Role of ATP-Sensitive K⁺ Channel on ECG ST Segment Elevation During a Bout of Myocardial Ischemia
A Study on Epicardial Mapping in Dogs

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Background. ATP-sensitive K⁺ channels are activated when the myocardium becomes ischemic. However, the role of the ATP-sensitive K⁺ current in the emergence of ECG ST changes during ischemia remained unclarified.

Methods and Results. The left anterior descending coronary artery (LAD) was cannulated and perfused with arterial blood from the carotid artery through a bypass tube in 8 anesthetized, open-chest dogs. An array of 60 unipolar electrodes mounted on a sock was used to record epicardial electrograms of the whole heart. Pinacidil (10 μg·kg⁻¹·min⁻¹), an ATP-sensitive K⁺ channel opener, was infused into the bypass tube for 2 minutes, and the electrograms were recorded before and after the infusion. The elevation of the ST segment and the increase of QTST area were observed spatially over the LAD-perfused region. At the electrode showing the largest ST segment elevation, the activation recovery interval, an index of action potential duration, was shortened from 202±9 to 111±18 milliseconds (P<.001). These electrographic changes were similar to those noted in 2-minute coronary occlusion (n=8). The extent of ST segment elevation during coronary occlusion was attenuated after the intravenous pretreatment with glibenclamide (0.3 mg/kg), a blocker of the KATP channel (n=5).

Conclusions. The findings of this study suggest that the activation of ATP-sensitive K⁺ channels during a bout of acute myocardial ischemia plays an important role in the emergence of ECG ST elevation.

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Key Words • glibenclamide • pinacidil • ST segments • ischemia • mapping

The role of ATP-sensitive K⁺ channels in the regulation of cardiovascular function during myocardial ischemia has recently been paid much attention clinically as well as experimentally.¹⁻¹⁸ Namely, ischemia activates ATP-sensitive K⁺ channels through intracellular metabolic alterations such as an increase in ADP²⁻³ and/or a decrease in pH⁴ and ATP.⁵⁻⁶ In experiments using microelectrodes, the activation of ATP-sensitive K⁺ channels has been shown to shorten the action potential duration.⁷⁻¹¹ However, the effects of ATP-sensitive K⁺ channels on the configuration of electrograms in the in situ beating heart remained unelucidated. The goal of this study was to examine the effects of intracoronary administration of pinacidil, an ATP-sensitive K⁺ channel opener,⁹ on epicardial electrograms in dogs and to compare these electrographic changes with those observed during a burden of acute myocardial ischemia. In addition, we examined the effects of glibenclamide, a blocker of ATP-sensitive K⁺ channels,¹¹ on electrograms after coronary occlusion to clarify the role of the KATP channel in the genesis of ischemic ECG ST changes.

Methods

Instrumentation
Twenty-two mongrel dogs (weight, 11 to 18 kg) were anesthetized with an intravenous administration of 30 mg/kg sodium pentobarbital. Under artificial ventilation with room air supplemented with oxygen (3 to 5 L/min), the thorax was opened in the fifth intercostal space, the pericardium was opened, and a pericardial cradle was made to support the heart at an appropriate position. The sinus node was crushed, and the right atrium was paced at a cycle length of 400 milliseconds. After an intravenous bolus administration of heparin (5000 IU), the left anterior descending artery (LAD) was cannulated and perfused with arterial blood from the carotid artery through a bypass tube. An electromagnetic flow probe and a pressure line to measure the coronary blood flow and coronary perfusion pressure were placed along the tube proximal to the cannulating site. The whole heart was wrapped up in an array of 60 unipolar electrodes. These electrodes were made of fine silver wires (0.005-in. diameter) that were insulated except at the point of attachment. The electrode array had six rows and 10 columns (A through J, Fig 1). All
Recording electrodes were referenced to the Wilson central terminal, and multichannel electrograms were sampled every millisecond using a multiplexed data recording system (CD-0055, Chunichi Denshi, Nagoya, Japan).19,20

**Experimental Protocol**

**Effects of intracoronary infusion of pinacidil and comparison with coronary occlusion.** Pinacidil was infused into the bypass tube of the LAD at a rate of 10 μg·kg⁻¹·min⁻¹ (30 mL/hr) for 2 minutes using an infusion pump (model SP-100, JMS, Hiroshima). The drug was dissolved in 0.1N HCl (pH was adjusted to 4.0 by adding 0.1N NaOH) and was diluted with distilled water. Epicardial electrograms, coronary blood flow, and coronary perfusion pressure were recorded just before the infusion, at the end of the infusion, and 15 minutes after the cessation of the infusion in 8 dogs. Then, 7 of 8 dogs were also used in the following experiments: Coronary flow through the bypass was ceased in 4 dogs, and pinacidil was infused into the bypass after an intracoronary infusion of glibenclamide in 3.

Myocardial ischemia was induced by clamping the bypass tube in 8 dogs. Epicardial electrograms were recorded before and 2 minutes after the clamping.

**Effects of glibenclamide.** Forty-eight milligrams of glibenclamide (Sigma Chemical Co, St. Louis, Mo) was dissolved in 0.2 mL dimethyl sulfoxide and was adjusted by 0.1 mol/L phosphate buffer solution. Glibenclamide was infused into the LAD bypass tube at a speed of 60 mL/hr or 10 μg·kg⁻¹·min⁻¹ in 5 dogs. After 5 minutes of infusion, pinacidil was infused into the LAD bypass tube at a rate of 10 μg·kg⁻¹·min⁻¹. Epicardial electrograms were recorded 2 minutes after the beginning of pinacidil infusion.

In another 8 dogs, LAD occlusion for 2 minutes was performed twice before and two times after an intravenous infusion of vehicle (n=3; 0.1 mol/L phosphate buffer solution plus 0.025 mL dimethyl sulfoxide; total, 100 mL) or glibenclamide (n=5; 0.3 mg/kg,12 100 mL). Each occlusion was performed after a pause of 10 minutes except that the third occlusion was done 20 minutes after the infusion of vehicle or glibenclamide. Epicardial electrograms were recorded just before and at the end of the each occlusion.

**Analysis of Multichannel Epicardial Electrograms**

A root mean square voltage versus time curve based on all leads was plotted to determine visually both the onset and offset of QRS and the end of the T wave.21 The flat portion of the PR segment was defined as the zero level. The amplitude of the ST segment was measured at 0.04 seconds after the offset of QRS. QRST area (AQRST) was calculated by integrating the electrogram over the QRST interval. Epicardial activation sequence was determined using the time of minimum derivative of each QRS.21 The earliest activation time measured on the cardiac surface was assigned to time zero, and an isochron map was constructed. The activation recovery interval was defined as the time interval from the minimum derivative of the QRS to the maximum derivative of the T wave.22

**Statistical Analysis**

Quantitative data are expressed as mean±SD. Statistical analysis was performed with paired and unpaired t tests. A value of P<.05 was considered significant.

**Results**

**Effects of Pinacidil**

**Activation sequence.** Fig 2A illustrates activation sequence maps before (control) and after pinacidil infusion (pinacidil) in representative dog h. A star indicates the site of epicardial breakthrough. There were no remarkable differences in activation sequences between control and pinacidil infusion in all 8 dogs as represented in Fig 2A.

**ST segment and QRST area.** ST maps and QRST area maps before and after pinacidil infusion, 15 minutes after the cessation of the infusion, and pinacidil infusion after glibenclamide in a representative dog (dog a) are shown in Fig 3A. Solid and dotted lines indicate positive and negative isopotential or isooarea lines, respectively. Two representative tracings of the mapped 60 unipolar electrograms, one (lead C) from the perfusion area of the LAD territory and the other (lead H) from the left circumflex artery (LCX) territory, are also presented in Fig 3A. After pinacidil, the ST segment elevated concomitantly with the increase of the QRST area on the LAD-perfused region. These changes were attenuated by the intracoronary pretreatment with glibenclamide.

At each lead, differences of ST segments and QRST areas were obtained by subtracting control values from values after pinacidil to evaluate the net effect of pinacidil. Table 1 represents subjects' characteristics of the leads and the extent of the maximal ST and QRST differences. The elevation of the ST segment and the increase of QRST area after pinacidil were consistently observed topologically over the LAD-perfused region in all dogs; however, the site of the maximum ST elevation was not identical with that of the maximal increase of QRST area. Fifteen minutes after the cessation of pinacidil infusion, changes of the ST segment and QRST area disappeared. Changes after pinacidil...
infusion were attenuated by the intracoronary pretreatment with glibenclamide (Table 1, n = 5).

**Activation recovery intervals.** At the electrode site showing the largest ST segment elevation after pinacidil, activation recovery intervals were measured before and after pinacidil infusion. Pinacidil significantly shortened the activation recovery intervals from 202±9 to 111±18 milliseconds (P<.001, Fig 4A).

**Hemodynamic change.** After pinacidil, coronary blood flow significantly increased from 20±6 to 40±8 mL/min (P<.01) and mean coronary perfusion pressure significantly decreased from 60±12 to 53±6 mm Hg (P<.05). These changes in coronary blood flow and coronary perfusion pressure disappeared 15 minutes after cessation of the pinacidil infusion (20±5 mL/min and 57±11 mm Hg, respectively).

**Effects of Myocardial Ischemia**

Fig 2B shows the activation sequence maps just before and 2 minutes after coronary occlusion. The effect of pinacidil on the activation sequence map of this particular dog is shown in Fig 2A. The delay of the ventricular conduction was observed in the LAD-perfused region as indicated by an arrow. Such conduction delay in the ischemic region was noted in 4 of 8 dogs (50%). Both ST segment elevation and the increase of QRST area were consistently observed over the LAD-perfused region after the coronary occlusion in all 8 dogs—phenomena similar to those after pinacidil infusion. At the electrode site showing the greatest ST segment elevation, the activation recovery intervals significantly decreased from 183±14 to 131±15 milliseconds (P<.001) after coronary occlusion (Fig 4B).

**Similarities in Electrophysiological Events Between Ischemia and KATP Opening**

In a representative case (dog h in Fig 5A), a direct linear relation was observed between the magnitude of ST segment elevation and the shortening of activation recovery interval during ischemia or pinacidil infusion. The extent of ST elevation was larger during myocardial ischemia (closed circles) than during pinacidil infusion (open circles, Fig 5A). Similar trends were noted in Fig 5B, in which ST segment elevation and shortening of activation recovery interval were plotted on the lead showing the greatest ST segment elevation in each dog. The extent of activation recovery interval shortening by pinacidil was significantly larger than that by ischemia (91±23 vs 49±13 milliseconds, P<.001). The magnitude of ST elevation was 3.2±1.8 mV and 4.3±1.9 mV in pinacidil infusion and ischemia, respectively (NS between groups).

**Effects of Glibenclamide on Ischemia-Induced Electrographic Changes**

Fig 3B represents a typical case of ST and QRST area maps during control state, during 2 minutes of coronary occlusion, after intravenous pretreatment with glibenclamide, and during 2 minutes of coronary occlusion with the presence of glibenclamide (dog p, Table 2). Two unipolar electrograms, one (lead E4) from the perfused area of the LAD and the other (lead I4) from that of the LCx are also presented. During myocardial ischemia, the ST segment elevated concomitantly with the increase of QRST area at the LAD-perfused region. These changes are markedly attenuated after the intravenous pretreatment with glibenclamide.
FIG 3. ST maps and QRST area (AQRST) maps. A, Before (control) and after pinacidil infusion (pinacidil), 15 minutes after the cessation of the infusion (recontrol), and pinacidil infusion after glibenclamide (glibenclamide+pinacidil) in representative dog a; B, during control state (control), 2 minutes of coronary occlusion (ischemia), after intravenous pretreatment with glibenclamide (glibenclamide), and 2 minutes of coronary occlusion with the presence of glibenclamide (glibenclamide+ischemia) in representative dog p. Two of the 60 electrograms, one (left) from the territory of the left anterior descending artery and another (right) from the territory of the left circumflex artery, are displayed. Solid and dotted lines represent positive and negative isopotential or isoarea lines, respectively.

The lead showing the greatest ST difference at the first coronary occlusion, which was always within the LAD-perfused region, was selected in each dog, and the magnitudes of the ST difference at four repetitive occlusion periods were measured (Table 2). There was no obvious difference in the degree of ST elevation in 3 dogs receiving the vehicle (dogs t through v), but ST elevation by coronary occlusion after an intravenous pretreatment with glibenclamide was consistently attenuated in all 5 dogs (dogs o through s). The increase in
TABLE 1. Site (Lead) and Magnitude of Maximal Changes in ST Elevation and QRST Area After intracoronary Infusion of Pinacidil and Magnitude After Intracoronary Infusion of Pinacidil With Glibenclamide

<table>
<thead>
<tr>
<th>Dog</th>
<th>Lead</th>
<th>P (n=10)</th>
<th>G+P (n=5)</th>
<th>Lead</th>
<th>P</th>
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<tr>
<td>a</td>
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<tr>
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<td>ND</td>
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<td>ND</td>
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<td>+0.1</td>
<td>A₁</td>
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<td>+2.5</td>
<td>+0.3</td>
<td>E₃</td>
<td>+648</td>
<td>+27</td>
</tr>
</tbody>
</table>

P indicates pinacidil; G+P, glibenclamide plus pinacidil; and ND, not determined. Leads with maximal ST and QRST differences were located within the perfusion area of the left anterior descending artery in all dogs.

QRST areas over the LAD-perfused region after coronary occlusion was also reduced by intravenous pretreatment with glibenclamide (Table 2).

Discussion

This study demonstrates that the intracoronary infusion of pinacidil produced the ST segment elevation along with simultaneous increase in QRST area and shortening of activation recovery interval on epicardial mapped electrograms in open-chest dogs. A positive linear relation between ST elevation and activation recovery interval shortening was observed in an intervention of pinacidil infusion as well as in acute myocardial ischemia. Glibenclamide, a blocker of the ATP-sensitive K⁺ channel, attenuated the emergence of ST segment elevation in both situations of acute myocardial ischemia and pinacidil infusion. These lines of evidence pharmacologically suggest a critical role of K_{ATP} channels on the formation of ischemic ST elevations.

Recently, intracoronary infusion of a large amount of glibenclamide (50 μg·kg⁻¹·min⁻¹) was shown to reduce coronary blood flow significantly and to elevate the ST segments. In the present study, we did not observe any ST elevation after intracoronary (10 μg·kg⁻¹·min⁻¹) or intravenous (0.3 mg/kg) infusions of glibenclamide. The smaller dosage might maintain physiologically adequate coronary perfusion despite some increases in coronary resistance.

The cell-attached, patch-clamp technique on a single ventricular myocyte of guinea pig heart demonstrated marked shortening of the action potential or activation of K_{ATP} after the administration of pinacidil as well as in the presence of metabolic derangements. Yan et al. recently questioned the role of K_{ATP} as the major cause of action potential shortening in ischemia of an isolated blood-perfused papillary muscle because of a clear dissociation among net cellular K⁺ loss, tissue ATP levels, and action potential shortening during hypoxia and ischemia. Since the effects of glibenclamide on ischemia-induced action potential shortening were not documented in isolated papillary muscle experiments, the role of K_{ATP} in repolarization during ischemia remained unclarified. Furukawa et al. demonstrated that ATP-sensitive K⁺ channels are activated more in epicardial cells than in endocardial cells during a small reduction of intracellular ATP. Thus, the ST segment elevation observed during acute myocardial ischemia may at least in part due to the different activation of ATP-sensitive K⁺ current between the epicardial and endocardial sites.

ST segment elevation was noted regionally at the LAD perfusion site after the intracoronary administration of pinacidil into the LAD. Coronary blood flow toward the LAD actually doubled after pinacidil despite the consistent elevation of the ST segment. It is exper-

![Fig 4. Changes in activation recovery interval (ARI) after the infusion of pinacidil (A) and after the coronary occlusion (B) at the electrode site showing the greatest ST elevation. Bars indicate mean±SD. Activation recovery intervals significantly decreased from 202±9 to 111±18 milliseconds (P<.001) after pinacidil infusion and from 183±14 to 131±15 milliseconds (P<.001) after coronary occlusion.](http://circ.ahajournals.org/DownloadedFrom)
immently shown that ischemia-induced ST segment elevation relates to a larger shortening of action potential duration of the epicardial myocytes than that of the endocardial myocytes. Accordingly, pinacidil-induced ST segment elevation with the absence of ischemia suggests the transmural emergence of heterogeneous shortening of action potential duration.

A derivation of measures related to recovery properties from the local electrograms has been justified theoretically and experimentally.\(^{22,24,25}\) Spatial and temporal correspondences between action potential duration and activation recovery interval was noted experimentally in studies on cycle length changes,\(^{22}\) norepinephrine infusion,\(^{22,24}\) sympathetic nerve stimulation,\(^{22,24}\) or myocardial ischemia.\(^{24}\) Thus, we believe that the reduction of activation recovery intervals after pinacidil or myocardial ischemia in the present in vivo study relates intimately to the shortening of action potential duration.

During ischemia, the evolution of marked ST elevation accompanies concomitant delay in the conduction velocity.\(^{13,26}\) Activation of the ATP-sensitive K\(^+\) channel was noted in the condition of extracellular accumulation of K\(^+\) during the early phase of ischemia,\(^{13-15}\) which invariably results in the delay in conduction velocity.\(^{13}\) Since pinacidil in the present study did increase coronary blood flow, any increase of effluent K\(^+\) due to K\(_{ATP}\) activation may be washed away immediately. Accordingly, apparent changes of the ventricular activation sequence were not observed in the present pinacidil study.

In the early stages of ischemia, ST segment elevation related largely to TQ segment depression,\(^{17}\) which is caused by a depolarization of the resting membrane potential because of the extracellular accumulation of K\(^+\), especially in the ischemic zone. However, from the shortening of activation recovery interval and the in-

### Table 2. Site (Lead) and Magnitude of Maximal Changes in ST Elevation and QRST Area at Four Repetitive Occlusion Periods

<table>
<thead>
<tr>
<th>ST Difference (mV)</th>
<th>QRST Difference (mV · milliseconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Control</strong></td>
</tr>
<tr>
<td><strong>Dog</strong></td>
<td><strong>Lead</strong></td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>E(_5)</td>
</tr>
<tr>
<td></td>
<td>E(_4)</td>
</tr>
<tr>
<td></td>
<td>E(_4)</td>
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<tr>
<td></td>
<td>D(_2)</td>
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<td></td>
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<td></td>
<td>D(_3)</td>
</tr>
<tr>
<td>Vehicle</td>
<td>D(_3)</td>
</tr>
<tr>
<td></td>
<td>D(_2)</td>
</tr>
</tbody>
</table>

G indicates glibenclamide; V, vehicle; 1st, 2nd, 3rd, and 4th indicate 1st, 2nd, 3rd, and 4th occlusions.
crease of QRST area, the action potential duration of the epicardium actually shortened in the presence of myocardial ischemia. A slope of the relation between ST segment elevation and activation-recovery interval shortening was larger in cases of myocardial ischemia than that of pinacidil infusion, which may represent the functioning of additional factors for the ischemia-induced ST elevation, including the increased amount of extracellular K+.

In fact, it is likely that the activation of the K<sub>ATP</sub> channel during ischemia elicits the accumulation of extracellular K<sup>+</sup>, which elevates the ST segment via decreasing the resting membrane potential. Therefore, the inhibitory effect of glibenclamide on ST segment elevation after coronary occlusion might be attributed not only to the diminution of the shortening of action potential duration but also to the reduction of K<sup>+</sup> efflux from the myocytes.

Accordingly, the present study demonstrated that the ST segment elevation during a bout of acute myocardial ischemia is closely related to the activation of ATP-sensitive K<sub>ATP</sub> channels. The extent of K<sub>ATP</sub> opening, in other words, the extent of action potential shortening, was measurable regionally on the body surface unipolar ECG. Namely, regional changes in the activation recovery interval may provide further insight into the pathologic ECG abnormalities related to myocardial ischemia.

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