to keep constant the number of electrodes. Analysis of these animals showed changes in activation similar to those of the animals without ventricular fibrillation.

Ventricular fibrillation. The incidence of ventricular fibrillation in each occlusion is summarized in table 2. Ventricular fibrillation occurred only in later occlusions (C_3 to C_5). Two of the five animals that fibrillated in C_4 did not fibrillate in C_5. Thus, in contrast to the occurrence of conduction block, the occurrence of ventricular fibrillation in a given occlusion did not predict its occurrence in subsequent occlusions.

Among the seven animals with ventricular fibrillation, we compared the values of [K+]e, pH_e, and activation delay measured just before the onset of ventricular fibrillation to those values at the same time in the immediately preceding occlusion in which ventricular fibrillation did not occur. We were unable to detect a significant difference in [K+]e change or activation at the onset of ventricular fibrillation compared with those occurring at the same time in the preceding occlusion in which ventricular fibrillation did not occur. The pH_e values were recorded in only two animals with ventricular fibrillation. In both experiments, pH_e at each electrode was slightly lower (0.05 to 0.10 pH units) in the preceding occlusion without fibrillation than in the occlusion with ventricular fibrillation, as predicted by the data shown in figures 5 to 8.

Discussion

In a series of 10 min coronary artery occlusions separated by 50 min of reperfusion, the following observations were made: (1) Changes in [K+]e during the initial occlusion differ from later occlusions, but changes in [K+]e eventually become reproducible. (2) Reproducibility of the change in [K+]e cannot be assumed until two matching occlusions are obtained. (3) The magnitude of extracellular acidosis decreases with each occlusion. (4) The change in local activation is characterized by a decreasing incidence of spontane-

FIGURE 9. A. Change in local activation at each minute of ischemia as measured by a bipolar electrode in the center of the ischemic zone during five serial 10 min occlusions of the LAD. B. Incidence of spontaneous improvement in activation delay recorded at the electrode sites demonstrating activation spikes throughout each of the five serial occlusions in the eight animals without ventricular fibrillation; n = 6 electrodes in C_1 (group A) and 13 electrodes in C_2 to C_5 (groups A and B).
FIGURE 10. A, Change in local activation at each minute of ischemia, as recorded by a single bipolar electrode in the center of the ischemic zone, during five serial occlusions of the LAD. In C2 the local activation spike was not discernible from 4 to 7 min of ischemia, but local activation was then restored by 8 min of ischemia. Activation block occurred during C3 to C5 and persisted until release of each occlusion. B, Incidence of activation block recorded at the electrode sites at which the activation block occurred during one or more of the serial occlusions of the LAD in the eight animals without ventricular fibrillation; n = 4 electrodes in C1 (group A) and 9 electrodes in C2 to C5 (groups A and B).

Nous improvement and an increasing incidence of local activation block. (5) Ventricular fibrillation is more common in later occlusions but is not reproducible. (6) The occurrence of ventricular fibrillation cannot be attributed solely to the magnitude of the \([K^+]_e\) rise or pH fall.

The different protocols (groups A and B) were used to determine whether the observed differences between C1 and C2 were attributable to the additional 50 min during which electrodes were in situ in the group A animals. Our hypothesis was as follows. If the differences between C1 and C2 were caused by time-dependent changes in electrodes and/or myocardial response characteristics, then changes in \([K^+]_e\) during C2 of group B animals should be identical to changes during C1 of group A animals, since in each case electrodes were in situ for 50 min before occlusion. Conversely, if differences between C1 and C2 were due to effects of the initial 10 min ischemic episode on subsequent changes, then the C2 occlusions of groups A and B should be similar, since in each case C2 followed an initial 10 min occlusion. The fact that C2 in groups A and B were similar indicates that the initial ischemic period was the critical factor responsible for the difference in subsequent occlusion. Additionally, we felt it important to demonstrate the reproducibility of \([K^+]_e\) changes with the group B protocol because the group B protocol offers the advantage of 1 hr less operative time than the group A protocol and permits the more precise placement of the electrodes.

Extracellular pH was measured by ion-selective (H+) electrodes similar in design and size to the K+-selective electrodes.26 These electrodes were used in the final eight animals of the series (six in group A, two in group B). The consistency of the results in these experiments was such that further experiments were not considered necessary.

We recognize that our measurements of local activation are inadequate to permit precise quantitative statements regarding activation time or sequence in the ischemic zone. It was our intent to use our measurements only to determine the reproducibility of the ischemia-induced change in local activation and to establish the qualitative nature of any changes in local activation delay associated with the repetitive occlusions.

The differences in the changes of \([K^+]_e\) and pH,
observed in the repetitive occlusions cannot be attributed to changes in the response characteristics of the electrodes because data were used only from electrodes that exhibited similar calibrations before and after each experiment. Other possible confounding influences such as changes in temperature and in K⁺-independent direct current potentials have previously been shown to be insignificant. We did not determine whether changes in collateral flow contributed to our results. However, it is unlikely that the development of collateral circulation contributed significantly, since collateral circulation in the pig is minimal. Furthermore, if collaterals were to develop during repetitive occlusions, it is likely that their influences would be more pronounced at the margin than at the center of the ischemic zone. The fact that similar patterns of change in \([K^+]_e\) and \(pH_e\) were observed at both locations argues against the possibility that changes in flow contributed substantially to our results.

We also cannot exclude a possible confounding effect of the long duration of our experiments. However, the reproducibility of the change in \([K^+]_e\) in the later occlusions and the equality of epicardial temperature in each occlusion suggest that this factor alone does not explain the progressive changes in \(pH_e\) and activation with each occlusion or the development of ventricular fibrillation during the later occlusions.

We have shown that successive periods of brief ischemia produce progressively less acidosis. This phenomenon may be significant in view of the possible role of intracellular acidosis in cellular necrosis and the protective effects of mild acidosis on hypoxic myocardium. The progressive decrease in extracellular acidosis with each occlusion may be explained by a decrease in acid production, a decrease in transport of intracellular protons into the extracellular space, and/or an increase in buffering capacity of the intracellular or extracellular compartments. The ischemia-induced \(H^+\) ions are probably derived from glycolytically produced lactic acid and the hydrolysis of ATP. Although our studies do not clarify the mechanism(s), it is possible that depletion of glycogen and/or ATP stores might contribute to our findings.

Our results indicate that the changes in \([K^+]_e\) and \(pH_e\) are not closely correlated. This lack of correlation is demonstrated by the following observations: (1) the changes in \([K^+]_e\), reached a plateau during the early minutes of C, whereas \(pH_e\) continued to fall throughout this occlusion, and (2) maximum \([K^+]_e\) values increased from C to C and then became reproducible in subsequent occlusions while acidosis decreased progressively. A close relationship between \(K^+\) efflux and intracellular acidosis during ischemia has been suggested, and other investigators have correlated the release of \(K^+\) during ischemia with release of lactate and phosphate. Our results do not necessarily suggest a lack of close relationship between \(K^+\) efflux and intracellular acidosis, since we measured only \(pH_e\). The relationship of \(pH_e\) to intracellular pH under conditions of ischemia is not known with certainty, and measurements of intracellular pH during ischemia by various techniques have shown differing results.

The diffusion of carbon dioxide, which rises quickly during ischemia, across cell membranes should tend to equalize pH in the intracellular and extracellular compartments, but differences in buffering capacities may cause differences in pH between the two compartments during ischemia despite similar values of \(PCO_2\).

The spontaneous improvement and return of local activation after an initial delay with or without block has been described previously and probably correlates with the spontaneous increase in action potential amplitude, recovery in resting membrane potential, decrease in ST and TQ potentials, and recovery of excitability that have been reported by others. The progressively more delayed activation observed in subsequent occlusions might be caused by depletion of factors that favorably affect propagation through acutely ischemic myocardium, such as endogenous catecholamines. Depletion of myocardial catecholamines by brief episodes of ischemia have been reported previously. Catecholamines may improve ventricular conduction during simulated ischemia and during ischemia by affecting resting membrane potential in depressed fibers, by increasing the magnitude of the slow inward current, and possibly by preventing cellular uncoupling. Thus their depletion could lead to the progressive delay in local activation seen in this study. This hypothesis remains to be tested.

We found the incidence of ventricular fibrillation to be greater in the later occlusions. Other investigators have implicated both an increase in \([K^+]_e\) and a slowing of ventricular activation in the genesis of ventricular fibrillation. We were unable to document a difference in \([K^+]_e\) or activation delay at the onset of fibrillation in the occlusions with and without ventricular fibrillation. This suggests that the occurrence of ventricular fibrillation may not be related solely to the magnitude of the change in \([K^+]_e\) or activation.

However, it does not exclude the possibility that ventricular fibrillation is related to more complex and subtle changes in \([K^+]_e\), \(pH_e\), and electrical properties.
than were measured in this study, such as the inhomogeneity of the ionic and electrical changes and/or the size of the central and marginal ischemic zones.

The implications of our study are twofold. From a clinical perspective, our results suggest that closely spaced episodes of reversible acute transmural ischemia of approximately equal duration, as may occur in patients with coronary vasospasm, may produce dissimilar ionic, metabolic, and electrical changes. Furthermore, these patients may be at risk for development of ventricular fibrillation in later episodes of ischemia, even if the initial episodes are free of arrhythmias.

From a laboratory investigatory perspective, our results indicate that studies designed to test the effects of pharmacologic interventions on the ionic and electrical events that characterize acute ischemia must take into consideration the differences in these parameters that occur in repeated ischemic periods. However, such studies can be meaningfully interpreted if it is appreciated that changes in [K⁺]ᵣ may not become reproducible until the third occlusion, that changes in pHₑ are not reproducible but the differences are predictable, that ventricular activation becomes progressively depressed with successive occlusions, that the presence of ventricular fibrillation in one ischemic episode does not invariably predict its presence in subsequent episodes, and that the occurrence of ventricular fibrillation is not determined solely by the magnitude of the change in [K⁺]ᵣ, pHₑ, or local activation.

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