Marked Activation Delay Caused by Ischemia Initiated After Regional $K^+$ Elevation in In Situ Pig Hearts

William F. Fleet, MD; Timothy A. Johnson, PhD; Wayne E. Cascio, MD; Jason Shen, MD; Connie L. Engle, RVMT; David G. Martin, BS; Leonard S. Gettes, MD

Background Conduction mediated by the slow inward ($Ca^{2+}$) current occurs in vitro under specific experimental conditions but has not been documented in ventricular muscle in vivo during regional myocardial ischemia, perhaps because certain constituents of ischemia (including hypoxia and acidosis) may inhibit the $Ca^{2+}$ current in this setting. We hypothesized that slow conduction mediated by the $Ca^{2+}$ current could occur during acute ischemia in situations in which the extracellular $K^+$ rise was more marked relative to the degree of acidosis, as may occur at ischemic boundaries.

Methods and Results In open-chest, anesthetized swine, an arterial shunt from the carotid artery to the mid–left anterior descending coronary artery was created through which a solution of KCl was infused to raise extracellular $K^+$ ([K$_e$]) to approximately 9.4 mmol/L before the initiation of ischemia, which we termed "$K^+$-modified ischemia." Ischemia initiated at a normal [K$^+$], ("unmodified ischemia") resulted in a mean activation delay in the center of the ischemic zone of $55\pm26$ milliseconds after 5 minutes of ischemia and a decrease in epicardial longitudinal conduction velocity from 53 to 21 cm/s before the onset of conduction block. $K^+$-modified ischemia resulted in a mean activation delay in the center of the ischemic zone of $181\pm8$ milliseconds and a decrease in epicardial longitudinal conduction to less than 10 cm/s. $K^+$-modified ischemia was associated with ventricular fibrillation in 85% of episodes compared with 28% of episodes of unmodified ischemia ($P<.01$). Verapamil prevented the occurrence of marked activation delay during $K^+$-modified ischemia, producing local activation block following a maximum activation delay of $74\pm25$ milliseconds. In two experiments, responses mediated by the slow inward current were produced by regional $K^+$ elevation to 15 to 16 mmol/L, followed by concomitant regional administration of epinephrine ($10^{-7}$ mol/L). Regional [K$^+$], elevation alone to this level resulted in local activation block following a maximum activity delay of 70 to 80 milliseconds, whereas administration of epinephrine in combination with high [K$^+$], resulted in return of local activation with an activation delay of 160 to 180 milliseconds (ie, similar to that during $K^+$-modified ischemia).

Conclusions Compared with unmodified ischemia, $K^+$-modified ischemia resulted in marked activation delay and a high incidence of ventricular fibrillation. Based on measurements of longitudinal conduction velocity, the inhibitory effect of verapamil, and the results of experiments with high [K$^+$], plus epinephrine, we conclude that the marked activation delay during $K^+$-modified ischemia represents conduction mediated by the slow inward current. Because the conditions produced by $K^+$-modified ischemia (high [K$^+$], with minimal acidosis) are similar to conditions in and near ischemic border regions, we hypothesize that responses mediated by the slow inward current may occur in such regions during unmodified ischemia and may participate in the development of reentrant arrhythmias. (Circulation. 1994;90:3009-3017.)

Key Words • conduction • calcium channel • potassium • ischemia

Acute regional myocardial ischemia results in a combination of ionic, metabolic, and electrophysiological alterations that produce changes in conduction within the ischemic zone, leading to reentrant arrhythmias. During the early phase of acute ischemia, the conduction slowing in the ischemic zone is primarily caused by changes in active membrane properties induced by the combination of high extracellular $K^+$ ([K$^+$]$_e$), hypoxia, acidosis, and other constituents of ischemia. It is generally believed that this conduction slowing is due to depression of the rapid inward ($Na^+$) current. However, this supposition does not preclude localized areas within an ischemic zone in which responses mediated by the slow inward ($Ca^{2+}$) current may occur.

Three-dimensional mapping studies by Pogwizd and Corr have shown discrete regions within an ischemic zone in which there was very slow conduction estimated at 7 to 9 cm/s. This conduction velocity is consistent with a propagated response mediated by the slow inward current. Conduction was blocked or less markedly slowed in other regions. In the center of the ischemic zone, the slow inward current may be inhibited by the acidosis that occurs simultaneously with the [K$^+$], rise. Regions exist near the ischemic/nonischemic border zone in which [K$^+$], rises, but acidosis is less severe, presumably because of the greater diffusibility of CO$_2$ relative to K$^+$ ions. We postulated that at such regions, responses mediated by the slow inward current might occur during ischemia. To test this hypothesis, we developed a model using the in situ porcine heart in which regional [K$^+$], was elevated before the induction
of acute no-flow ischemia. By so doing, we were able to create an ischemic zone in which [K+] was elevated and acidosi was minimal. This resulted in marked activation delay in the center of the ischemic zone that correlated with an epicardial longitudinal conduction velocity of less than 10 cm/s. Our results suggest that propagated responses mediated by the slow inward current may occur during acute regional ischemia within discrete regions where a critical [K+]-pH relation exists and that these regions may contribute significantly to the development of reentry.

Methods

Experimental Preparation

The experimental preparation is similar to that which we used previously.9-11 Domestic swine of either sex weighing 30 to 35 kg were anesthetized with thiamylal sodium (25 mg/kg) followed by α-chloralose as needed. Mechanical ventilation and supplemental oxygen were supplied via an endotracheal tube and a Harvard ventilator. Arterial blood gas samples were monitored at frequent intervals, and appropriate ventilator adjustments were made to maintain arterial Po2 at >80 mm Hg and PCO2 at 35 to 40 mm Hg. Femoral artery and femoral venous catheters were used for monitoring arterial pressure (Millar pressure transducer) and for administration of fluids and drugs. Core temperature was continuously monitored with a temperature probe (Yellow Springs Instrument Co). Heating blankets were used as needed to maintain body temperature at 36° to 37°C.

The heart was exposed via a median sternotomy and suspended in a pericardial cradle. A site midway along the length of the left anterior descending coronary artery (LAD), which was free of branches, was selected for cannulation and dissected from surrounding tissue. The epicardial margin between ischemic and nonischemic tissue was identified by brief occlusion of the vessel at this site, and multiple ion-selective/bipolar plunge electrodes were placed at multiple locations within the center of the ischemic zone and in the normal (nonischemic) zone. After electrode placement, systemic heparin (10 000 U followed by 2000 U/h) was administered. An aorta-to-LAD shunt was created by placing a polyethylene catheter (Intramedic ID 1.77 mm) into the aortic arch through the right carotid artery, routing the catheter through a Masterflex roller pump, and connecting the distal end to a cannula (Insul-Tab 7444 AWG 19, 0.07 in OD) that was placed into the LAD at the previously selected site. The LAD was ligated just proximal to the cannula insertion site. Placement of the shunt into the LAD routinely took approximately 2 to 3 minutes. To ensure that all preparations were similar with respect to the duration of ischemia during shunt placement, ischemia was maintained for a total of 5 minutes in each case during shunt placement. Perfusion of the distal LAD by the shunt was maintained at 1.5 mL·kg body wt·min⁻¹, which we have previously shown to provide 1.2 to 1.5 mL·g of heart tissue·min⁻¹.9-11 A Doppler flow probe placed in the shunt was used to monitor the flow in the shunt. A sidearm in the shunt catheter was used for direct infusion of KCl solution into the distal LAD bed. Flow through this sidearm was controlled by a second roller pump that was calibrated between 0 and 2 mL/min. A diagram of the experimental preparation is given in Fig 1.

A glass cover was placed over the sternotomy to maintain the temperature and humidity on the surface of the heart. A temperature probe (Yellow Springs Instrument Co) was placed intramurally within the bed perfused by the LAD shunt to monitor intramural temperature. Atrial pacing was used as necessary to maintain heart rate between 100 and 120 beats per minute during all experimental events.

Electrodes

Ion-selective plunge electrodes were fashioned and calibrated by methods detailed previously.12 Briefly, one end of Teflon-coated silver wire (0.007-6 in diameter) was chloridized by soaking it in sodium hypochlorite, covered with a cellulose acetate–titanium dioxide sponge. K⁺-sensitive electrodes were made by covering the sponge with a polyvinylchloride-valinomycin–based K⁺-selective membrane, and H⁺-sensitive electrodes were made by covering the sponge with polyvinylchloride-based membrane containing the H⁺ ionophore tridodecyamine. Reference electrodes were fashioned in an analogous manner but lacked the ion-selective membrane. Electrodes were calibrated before each experiment in standard solutions (3 and 10 mmol/L KCl for K⁺ electrodes, pH 6.0, and 8.0 for H⁺ electrodes). Only electrodes that demonstrated a stable baseline (drift less than 1 mV/h) and 95% to 105% of the predicted Nernstian slope (56- to 62-mV shift per decade change in K⁺ or H⁺ activity at room temperature) were used. After electrode insertion, the in vivo performance of the K⁺ electrodes was tested by methods that we have used previously.12-14 At the end of each experiment, the electrodes were removed from the heart and retested in vitro to confirm stable function throughout the experiment.

Multiple pairs of Teflon-coated stainless steel wires were used to record bipolar electrograms from which activation times were determined. One K⁺ or H⁺-sensitive electrode, along with its reference and two stainless-steel wires for recording bipolar electrograms, constituted one electrode group. The electrode group was threaded into a 20-gauge hypodermic needle, which was used to insert the electrodes into the midmyocardium to a depth of 4 to 6 mm. The needle was then withdrawn, leaving the electrode group embedded in the myocardium. As many as 25 electrode groups were used in each experiment.
In three experiments, epicardial conduction velocity in the center of the ischemic zone was measured using an epicardial plaque electrode with 90 closely spaced (500- to 900-μm interelectrode distance) unipolar electrode sites. The outside dimension of the plaque was 43×43 mm. A row of bipolar pacing leads at the lateral edge of the plaque oriented perpendicularly to the long axis of the epicardial fibers was used to pace the ventricles at 110 to 120 beats per minute. Activation times for all recording sites were used to generate activation sequence maps, which were then used to calculate conduction velocities along the long axis of the epicardial fibers.

Experimental Protocol

No intervention was performed for 40 minutes after electrode placement and cannulation of the LAD. We then performed several interventions in varying order, each separated by 50 minutes of recovery. Myocardial ischemia was induced by the abrupt cessation of flow through the LAD shunt. Episodes of ischemia without prior K+ elevation, which we refer to as “unmodified ischemia,” were of 8 minutes’ duration. Preischemic elevation of [K+] in the myocardium supplied by the shunt was accomplished by infusing a 167 mmol/L solution of KCl into the sidearm of the shunt at a rate that was adjusted to raise [K+] in the center of the zone with a rate and magnitude (of [K+] change) similar to those seen during unmodified ischemia. The KCl infusion rate ranged from 0.5 to 1.0 mL/min (0.085 to 0.170 mEq/min). When the target [K+] level (9.0 to 10.0 mmol/L) in the center of the zone was reached, flow into the LAD shunt and sidearm was abruptly terminated for 5 minutes or until ventricular fibrillation ensued. We refer to this process as “K+-modified ischemia.” When ventricular fibrillation occurred, shunt flow was restored, and direct current defibrillation was performed. In seven experiments, sequential episodes of K+-modified ischemia were performed. In an additional five experiments, the effects of verapamil were studied during K+-modified ischemia. In these experiments, a “control” episode of K+-modified ischemia was followed by a second episode of K+-modified ischemia that was identical to the control episode except that verapamil was infused along with the KCl solution into the LAD shunt for 5 minutes at a rate of 0.025 mg/min (calculated to deliver 0.5 μm/mL of verapamil). In an additional four experiments, a similar protocol was used to study the effects of glibenclamide during K+-modified ischemia.

The regional infusion of KCl produced no change in LAD flow as measured by the Doppler flow probe located in the shunt. Intramyocardial temperature within the distal LAD bed did not differ from intramyocardial temperature outside the zone perfused by the LAD shunt or from the core temperature. Arrest of flow through the LAD shunt produced a fall in intramyocardial temperature of less than 0.5°C. Regional KCl infusion produced no rise in the arterial K+ or in the myocardial [K+], outside the zone perfused by the shunt.

Data Collection and Analysis

The signals from all electrodes were individually amplified by high-impedance amplifiers. The amplified signals from all electrodes, along with a lead II ECG, were digitized (Phoenix Data analog-to-digital converter) and simultaneously sampled (100 samples per second) for 1 second every 5 to 15 seconds by a MicroVAX II/GPX computer. Values of [K+] were calculated from measured millivolt changes using the calibration curve of each electrode, the myocardial temperature, and the systemic [K+], determined from an arterial blood sample obtained immediately before the event. An activity coefficient of .746 was used in calculating [K+] concentration. Values of pH were similarly calculated from the measured millivolt changes from the pH electrodes. Signals from bipolar electrograms were filtered between 50 and 500 Hz (-1 dB). Local activation was taken as the peak of the high-frequency deflection in the local electrogram. Activation delay at each point in time was calculated individually for each electrode by subtracting the activation time (as referenced to an electrode in the nonischemic zone) at baseline from that at each point in time. Local activation block was defined as the absence of a local activation spike of at least 1 mV. Only sinus (or atrial paced) beats were analyzed. The number of acceptable electrodes in each experiment ranged from 3 to 8 for [K+], and pH and from 8 to 20 for activation.

For each variable studied ([K+], pH, and activation delay), mean values were first calculated for each experiment individually. These mean values were then used to calculate a mean for the experimental group as a whole. Statistical analysis was performed using two-way ANOVA with repeated measures. A value of P≤.05 was considered statistically significant. Data are presented as ±1 SD unless otherwise indicated.

Results

Unmodified Ischemia

The changes in [K+], pH, and activation during unmodified ischemia are summarized in Fig 2A and 2B. Unmodified ischemia resulted in a maximum [K+] of 9.4±0.7 mmol/L, whereas pH fell to 6.75±0.17 (Fig 2A). Activation delay (Fig 2B) reached a maximum of 55±26 milliseconds after 5 minutes of ischemia. In each experiment, the maximum activation delay was then followed by one of two patterns: (1) a plateau or partial recovery (decrease) in activation delay or (2) local activation block within the ischemic zone. The decrease in the mean activation delay shown in Fig 2B reflects the combined effects of both of these patterns. Thus, despite continued ischemia, activation delay did not continue to increase progressively. Ventricular fibrillation occurred in 9 of 32 episodes (28%) of unmodified ischemia (8 of 26 animals). The mean time to the onset of ventricular fibrillation was 4.6 minutes, with a range of 2.75 to 6.0 minutes.

K+-Modified Ischemia

The changes in [K+], pH, and activation during K+-modified ischemia are summarized in Fig 2C and 2D. The infusion of KCl that preceded the onset of K+-modified ischemia produced a [K+] rise to 9.4±2.3 mmol/L and activation delay of 24±22 milliseconds. This KCl infusion produced no arrhythmias or change in pH.

After the onset of K+-modified ischemia (identified at time=0 minutes), [K+], and pH changed minimally for the first 1 to 2 minutes and then more rapidly thereafter. Activation delay increased minimally during the first minute of K+-modified ischemia, but thereafter activation became progressively and markedly delayed, reaching 181±8 milliseconds after 2.75 minutes. K+-modified ischemia resulted in ventricular fibrillation in 27 of 37 episodes (73%) in 22 of 26 animals (P<.01 compared with unmodified ischemia). The mean time to onset of ventricular fibrillation during K+-modified ischemia was 2.2±0.5 minutes, with a range of 1.25 to 4.0 minutes. The data concerning K+-modified ischemia shown in Fig 2 do not extend beyond 2.75 minutes since the majority of hearts had fibrillated beyond this time.

In seven experiments, repeated episodes of K+-modified ischemia were performed to determine the reproducibility of the changes in [K+], pH, and activation delay. In five of these experiments, three sequential
episodes were performed, whereas in the remaining two experiments, two episodes of K'-modified ischemia were performed. In each experiment, the \([K^+]_e\), pH, and activation changes were reproducible during these sequential episodes of K'-modified ischemia. In three of these seven experiments, ventricular fibrillation occurred in each of three sequential episodes of K'-modified ischemia, and the time to ventricular fibrillation was reproducible to within 0.5 minute in these three experiments. In the remaining four experiments, ventricular fibrillation did not occur during any of the sequential episodes of K'-modified ischemia.

An example of the marked activation delay that occurs during K'-modified ischemia is shown in Fig 3, which shows the surface ECG (channel 1), one bipolar electrogram in the nonischemic zone (channel 2), and three bipolar electrograms from the center of the ischemic zone (channels 3 through 5). Fig 3A shows recordings at baseline, Fig 3B shows recordings at the peak of KCl infusion to a [K'] = 9.0 mmol/L, and Fig 3C shows recordings 2.5 minutes after the onset of K'-modified ischemia. After 2.5 minutes of K'-modified ischemia (immediately preceding ventricular fibrillation), activation delay reached 234 to 288 milliseconds. In addition, 2:1 activation block is present, which was a frequent occurrence immediately preceding the onset of ventricular fibrillation.

**Conduction Velocity**

We measured epicardial longitudinal conduction velocity during both unmodified ischemia and K'-modified ischemia in three experiments using an epicardial plaque electrode. The results of one such experiment are shown in Fig 4. During unmodified ischemia, conduction velocity fell to 21 cm/s, after which conduction block occurred at 6 minutes into ischemia. During K'-modified ischemia in the same animal, longitudinal conduction velocity fell to 9 cm/s, after which ventricular fibrillation occurred. Similar results were observed in two additional experiments with K'-modified ischemia producing an epicardial longitudinal conduction velocity of less than 10 cm/s.

**Effects of Verapamil**

We measured the effects of verapamil on activation delay during K'-modified ischemia in five experiments. The results of one such experiment are shown in Fig 5. During the control episode of K'-modified ischemia, activation delay reached 205 milliseconds, culminating in ventricular fibrillation. The same protocol was then repeated in the presence of verapamil. Verapamil had no effect on the activation delay associated with the KCl infusion. During the initial minutes of K'-modified ischemia, verapamil slowed the development of further activation delay. After several minutes of K'-modified ischemia, activation became progressively more delayed, but the marked activation delay that occurred during the control episode did not occur in the presence of verapamil. Instead, local activation block occurred after activation delay reached a maximum of 85 milliseconds. Three additional experiments produced similar results, i.e., inhibition of marked activation delay by producing local activation block following activation delay of approximately 60 to 80 milliseconds. In this
group of four experiments, the control episodes of K+-modified ischemia resulted in a mean activation delay of 150±45 milliseconds before the onset of ventricular fibrillation, whereas the verapamil-treated episodes of K+-modified ischemia resulted in a maximum activation delay of 74±25 milliseconds before the occurrence of local activation block within the ischemic zone. In each of these experiments, ventricular fibrillation, which occurred during the control episodes of K+-modified ischemia, was prevented by verapamil. In a fifth experiment, ventricular fibrillation was not prevented by verapamil. In this experiment, ventricular fibrillation occurred after 3 minutes of K+-modified ischemia in the presence of verapamil, at which time activation delay had increased to only 30 milliseconds. Thus, marked activation delay (ie, >100 milliseconds) was never observed during K+-modified ischemia in the presence of verapamil.

Effect of Glibenclamide

In addition to inhibiting the slow inward (Ca2+) current, verapamil has recently been shown to inhibit the ATP-sensitive K+ channel.15 To determine if the effects of verapamil that we observed during K+-modified ischemia might be related to the K+ATP channel—blocking effects, we studied the effects of the K+ATP channel—blocking agent glibenclamide during K+-modified ischemia in four experiments. The results of these four experiments are summarized in Fig 6, which shows activation delay during K+-modified ischemia in the absence and presence of glibenclamide (10 to 30 μmol/L). This concentration is similar to that used by others in isolated, perfused rat16 and rabbit17 hearts and produces blood levels 20 to 60 times greater than that observed during the intravenous administration of 1.5 mg/kg in the in situ dog heart.18 Moreover, we observed in a pilot series of experiments that the intracoronary administration of 10 to 30 μmol/L glibenclamide less-
ened the rise in extracellular K⁺ induced by a 10-minute period of no-flow ischemia. As shown in the figure, glibenclamide had no effect on activation delay during K⁺-modified ischemia and did not inhibit the development of marked activation delay in this setting. Glibenclamide did not prevent the occurrence of ventricular fibrillation during K⁺-modified ischemia in any of the four experiments.

**High [K⁺], Plus Epinephrine**

To determine the magnitude of the activation delay associated with responses known to be mediated by the slow inward current,1⁴,1⁹ we performed two experiments in which we raised the regional [K⁺] to 15 mmol/L to fully inactivate the rapid inward current, and then we simultaneously administered epinephrine (10⁻⁷ mol/L). The results of one such experiment are shown in Fig 7. Infusion of KCl resulted in progressive activation delay and ultimately in local activation block after [K⁺] reached 13 mmol/L. The maximum activation delay before the onset of block was 78 milliseconds. Administration of epinephrine resulted in return of conduction within the zone but with an activation delay of 140 to 150 milliseconds, which is similar to the activation delay during K⁺-modified ischemia. In a second similar experiment, regional infusion of KCl resulted in local activation block following a maximum activation delay of 75 milliseconds, whereas coadministration of epinephrine resulted in return of local activation with an activation delay of 180 milliseconds. In both of these experiments, frequent episodes of nonsustained ventricular tachycardia occurred during the local epinephrine administration, but ventricular fibrillation did not occur.

**Discussion**

The conduction slowing that occurs during the first 10 minutes of acute ischemia is believed to be due to depression of the rapid inward (Na⁺) current.¹¹ Responses mediated by the slow inward (Ca²⁺) current have been produced experimentally by inactivating the rapid inward current with the high [K⁺], or tetrodotoxin⁴,¹⁹-²¹ (usually in combination with exogenous catecholamines as well) but have not previously been identified during acute ischemia. In this study, we have shown that altering the ionic conditions by raising [K⁺] before the onset of ischemia (K⁺-modified ischemia) results in marked conduction slowing that we believe is mediated by the slow inward current. The experimental evidence supporting the assertion that K⁺-modified ischemia results in conduction mediated by the slow inward current is summarized in Fig 8 and includes the magnitude of the conduction slowing, the effect of verapamil, and the effect of high [K⁺], plus epinephrine.
Magnitude of Conduction Slowing

Responses mediated purely by the slow inward current conduct very slowly (<10 cm/s). In contrast, responses mediated by the rapid inward current demonstrate a minimum conduction velocity of approximately 20 cm/s, after which further inhibition of the Na⁺ current results in failure of impulse propagation rather than further conduction slowing. During K⁺-modified ischemia, epicardial longitudinal conduction velocity fell to 10 cm/s or less. In an experimental model very similar to our own,19 propagating responses mediated by the slow inward current conducted with an epicardial longitudinal conduction velocity of 12 cm/s. Thus, the very slow conduction measured during K⁺-modified ischemia is consistent with responses mediated by the slow inward current.

Effect of Verapamil

Verapamil has been shown to inhibit responses mediated by the slow inward current and has been used to differentiate responses mediated by the slow inward current from those mediated by a depressed Na⁺ current,22 which are not sensitive to verapamil. During K⁺-modified ischemia, verapamil prevented the marked activation delay (which was observed during the control episodes) by producing local activation block within the ischemic zone following a maximum activation delay of 74±25 milliseconds. The inhibition of the marked activation delay by verapamil is consistent with the hypothesis that slow channel–mediated responses were responsible for the marked activation delay.

Verapamil has also been shown to lessen the rise in extracellular K⁺ associated with ischemia23 to delay cellular uncoupling induced by both true and simulated ischemia24,25 and to lessen the activation delay induced by unmodified ischemia.23,26 Diltiazem has been shown to retard the decrease in ATP and the rise in intracellular calcium induced by ischemia. All of these actions could be attributed to the effects of blocking the L-type calcium channel. However, verapamil has also been reported to inhibit the Kᵥ₅ channel.15 We questioned whether inhibition of the Kᵥ₅ channel by glibenclamide would reproduce the verapamil results and prevent the marked activation delay induced by K⁺-modified ischemia. We found in four experiments that it did not. This result indicates that the effect of verapamil is unlikely to have been the result of Kᵥ₅ channel inhibition. Verapamil also dilates the coronary vasculature.28 In our experiments, coronary flow to the ischemic segment was regulated by the infusion pump; thus, we do not believe that this mechanism contributed to our results.

High [K⁺], Plus Epinephrine

Responses mediated by the slow inward current have been produced in an experimental model similar to our own by raising [K⁺], to approximately 17 mmol/L and adding epinephrine.19 A similar protocol was performed in our experimental model. Regional infusion of KCl produced a maximum activation delay of 76 milliseconds (mean of two experiments), which occurred at a [K⁺] of approximately 13 mmol/L. Raising the [K⁺], further resulted in local activation conduction block within the zone. As is shown in Fig 8, the maximum activation delay during regional KCl infusion (in the absence of epinephrine) was very similar to the maximum activation delay during K⁺-modified ischemia in the presence of verapamil. In both circumstances, this maximum activation delay represents the maximum degree of conduction slowing of Na⁺ channel–mediated responses before failure of impulse propagation. Although high [K⁺], alone produced a maximum activation delay of 76 milliseconds before the onset of local activation block, local activation could be restored by regional infusion of epinephrine. As shown in Fig 8, the mean activation delay of these slow channel–mediated responses in these two experiments was similar to the activation delay observed during K⁺-modified ischemia.

The assertion that the marked activation delay during K⁺-modified ischemia represents slow channel–mediated conduction is further supported by studies that we have performed in the arterially perfused rabbit papillary muscle in which K⁺-modified ischemia was produced in a manner similar to that reported in this study, resulting in slow responses and a conduction velocity of 5 cm/s. The very slow conduction in the rabbit papillary muscle was likewise inhibited by verapamil.

As referred to above, the conduction slowing that occurs before the onset of local activation block in the center of the ischemic zone during unmodified ischemia has been attributed to depression of the rapid inward (Na⁺) current1-19 rather than to activation of the slow inward current. In the center of the ischemic zone, the absence of responses mediated by the slow inward current during unmodified ischemia may relate to the associated fall in pH. It has been shown that the slow inward current is inhibited by acidosis.3-7 During acute ischemia, acidosis occurs concurrently with the [K⁺] rise.14 Therefore, by the time the rise in [K⁺], reaches a level sufficient to fully inactivate the Na⁺ current, the concomitant acidosis would be expected to prevent the emergence of the slow inward current and thereby prevent slow channel–mediated conduction. In this circumstance, conduction block will occur once the Na⁺ current is inactivated.

During K⁺-modified ischemia, extracellular acidosis is minimal relative to the level of [K⁺], elevation. The combination of high [K⁺], with minimal acidosis may be the critical factor that allows the occurrence of conduction mediated by the slow inward current in this model. Wilensky et al10 demonstrated a zone along the subendocardium of the rabbit interventricular septum in which [K⁺], was elevated but acidosis was minimal, a finding that is consistent with the greater diffusibility of CO₂ than of K⁺ ions.30,31 Based on our observations of slow conduction during K⁺-modified ischemia, we speculate that very slow conduction mediated by the slow inward current may occur during unmodified ischemia in these discrete border regions in which [K⁺], is high relative to the degree of acidosis. The three-dimensional mapping studies of Pogwizd and Corr23 demonstrated discrete regions in the subendocardium in which very slow conduction velocities of 7 to 9 cm/s occurred during acute ischemia. We speculate that this very slow conduction identified by these investigators may represent conduction mediated by the slow inward current that occurred as a result of the critical [K⁺]ₕ–pH relation.
in these regions. We recognize that our model is not entirely analogous to the changes existing across the endocardial and lateral border zone during acute ischemia. However, the data from Wilensky et al demonstrate that regions with K+ and pH values similar to our model should be present along the subendocardial border, and we have observed such K+ and pH values in the lateral border zone.32 Thus, we suggest that K+-modified ischemia produces, on a larger scale, the [K+]pH combination that may be critical to the development of very slow conduction within discrete regions of an ischemic zone during unmodified ischemia. That such regions of very slow conduction may be important in the genesis of spontaneous reentry and ventricular fibrillation that occurs in this setting is suggested by our observation that ventricular fibrillation occurred more often during K+-modified ischemia (27 of 37 ischemic episodes) than during unmodified ischemia (9 of 32 ischemic episodes) despite equally sized ischemic zones. It is also supported by our observation that verapamil prevented both the marked activation delay and the occurrence of ventricular fibrillation during K+-modified ischemia. However, the absence of ventricular fibrillation during the high [K+]pH-epinephrine experiments suggests that factors in addition to very slow conduction are required to induce ventricular fibrillation. Such factors may include the inhomogeneities in the metabolic and ionic changes that characterize acute ischemia.13 The failure of verapamil to prevent the onset of ventricular fibrillation during K+-modified ischemia in one experiment may relate to the presence of nonreentrant mechanisms: preceding the onset of ventricular fibrillation in approximately 25% of instances.23

In summary, we have observed that K+-modified ischemia results in marked activation delay and a high incidence of ventricular fibrillation. Our observations strongly suggest that this marked activation delay represents very slow conduction mediated by the slow inward current. It is highly likely that the particular [K+]pH relation created by K+-modified ischemia may exist at discrete areas near the margins of the ischemic zone (during unmodified ischemia) and may be responsible for very slow conduction in these regions. It is possible that premature beats arising in close proximity to the areas of very slow conduction may then reenter and lead to ventricular fibrillation.

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