Effects of verapamil on ischemia-induced changes in extracellular K+, pH, and local activation in the pig

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ABSTRACT In experimental animals, the calcium channel–blocking agents lessen the arrhythmogenic, ionic, metabolic, and electrical changes that occur during acute myocardial ischemia. To date, these effects have been studied separately, and the effects of these agents on local activation have not been correlated with ionic or metabolic effects. In open-chest, anesthetized swine, we used bipolar and ion-selective plunge electrodes to simultaneously measure ischemia-induced changes in left ventricular local activation, extracellular K⁺ ([K⁺]ₑ), and extracellular pH (pHₑ). The effects of verapamil (0.2 mg/kg) on these variables were studied during a series of 10 min occlusions of the left anterior descending coronary artery. Compared with control occlusions, verapamil (1) slowed the rise in [K⁺]ₑ at the center of the ischemic zone and at its lateral margin and decreased the peak [K⁺]ₑ by 0.9 mM at the center (p < .05) and by 0.1 mM at the margin (p = .10); (2) slowed the development of acidosis and decreased the peak level of acidosis beyond that expected solely as a result of serial occlusions by 0.19 pH units at the center (p < .05) and by 0.07 pH units at the margin (p = .10); and (3) slowed the development of local activation delay and often prevented the local activation block that was observed during control occlusions. Effects on local activation became less marked at [K⁺]ₑ levels greater than 9.0 mM, and the effects of verapamil on local activation were not explained solely by its effects on the local rise in [K⁺]ₑ or fall in pHₑ. A possible mechanism for this additional effect on local activation is suggested by preliminary results showing a diminution by verapamil of ionic inhomogeneity. Circulation 73, No. 4, 837–846, 1986.

However, the effects of calcium blockers on the metabolic, electrical, and ionic changes during ischemia have not been correlated in the same experimental preparation. Nor have these effects been demonstrated in an experimental preparation with low collateral flow, such as the pig.28,29

We have recently reported that serial 10 min coronary occlusions in the swine heart in situ provide a useful method of studying the ischemia-induced changes in myocardial [K⁺]ₑ, extracellular pH (pHₑ), and local activation.30 These studies showed that when two consecutive occlusions yielded matching changes in [K⁺]ₑ, the subsequent two occlusions yielded reproducible changes in [K⁺]ₑ. However, the changes in pHₑ were progressively but predictably less marked in sequential occlusions, and local activation delay became progressively more marked.

We have used this preparation to assess the effects of verapamil on ischemia-induced changes in [K⁺]ₑ, pHₑ, and local ventricular activation. We specifically sought to determine whether the drug’s effect on local activation correlated with its effects on increases in [K⁺]ₑ and/or decreases in pHₑ. Our studies indicate that...
although verapamil administered before an experimental coronary artery occlusion significantly lessens the changes in [K\(^+\)]\(_s\), pH\(_s\), and local activation, the effects on local activation cannot be correlated with the effects on the rise in [K\(^+\)]\(_s\) or the fall in pH\(_s\).

**Methods**

Miniature K\(^+\) -sensitive and H\(^+\) -sensitive plunge electrodes, modified from earlier designs,\(^{10}\) were fashioned by methods described in detail elsewhere.\(^{30}\) In brief, the cut ends of Teflon-coated silver wires (0.003 inch diameter) were chloridized and covered with a cellulose acetate/titanium dioxide mixture. The K\(^+\) -sensitive electrodes were made by soaking the wires in 3 mM KCl and covering the tip with the polyvinylchloride-valinomycin membrane. The H\(^+\) -sensitive electrodes were made by soaking in citrate buffer, then covering the tip with the H\(^+\) -ionophore (OCPH) in a polyvinylchloride-based membrane. Reference electrodes were constructed similarly but lacked any ion-selective membrane. Each electrode was loaded along with its reference into a 20-gauge needle and inserted into the myocardium. The needle was then withdrawn, leaving the electrodes embedded in the myocardial tissue. In most instances, K\(^+\) -sensitive and H\(^+\) -sensitive electrodes were loaded together with a common reference electrode into the same needle. The effect of verapamil on electrode sensitivity was tested in vitro, and verapamil was found to have no effect on electrode sensitivities even at concentrations 1000 times greater than the measured serum levels.

The electrodes were calibrated in vitro before and again after each experiment. The K\(^+\) -sensitive electrodes were calibrated in solutions of 3, 10, and 20 mM KCl, and the H\(^+\) -sensitive electrodes were calibrated in solutions of pH 6, 7, and 8. Data were accepted only from electrodes that demonstrated a stable baseline throughout the study and a 57 to 61 mV shift per 10-fold change in K\(^+\) or H\(^+\) activity both before and after an experiment. The integrity of the electrodes in vivo was determined before both control and postverapamil occlusions by the rapid injection of a solution containing 3 meq KCl and by 60 sec periods of respiratory acidosis. Data were accepted only from electrodes that demonstrated reproducibility of response to each K\(^+\) bolus and period of acidosis. Approximately 75% of all electrodes were acceptable by these criteria.

The amplified signals from all ion-selective electrodes were sampled every 15 sec by a DEE PDP-11/03 minicomputer during the T-Q segment of the cardiac cycle. Epicardial temperature was continuously monitored with a Yellow Springs temperature probe. The Nernst equation was used to calculate myocardial K\(^+\) activity and pH from measured millivolt changes with the calibration curve for each electrode, the epicardial temperature, and the serum [K\(^+\)] and pH determined from an arterial blood sample obtained just before occlusion. An activity coefficient of .746 was used to convert K\(^+\) activity to K\(^+\) concentration ([K\(^+\)]). As many as nine K\(^+\) and nine pH electrodes were placed in the mid-myocardium at various locations within the ischemic area. The precise position of the electrodes was determined by dissecting each electrode out of the surrounding myocardial tissue after each experiment and measuring their depths and relative positions. Electrodes that were within 5 mm of the visible cyanotic border during control occlusions were categorized as “margin” electrodes.\(^{32}\) All other electrodes were categorized as being in the center of the ischemic zone. In four experiments, thiocilavamine S (1.0 g) was injected intravenously with the left anterior descending coronary artery (LAD) occluded 30 sec before the animal was killed, and an ultraviolet lamp was used to identify the extent of the nonperfused area. Localization of the electrodes by this technique confirmed our measurements with the visible cyanotic border as a reference.

Local bipolar ventricular electrograms were measured by five Teflon-coated stainless steel bipolar plunge electrodes placed in the midmyocardium. One electrode was placed in the nonischemic zone, one at the lateral margin of the ischemic zone, and three in the center of the ischemic zone. At least one K\(^+\) pH electrode was placed within 2 mm of each bipolar electrode. The bipolar electrograms were filtered between 50 and 500 Hz and continuously monitored along with a lead I electrocardiogram on a Honeywell visicoarder. Recordings were made just before each occlusion and at least every minute during occlusions at paper speeds of 200 and 400 mm/sec. Local activation time was measured as the time from onset of the QRS complex in the electrocardiogram to the peak of the high-frequency deflection in each local electrogram. Only normal sinus beats were analyzed. The initial activation time was subtracted from activation times at each minute of ischemia to determine activation delays. Activation block was defined as the absence of high-frequency deflections in the local electrogram.

The results of control and postverapamil occlusions were compared on an individual electrode basis. Thus each electrode served as its own control. Comparisons were made between the second of the two control occlusions that yielded matching changes in [K\(^+\)] and the subsequent occlusion that was performed after the administration of verapamil. Statistical analysis was performed with paired t tests.

Rats weighing 20 to 30 kg were anesthetized with o-chloralose, 50 mg/kg, and ventilated via an endotracheal tube by a Harvard ventilator to maintain arterial oxygen saturation greater than 95%, carbon dioxide tension 35 to 45 mm Hg, and pH 7.35 to 7.45. The right femoral vein was canulated and used for infusion of 0.9% saline solution (100 ml/hr), anesthetics, and verapamil. A cathether was positioned in the descending aorta via the right femoral artery and was used for arterial pressure measurement by a Millar pressure transducer and for obtaining arterial blood samples. The arterial pressure, a lead I electrocardiogram, and the amplified signals from six of the ion-selective electrodes were continuously displayed on a Grass model 7 polygraph. A Millar pressure transducer was introduced into the left ventricle retrogradely across the aortic valve via the right carotid artery and was used to continuously record left ventricular pressure and its first derivative with respect to time (dP/dt). After a midsternal thoracotomy, the pericardial sac was entered, and the LAD was dissected free of surrounding tissue below its first diagonal branch. A snare of silicone tubing was positioned around the artery, which allowed reversible total occlusion. Isothermia was maintained with a heating pad, and the open chest was covered to maintain epicardial temperature and moisture. During an initial 10 min occlusion of the LAD, the electrodes were positioned in the center of the ischemic zone and along its lateral margin, which was easily identified by the junction of cyanotic and perfused tissue. The occlusion was then released. Fifty minutes later, the first in a series of 10 min LAD occlusions was performed. Each occlusion was followed by 50 min of reperfusion.

When two consecutive “control” occlusions yielded matching changes in [K\(^+\)]\(_s\), which required no more than three control occlusions, 0.2 mg/kg verapamil was infused intravenously over a 25 min period followed by a continuous infusion of 0.0065 mg/kg/hr. The postverapamil occlusion was then performed 25 min after the completion of the 0.2 mg/kg infusion of verapamil. A venous sample was drawn immediately before this occlusion for the subsequent determination of the serum verapamil level, generously performed by Dr. Russell McAllister at the Veterans Administration hospital in Lexington, KY, by using the high-performance liquid chromatographic method.
The administration of verapamil did not alter the sinus rate by more than ± 15 beats/min. If the rate slowed, the right atrium was paced to equal the spontaneous rate of the control occlusions. No adjustment was made if the rate increased after administration of verapamil.

Results

A total of 12 animals were studied. Table 1 shows mean values just before both control and postverapamil occlusions of arterial [K+] and pH, heart rate, mean arterial pressure, and maximum left ventricular dP/dt. There were no significant differences in arterial [K+], arterial pH, and heart rate, but verapamil caused a decrease in mean arterial pressure of 21 mm Hg and a decrease in dP/dt of 30%. The dose of verapamil (0.2 mg/kg) produced a mean serum level of 135 ng/ml (range 108 to 153), which is within the clinically relevant range.33

Administration of verapamil produced no change in [K+]e, pHc, or local ventricular activation before the onset of ischemia.

Figure 1 shows the effects of verapamil on the changes in [K+]e measured by a K+-sensitive electrode in the center of the ischemic zone and a K+-sensitive electrode at the lateral margin during a typical experiment. At both locations, verapamil delayed the time to onset of the rise in [K+]e slowed the rate of the [K+]e rise, and decreased the maximum [K+]e value at the end of 10 min of ischemia.

Figure 2 summarizes the results from all experiments and shows the mean (± SEM) [K+]e at each minute of ischemia during the control and postverapamil occlusions. Differences in [K+]e were statistically significant from 1 to 10 min of ischemia at the center of the zone and from 2 to 8 min of ischemia at the margin. Verapamil caused a mean decrease in peak [K+]e of 0.9 mM at the center and of 0.1 mM at the margin.

Although verapamil consistently and significantly slowed the rate of rise in [K+]e in the center and at the lateral margin, the effect on the peak [K+]e, attained by the end of the 10 min occlusion was not always observed. In two experiments, verapamil did not cause a decrease in the peak [K+]e in the center of the ischemic zone, and in five experiments there was no change in the peak [K+]e observed at the margin.

Figure 3 shows the typical effects of verapamil on changes in pHc at the center and margin of the ischemic zone. During the postverapamil occlusion, the rate of development of acidosis was slower and the maximum level of acidosis was decreased by 0.26 pH units in the center and by 0.11 pH units at the margin. We previously reported30 that the changes in pHc in sequential occlusions were not reproducible but were predictable. To separate the effects of verapamil from the effects of sequential occlusions alone, we compared the values of pHc during the postverapamil occlusions to the pHc values expected during comparable occlusions in the absence of verapamil. The latter were derived from our earlier experiments.30 Figure 4 summarizes this comparison. The solid line with open data points represents the mean values of pHc obtained during the control (preverapamil) occlusions. The broken line shows the values of pHc anticipated on the basis of our earlier experiments.30 The solid line with filled data points shows the actual mean changes in pHc during the postverapamil occlusions. The observed differences in pHc

![Figure 1](image-url)

**FIGURE 1.** Local midmyocardial [K+]e measured by a single ion-selective electrode in the center of the ischemic zone (CZ) and by a single ion-selective electrode at the lateral margin of the ischemic zone (MZ) during control and postverapamil occlusions.

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<th>TABLE 1</th>
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<td><strong>Mean data (± SEM) obtained just before onset of the control (C) and postverapamil (V) occlusions</strong></td>
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during the postverapamil occlusions were statistically significant compared with that expected in the absence of verapamil from 2 through 10 min of ischemia in the center of the ischemic zone. The same trend was observed at the margin, but statistical significance was attained at 5 and 6 min of ischemia only. Verapamil decreased the peak level of acidosis beyond that expected solely as a result of serial occlusions by 0.19 pH units at the center and by 0.07 pH units at the margin.

Figure 5 shows the effect of verapamil on activation delay measured by a midmyocardial bipolar electrode in the center of the ischemic zone. In this typical experiment, verapamil delayed the time to the onset of the activation change by 4 min, slowed the development of the activation delay, and prevented the activation block that was observed after 8 min of ischemia in the control occlusion. This effect of verapamil was observed in all experiments and contrasts markedly with our previous observations that in repeated control occlusions, activation block, once observed, occurred in all subsequent occlusions after equivalent or fewer minutes of ischemia.

Verapamil's effect on local activation could not be correlated directly to its effects on $[K^+]_e$ and $pH_e$. This is illustrated in figure 6, which shows the activation data from figure 5 replotted as a function of $[K^+]_e$ during control and postverapamil occlusions. The values of $pH_e$ at each point in time are also shown. This figure illustrates that activation delay after treatment with verapamil is decreased despite equal values of $[K^+]_e$ (e.g., point 1). The figure also shows that when $pH_e$ was matched in control and postverapamil occlusions, activation delay was shorter in the postverapamil occlusions (e.g., point 2). Activation was blocked at a $[K^+]_e$ of 8.8 mM during the control occlusion. After verapamil, local activation was preserved despite an equivalent $[K^+]_e$. However, acidosis was less marked during the postverapamil occlusion at these higher $[K^+]_e$ values, making direct comparisons at comparable $[K^+]_e$ and $pH_e$ levels impossible at high levels of $[K^+]_e$. The difference in activation delay during control and postverapamil occlusions was most marked at low to moderate $[K^+]_e$ levels (5.0 to 8.0 mM) and decreased at higher $[K^+]_e$ levels ($>9.0$ mM). This is more evident in the experiment shown in
verapamil reduces the ischemia-induced activation delay and preserves local activation at sites that demonstrate activation block during control occlusions. The effect of verapamil on activation was more marked than anticipated by its effect on local \([K^+]_e\), but the effect of verapamil on local activation was less marked at higher \([K^+]_e\) values. By accepting information only from electrodes that exhibited similar calibrations before and after an experiment and that responded reproducibly to testing in vivo (KCl bolus or acidosis), the confounding influences of changes in electrode sensitivity were avoided.

The rise in \([K^+]_e\) and the slowed conduction through ischemic tissue have been implicated by a number of investigators as important arrhythmogenic factors. In addition, it has been suggested that the rate of \([K^+]_e\) rise as well as its peak value may be important in the genesis of arrhythmias. The ability of verapamil to slow the rise in \([K^+]_e\) therefore provides an antiarrhythmic effect that is additional to the decrease in peak \([K^+]_e\) levels and to the decrease in local activation delay.

The mechanisms by which verapamil slows the
changes in $[K^+]_e$, pH_e, and local activation are not established. Verapamil dilates peripheral\textsuperscript{35} and coronary\textsuperscript{36} circulatory beds and antagonizes the slow calcium-dependent inward current. The potential mechanisms of verapamil’s effects on $[K^+]_e$, pH_e, and local activation therefore include afterload reduction, improved blood supply to ischemic areas, and inhibition of effects of the inward movement of Ca$^{++}$ into ischemic myocardial cells.

Afterload reduction is unlikely to account for the effects of verapamil observed in this study, since decreased arterial pressure may cause increased ischemic damage\textsuperscript{37} by decreased coronary perfusion pressure, and afterload reduction alone does not lessen ischemia-induced conduction slowing.\textsuperscript{39}

Verapamil dilates the coronary vasculature\textsuperscript{38} but no consistent effect on blood supply to an ischemic area has been demonstrated.\textsuperscript{21, 38} Diltiazem has been shown to improve blood flow to partially perfused areas in the pig,\textsuperscript{30} but no effects on blood flow to severely ischemic areas were seen. In view of these findings and the minimal collateral circulation in the swine heart,\textsuperscript{40} it seems unlikely that the coronary vasodilating effects of verapamil account for the effects on $[K^+]_e$ and pH_e at least in the center of the ischemic zone. Indeed, it has been shown in the isolated globally ischemic heart,\textsuperscript{20, 41} in which the effects of afterload reduction and improved collateral blood supply are removed, verapamil nevertheless slows K$^+$ release and lessens conduction delay.\textsuperscript{20, 41}

It is more likely that the primary mechanism by which verapamil decreases ischemia-induced changes in $[K^+]_e$, pH_e, and activation is by antagonism of the slow calcium sensitive inward current. Antagonism of the slow inward current and the resulting metabolic protection\textsuperscript{24} may slow the development of intracellular acidosis and thereby slow K$^+$ efflux and the development of activation delay. Verapamil has been shown to slow the depletion of endogenous ATP and creatine phosphate in hypoxic\textsuperscript{32} and ischemic\textsuperscript{23, 24} myocardium, to preserve mitochondrial function,\textsuperscript{23, 24} and to decrease myocardial oxygen demand.\textsuperscript{42} Weiss and Shine\textsuperscript{43} have shown that lowered extracellular Ca$^{++}$ activity slowed the rate of $[K^+]_e$ rise during global ischemia in the rabbit septum, supporting this hypothesis.

Preservation of ATP stores could account for the effects of verapamil observed in this study. Gevers\textsuperscript{44}
has postulated that ATP hydrolysis accounts for a significant proportion of protons generated during acute ischemia. Thus a decrease in ATP hydrolysis would lessen $H^+$ production. It is also possible, but less likely, that the ability of verapamil to lessen the extracellular acidosis during ischemia represents a decrease in proton movement into the extracellular space or an increase in buffering capacity. Our finding of a decrease in extracellular acidosis by verapamil is consistent with the report that verapamil lessens acidosis in a low-flow model of ischemia in the dog.45

A relationship between intracellular acidosis and $K^+$ efflux has been suggested.46-48 Therefore a decrease in intracellular acidosis might account for the slowing of $[K^+]_c$ accumulation by verapamil. In addition, a decrease in osmotic fluid movement and preservation of Na+/K+-ATPase pump activity may contribute to the slowing of the rise in $[K^+]_c$ that followed verapamil treatment.

Previous work has shown that verapamil lessens the degree of ischemia-induced conduction slowing in the dog17,18 and in the isolated rabbit heart.20 Our results confirm these observations and show that verapamil may preserve electrical activity in areas made inexcitable during control occlusions. The slowing of the rise in $[K^+]_c$ and the fall in $pH_c$ after verapamil pretreatment undoubtedly contributes to the lessening of the local activation delay. However, the effects of verapamil on local activation persisted when matched for equivalent $[K^+]_c$ or $pH_c$ values. At comparable $pH_c$ levels, activation delay was greater during control occlusions than during the verapamil occlusions despite the finding that the $[K^+]_c$ levels that accompanied the compared values of $pH_c$ were lower during the control occlusions. It was not possible to compare activation delay in control and postverapamil occlusions at simultaneously equivalent $[K^+]_c$ and $pH_c$ levels because at all comparable $[K^+]_c$, levels acidosis was less marked during the postverapamil occlusions, and at all comparable $pH_c$ values $[K^+]_c$ was higher during the postverapamil occlusions. However, frequently the differences in $pH_c$ were small at the times of these comparisons while the differences in activation delay were marked. Thus, although the less depressed $pH_c$ levels (i.e., less marked acidosis) may have contributed to the observed effect of verapamil on activation delay at comparable $[K^+]_c$ levels, it is likely that verapamil favorably affects activation delay by mechanism(s) in addition to its effects on local $[K^+]_c$ and $pH_c$. This observation is consistent with previous observations that verapamil improves conduction in superfused canine septum under identically altered perfusion conditions49 and that verapamil improves conduction in globally ischemic rabbit hearts at concentrations that do not affect the rise in $[K^+]_c$.20 One possible mechanism to account for these findings is that verapamil affects the relationship of $[K^+]_c$ to $V_{max}$ of the action potential upstroke. However, this has been tested in guinea pig papillary muscles49 and shown not to occur.

In our experiments, as in the studies of others,17,18 the effect of verapamil (or diltiazem) on activation was assessed by a relatively small number of electrodes placed at random in the ischemic area. The changes in activation recorded by these electrodes depend on the changes occurring “upstream” to the recording site as well as the changes occurring in close proximity to the recording site. Previous studies from our laboratory have shown that the changes in $[K^+]_c$ after coronary occlusions are inhomogeneous and that the changes in the subendocardium are greater than the changes in the midmyocardium or the epicardium.10 For this reason, the changes in resting potential, in the $V_{max}$ of the action potential upstroke, and in conduction induced by the changes in $[K^+]_c$ may be more pronounced in the subendocardium than in the midmyocardium and may influence the changes in activation recorded in the midmyocardium. Furthermore, inhomogeneous ionic changes would favor more circuitous routes of activation and thereby influence activation delay measured in the midmyocardium.

The changes in $K^+$, $pH$, and $pO_2$, associated with ischemia are capable of uncoupling myocardial cells.51 Similar simulations of ischemia uncouple cells at the Purkinje-papillary muscle junction.52 These changes in cellular coupling at local and “upstream” sites may also contribute to the changes in activation induced by acute ischemia.

Thus it is possible that the effect of verapamil on local activation may reflect changes in the inhomogeneity of the $[K^+]_c$, rise and/or changes in the cellular uncoupling associated with ischemia. Preliminary evidence supports both of these mechanisms. We estimated the inhomogeneity of the $[K^+]_c$ rise by computing the statistical variance of the $[K^+]_c$ changes obtained simultaneously from at least four electrodes in the center or margin of the ischemic zone at each minute of ischemia. Figure 8 shows the results of a single experiment in which the statistical variance was computed during control and postverapamil occlusions. The figure suggests that verapamil decreased the inhomogeneity of the $[K^+]_c$ rise in both the center and margin of the ischemic zone. Figure 9 summarizes the results from the six experiments in which at least four functioning $K^+$-sensitive electrodes were located in the
center of the ischemic zone and the four experiments in which at least four electrodes were located at the margin of the ischemic zone. The variance in \([K^+]_e\) was less marked in the postverapamil occlusions than in the preceding control occlusions in both the center and the margin, but the differences reached statistical significance only in the center. We consider these results preliminary for the following reasons: (1) the number of experiments in which we could calculate a variance was small, (2) four electrodes in a given location may not be sufficient for the precise quantitation of the variance of \([K^+]_e\) change, and (3) our experimental methods were not sufficiently rigorous to guarantee that the calibration and response characteristics of the electrodes in vivo were identical. This does not affect the remainder of our data, since these require only that the response of each electrode remain constant throughout the experiment, a condition that was met in each case. However, the precise quantitation of variance requires that the calibration and response characteristics of all electrodes in vivo be identical or that any differences be considered in the calculation.

The hypothesis that verapamil may also protect against cellular uncoupling, most likely by preventing the movement of calcium across the membrane, is suggested by previous studies of De Mello\(^53\) and supported by preliminary results in our laboratory.\(^56\) De Mello showed that an increase in intracellular \(Ca^{++}\) and a decrease in intracellular pH uncouple cells\(^53\) and that cellular uncoupling induced by dinitrophenol and \(H^+\) is prevented by the iontophoresis of Na EDTA.\(^53\) Our preliminary results, obtained in guinea pig papillary muscles, indicate that the increase in internal longitudinal resistance, an index of cellular uncoupling, induced by simulated ischemia is slowed by verapamil.\(^56\)

We showed that the effect of verapamil on local activation was abolished when \([K^+]_e\) was greater than 9.0 to 10.0 mM. The following explanation is suggested: At low to moderate \([K^+]_e\) levels ( < 9.0 mM)
verapamil lessens local activation delay, not only by its effects on $[K^+]$, and pH, but also by additional mechanisms, such as a lessening of cellular uncoupling and a decrease in the ionic inhomogeneities. As the ischemia becomes prolonged, $[K^+]_e$ eventually rises to levels in excess of 9.0 to 10.0 mM, even in the presence of verapamil. At these levels, the changes in resting membrane potential, $V_{max}$ of the action potential upstroke, and excitability are such that propagation fails, even in the absence of cellular uncoupling. Verapamil prolongs the time required for these changes to occur but does not prevent them.

In summary, our results suggest that the dominant effect of verapamil is to reduce the metabolic and electrical abnormalities associated with an ischemia-induced increase or redistribution in intracellular calcium, possibly mediated via the slow calcium-sensitive inward current. This results in a lessening in intracellular and extracellular acidosis, a decrease in the rise of potassium in the interstitial space, and a decrease in local ventricular activation delay. The lessened activation delay probably occurs as a result of the local ionic effects, effects on cell-to-cell coupling, and effects on the inhomogeneity of the ionic changes. However, verapamil does not prevent the eventual progression of the metabolic and ionic derangements that result ultimately in depressed conduction and activation block. Further work is needed to test these various hypotheses.

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