Introduction

Acute myocardial ischemia causes an increase in extracellular K\(^+\) ([K\(^+\)]\(_e\)) and a decrease in extracellular pH (pHe). We examined the effects of these changes on conduction and the effective refractory period (ERP) during acute myocardial ischemia.

Methods: We inserted K\(^+\)-sensitive electrodes into the mid-myocardium and bipolar plunge electrodes into the subendocardium and subepicardium of in-situ canine hearts. A unipolar electrode was inserted into the mid-myocardium. The carotid artery was shunted to the LAD through a roller pump, and KCl was infused into the side arm of the shunt. Systematic metabolic acidosis (MA) and respiratory acidosis (RA) were induced in 10 animals each by infusion of NH\(_4\)Cl and inhalation of CO\(_2\), respectively.

Results: Under regional hyperkalemia ([K\(^+\)]\(_e\) = 10.23 ± 1.15 mM in the MA group and 9.28 ± 1.19 mM in the RA group), the intramyocardial conduction time (CT) increased by 20%. The CT did not change under RA or MA alone. When regional hyperkalemia plus MA ([K\(^+\)]\(_e\) = 8.94 ± 1.87, pH = 7.06 ± 0.06) or RA ([K\(^+\)]\(_e\) = 9.33 ± 0.63, pH = 6.75 ± 0.20) were both induced, the CT increased further by 50% compared to the control/baseline state. The ERP did not change significantly with regional hyperkalemia or regional hyperkalemia plus RA or MA.

Conclusion: Our data indicate that the fall in pHe that results from myocardial ischemia enhances the conduction slowing induced by the rise in [K\(^+\)]\(_e\).

Key words: myocardial ischemia, extracellular K\(^+\), acidosis, effective refractory period

was selected for cannulation and dissected from the surrounding tissue. The epicardial margin between perfused by the cannulated artery was identified by brief occlusion of the vessel at this site, and 1–2 K⁺-sensitive electrodes were placed in the midmyocardium, and 2 Teflon-coated stainless steel bipolar plunge electrodes were placed in the subendocardium and subepicardium at the center of the myocardium perfused by the cannulated artery, defined as the region > 10 mm inside the visible cyanotic border, and in the subendocardium and subepicardium outside of the cyanotic border zone. A Teflon-coated silver unipolar plunge electrode was placed at the site of bipolar plunge electrode placement and was used to measure the effective refractory period (ERP). An indifferent electrode was placed at the aortic root.

After electrode placement, systemic heparin (a bolus of 5,000 U followed by infusion at 1,000 U/hour) was administered. A carotid artery-to-LAD shunt was created by placing a polyethylene catheter between the right carotid artery and the LAD at a previously selected site. Atrial pacing was used to maintain constant heart rate at 150 bpm throughout the experiment. Aortic pressure and a lead II electrocardiogram (ECG) were recorded by means of a polygraph system (MTI-880T, Fukuda Denshi Co, Tokyo, Japan), projected onto a cathode-ray tube monitor, and monitored continuously. The lead II ECG and bipolar electrograms were recorded on a 3-channel recorder at a paper speed of 200 mm/second (Rapicorder RMV540A, Kyowa Dengyo Co, Tokyo, Japan). Intramyocardial conduction time (CT) was measured as the time difference between subendocardial activation and subepicardial activation. For measurement of the ERP, a premature ventricular stimulus at twice the diastolic threshold and pulse width of 2 ms was delivered after every 10 paced right atrial beats. Stimulus delivery was from a silver unipolar electrode used as the cathode, and the ERP was defined as the longest time interval between the first peak of the subendocardial electrogram deflection and the ventricular pacing spike without ventricular activation. Delivery of the premature ventricular stimuli was decreased successively by 5 ms, and if the premature stimulus failed to pace the ventricle, the interval was increased by 10 ms and then decreased incrementally by 1 ms.

**K⁺-selective electrodes**

K⁺-selective plunge electrodes were fashioned and calibrated as described previously (Fig. 2) [19, 20]. Electrodes were calibrated before each experiment in standard solution (3 or 10 mmol/L KCl). Only electrodes with a stable baseline drift (< 1 mV/hour) and 95–105% of the predicted Nernstian slope (56–62 mV shift per decade change in K⁺ activity at room temperature) were used. The in vivo performance of these electrodes was tested by methods described previously [19, 20]. At the end of each experiment, the electrodes were removed from the heart and retested in vitro to confirm stable function throughout the experiment. Direct current electrograms recorded from the K⁺-selective electrodes were amplified by a custom-made device and recorded on a Rapicorder RMV 540A (Kyowa Dengyo Co.) at 60 mm/minute [20].

**Experimental protocol**

No intervention was performed for 30 minutes after placement of the K⁺-sensitive and bipolar plunge electrodes. A 167-mM solution of KCl was then infused into the side arm of the shunt at a rate adjusted to raise [K⁺]e in the myocardium supplied by the shunted blood at a rate and magnitude of change in [K⁺]e similar to those seen during myocardial ischemia [16, 20]. In 10 animals, systemic MA was induced by intravenous infusion of 1M NH₄Cl to produce an arterial pH of 6.6–7.1, a value similar to that recorded in the center of the myocardial ischemic zone in pigs, and in the other 10 animals, systemic RA was induced by introducing CO₂ into the ventilator at 0.5–2.0 L/minute [16]. Thus, 4 different conditions were established.
in each of the 2 groups of animals: a Control condition, i.e., the pre-KCl-infusion condition; a High $[K^+]_e$ condition, i.e., the post KCl-infusion condition; Acidosis, i.e., the 6.6−7.1-arterial pH condition; a High $[K^+]_e$ plus Acidosis condition. The following variables were measured under each of the 4 conditions in each group of animals: $[K^+]_e$, pH, CT, and ERP.

**Statistical analyses**
Values are shown as mean ± SD unless otherwise indicated. Differences in the study variables measured under each of the 4 conditions were evaluated in each group by Wilcoxon signed-rank test. All statistical analyses were performed with Stat View 5.0 (SAS Institute, Cary, NC, USA), and $P < 0.05$ was considered significant.

**Results**
Values obtained under each of the 4 conditions in each of the 2 study groups are shown in Table 1. Representative electrode recordings from each of the 2 study groups are shown in Figs. 3 and 4.

![Graph](image)

**Table 1** $[K^+]_e$, pH, CT, and ERP measured under the 4 study conditions in the 2 study groups

<table>
<thead>
<tr>
<th></th>
<th>Metabolic acidosis</th>
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<th>Respiratory acidosis</th>
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<tbody>
<tr>
<td></td>
<td>$[K^+]_e$ (mM)</td>
<td>pH</td>
<td>CT (ms)</td>
<td>ERP (ms)</td>
</tr>
<tr>
<td>Before KCl infusion</td>
<td>3.62 ± 0.13</td>
<td>7.36 ± 0.07</td>
<td>15.5 ± 3.3</td>
<td>192.4 ± 13.2</td>
</tr>
<tr>
<td>(control)</td>
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<tr>
<td>After KCl infusion</td>
<td>10.23 ± 1.15</td>
<td>7.17 ± 0.05</td>
<td>18.7 ± 4.1†</td>
<td>196.8 ± 15.9‡</td>
</tr>
<tr>
<td>Acidosis</td>
<td></td>
<td></td>
<td>16.0 ± 3.0</td>
<td>192.4 ± 22.6</td>
</tr>
<tr>
<td>High $[K^+]_e$ plus acidosis</td>
<td>8.94 ± 1.87*</td>
<td>7.06 ± 0.06**</td>
<td>22.0 ± 5.9†</td>
<td>199.9 ± 26.7</td>
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<tr>
<td></td>
<td>3.70 ± 0.10</td>
<td>7.42 ± 0.08</td>
<td>15.9 ± 4.4</td>
<td>188.9 ± 26.9</td>
</tr>
</tbody>
</table>

* $P = 0.0117$ vs. High $[K^+]_e$, ** $P = 0.0117$ vs. Acidosis, † $P = 0.058$ vs. Control, ‡ $P = 0.0496$ vs. High $[K^+]_e$, †† $P = 0.0505$, ‡‡ $P = 0.0033$ vs. Control, †† $P = 0.0051$ vs. High $[K^+]_e$.

**Metabolic acidosis**

![Fig. 3](image)

**Fig. 3** A representative experiment of the metabolic acidosis and high extracellular potassium on changes in CT and ERP. MA: metabolic acidosis, CT: intramyocardial conduction time, ERP: effective refractory period.
and then to 6.71 ± 0.18 in the High \([K^+]\) plus Acidosis condition. These values did not differ significantly.

Intramyocardial CT

In the MA group, intramyocardial CT increased from a control value of 15.5 ± 3.3 ms to 18.7 ± 4.1 ms in the High \([K^+]\) condition. It dropped to 16.0 ± 3.0 ms in the Acidosis condition but increased to 22.0 ± 5.9 in the High \([K^+]\) plus Acidosis condition. The difference in intramyocardial CT between the High \([K^+]\) plus Acidosis condition and High \([K^+]\) condition was significant (\(P = 0.0496\)).

In the RA group, intramyocardial CT increased significantly from a control value of 15.9 ± 4.4 ms to 19.1 ± 3.3 ms in the High \([K^+]\) condition (\(P = 0.0033\)), decreased to 13.3 ± 4.1 ms in the Acidosis condition, and then increased significantly to 23.3 ± 5.4 ms in the High \([K^+]\) condition (\(P = 0.0051\)).

ERP

In the MA group, the ERP changed very little from a control value of 192.4 ± 13.2 ms to 196.8 ± 15.9 ms in the High \([K^+]\) condition, 192 ± 22.6 in the Acidosis condition, and 199.9 ± 26.7 in the High \([K^+]\) condition, plus Acidosis condition.

In the RA group, ERP also changed very little from a control value of 188.9 ± 26.9 ms to 190.0 ± 29.4 ms in the High \([K^+]\) condition, 183 ± 26.5 in the Acidosis condition, and 190.6 ± 18.3 in the High \([K^+]\) condition, plus Acidosis condition.

Discussion

Overall, we observed a modest increase in intramyocardial CT under the High \([K^+]\) condition induced by local infusion of KCl but, despite the acidosis, we observed no change in intramyocardial CT when the \([K^+]\) level remained stable. However, when the \([K^+]\) level was increased in the acidosis condition, intramyocardial CT increased significantly.

\([K^+], \text{ and pH} \text{ during acute myocardial ischemia}\)

Acute myocardial ischemia causes a rise in \([K^+]\) and a fall in \(pH\). In a previously reported porcine study, \([K^+]\) and \(pH\) reached 9–11 mM and 6.7–6.9, respectively after 10 minutes of coronary artery occlusion, and in a previously reported canine study, \([K^+]\) reached 9 mM after 15 minutes of coronary artery occlusion.

\([K^+], \text{ CT, and ERP}\)

According to Buchanan et al., conduction velocity (CV) measured in guinea pig papillary muscle at a \([K^+]\) level of 5.4 mM increased when the \([K^+]\) level reached 7–11 mM, despite a decrease in the maximum rate of rise of the action potential upstroke (\(dV/dt_{\text{max}}\)), and CV then decreased when the \([K^+]\) level was ≥ 12 mM. The reason for the increase in CV despite the decrease in \(dV/dt_{\text{max}}\) was explained by the decrease in resting membrane potential and threshold potential for depolarization. In our study, intramyocardial CT decreased at a \([K^+]\) level of 9–10 mM. Tsuboi et al. showed augmentation of anisotropic conduction properties of canine ventricular muscle with increases in \([K^+]\), and Delgado et al. showed directional differences in excitability and that the margin of safety for propagation in sheep epicardial muscle was augmented when \([K^+]\) was high. Thus, our results might be explained by a directionally based difference in excitability between ventricular endocardium and ventricular epicardium and also to a difference in their sensitivity.

![Fig. 4](image-url)

Fig. 4  A representative experiment of the respiratory acidosis and high extracellular potassium on changes in CT and ERP. RA: respiratory acidosis, CT: intramyocardial conduction time, ERP: effective refractory period.
to increased $[K^+]_e^{25}$. Although ventricular action potential duration (APD) has been shown, in in vivo porcine hearts, to shorten with an increase in $[K^+]_e$, produced by infusion of KCl, APD at a similar $[K^+]_e$ level during ischemia was longer than anticipated by the rise in $[K^+]_e^{26}$. In our study, ERP at a high $[K^+]_e$ level was only slightly longer than ERP at the control $[K^+]_e$ level. Cobbe et al. and Carro et al. showed that hyperkalemia shortened the APD but lengthened the ERP (post-repolarization refractoriness)$^{27,28}$.

**Acidosis, CT, and ERP**

Regardless of the conditions, we observed little change in intramyocardial CT, regardless of how acidosis was induced. Vorperian et al. showed, in anesthetized dogs, that when arterial pH was reduced to $6.70 \pm 0.4$ by increasing the fraction of inhaled CO$_2$ to 40%, epicardial transverse CV fell by $16 \pm 8\%$, whereas epicardial longitudinal CV did not change. In contrast, when the same degree of acidemia was produced by HCl infusion, longitudinal CV fell by $8 \pm 7\%$, coincident with a rise in serum $[K^+]_e^{29}$. We measured intramyocardial CT from the subendocardium to subendocardium, so it is possible that the discrepant results are due to a directionally based difference in excitability between ventricular endocardium and epicardium, to a difference in sensitivity to acidosis between ventricular endocardium and epicardium, and to the lesser degree of acidosis produced in our study. Kagiyama et al. reported that ADP increased under MA (pH 6.5) but that it did not change under RA (pH: 6.5) at $[K^+]_e$, 5.4 mM$^{19}$. Henry et al. showed, in patch-clamp experiments, both inhibition of the transient outward $K^+$ current and activation of ATP-sensitive $K^+$ current during simulated ischemia$^{29}$. Komukai et al. showed, also in patch-clamp experiments, that acidosis decreased steady-state current leading to increased APD and increased inwardly rectifying chloride currents leading to decreased resting membrane potential$^{31}$. Bethell et al. showed, in Langendorf-perfused ferret heart, that MA and RA first lengthened then shortened APD$^{32}$. We did not see a change in the ERP in either the MA or RA condition at a normal $[K^+]_e$ level. However, this could be due to the lesser degree of MA established in our animals (arterial pH = 7.17) than in animals in previously reported studies. It could also be due to the balance between inhibition of the transient outward $K^+$ current and activation of the ATP-sensitive $K^+$ current established in our animals.

**Combined effects of high $[K^+]_e$ and acidosis on ventricular CT and the ERP**

In our study, high $[K^+]_e$, together with acidosis, either MA or RA, increased the intramyocardial CT significantly, but high $[K^+]_e$, together with acidosis did not affect the ERP significantly. Kagiyama et al. showed that the conduction slowing induced by acidosis was greater when potassium was 9 mM or 13 mM than when potassium was 5.4 mM because of changes in the resting membrane potential-dV/dt$_{max}$ relation$^{18}$. They also showed an increase in APD in the presence of MA at potassium levels of 9 mM and 13 mM. The discrepancy between the changes in ERP reported by Kagiyama et al. and those we observed may be related to the lesser degree of MA (arterial pH = 7.06) we produced, the directionally based difference in excitability between ventricular endocardium and epicardium, or the difference in sensitivity to acidosis between ventricular endocardium and epicardium$^{25}$. Another possibility is the balance between inhibition of the transient outward $K^+$ current and activation of the ATP-sensitive $K^+$ current established in our animals.

Therefore, the effects of acute ischemia on slowing of intraventricular conduction can be mimicked in part by the combined effects of extracellular acidosis and an increase in $[K^+]_e$.

**Study limitations**

Our findings should be interpreted in light of the study limitations. It is possible that hemodynamic changes induced by the MA or RA influenced our experimental results. In addition, the number of animals in each experimental group was small.

**Conclusion**

The fall in pH that occurs with myocardial ischemia enhances conduction slowing induced by the concomitant rise in $[K^+]_e$.

**Conflict of interest**

The authors have no financial conflicts of interest to report.

**References**


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