Continuous Coronary Venous K\(^+\) Monitoring During Myocardial Ischemia in Swine Hearts

Ichiro Watanabe\(^1\) and Leonard S. Gettes\(^2\)

\(^1\)Division of Cardiology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan
\(^2\)Division of Cardiology, Department of Medicine, University of North Carolina at Chapel Hill, NC, USA

**Background:** Myocardial ischemia causes accumulation of extracellular myocardial K\(^+\) ([K\(^+\)\(_e\)]. However, the relation between [K\(^+\)\(_e\)], and local coronary venous K\(^+\), i.e., K\(^+\) in the great coronary vein ([K\(^+\)\(_{gcv}\)]) has not been established. To determine the sensitivity of [K\(^+\)\(_{gcv}\)] as a marker of myocardial ischemia, we continuously measured [K\(^+\)\(_e\)], using intramyocardial K\(^+\)-selective plunge electrodes, and [K\(^+\)\(_{gcv}\)], using a catheter-tip K\(^+\) electrode inserted into the great cardiac vein, during two types of ischemia.

**Methods and Results:** In in-situ pig hearts, ischemia was induced by implementing a progressive decrease in carotid-to-left anterior descending artery (LAD) shunt flow from 40 to 0 mL/min at constant heart rate (100–130/min) and a progressive increase in heart rate from 100 to 160 beats/min at the threshold flow. The progressive decrease in LAD flow to 5 mL/min caused parallel increases in [K\(^+\)]\(_e\), (from 3.87 ± 0.37 to 8.65 ± 1.13 mM) and [K\(^+\)]\(_{gcv}\), (from 3.87 ± 0.37 to 4.84 ± 0.43 mM). However, below 5 mL/min, [K\(^+\)\(_{gcv}\)] failed to reflect the increase in [K\(^+\)]\(_e\), and often decreased. The progressive increase in heart rate at the threshold flow caused parallel changes in [K\(^+\)]\(_e\), (from 4.08 ± 0.36 to 4.87 ± 0.14 mM, n = 3) and [K\(^+\)\(_{gcv}\)], (from 3.08 ± 0.42 to 4.18 ± 0.43 mM). The verapamil- and propranolol-induced changes in [K\(^+\)\(_e\)], during low-flow ischemia were reflected by changes in [K\(^+\)\(_{gcv}\)].

**Conclusions:** Change in [K\(^+\)\(_{gcv}\)] is a sensitive marker of myocardial ischemia, except at very low coronary flow. Thus, [K\(^+\)\(_{gcv}\)] can be used to detect early myocardial ischemia.

**Key words:** myocardial ischemia, extracellular myocardial K\(^+\), coronary venous K\(^+\) (J. Nihon Univ. Med. Ass., 2017; 76 (2): 59–67)

**Introduction**

Acute myocardial ischemia results in a variety of ionic, electrical, and mechanical alterations. These include (1) a decrease in energy-rich substrates, (2) an increase in extracellular potassium, (3) a decrease in extracellular and intracellular pH, (4) a decrease in resting membrane potential and shortening of action potential duration, (5) slowing of conduction, (6) TQ-ST segment deviation, and (7) decreases in the rate and magnitude of muscle fiber shortening. Previously, we examined the sensitivities of extracellular potassium ([K\(^+\)\(_e\)], extracellular pH (pH\(_e\)), local activation, intramural and epicardial TQ-ST segments, monophasic action potential duration (MAPD), and myocardial fiber shortening in response to graded reductions in left anterior descending artery (LAD) flow in open-chest pigs and showed the threshold LAD flow for the initial change in each variable. These variables responded to threshold decreases in flow in the following order: mid-myocardial [K\(^+\)], pH\(_e\), and TQ-ST segment; subepicardial [K\(^+\)], and TQ-ST segment; segmental shortening; local activation and epicardial TQ-ST segment; and epicardial MAPD. We also examined the effects of calcium channel blocker and \(\beta\)-adrenergic-blocking agent on these variables. However, these variables cannot be measured clinically. Therefore, in the study described herein, we measured mid-myocardial [K\(^+\)], and coronary venous K\(^+\) ([K\(^+\)\(_{gcv}\)], simultaneously in in-situ pig hearts and then examined changes in [K\(^+\)\(_e\)], and [K\(^+\)\(_{gcv}\)], during graded coronary flow reduction and pacing-induced myocardial ischemia at the reduced LAD flow. We also examined the effects of calcium channel blocker and \(\beta\)-adrenergic-blocking agent on [K\(^+\)], and [K\(^+\)\(_{gcv}\)].

**Methods**

**In-situ pig heart preparations:** Preparation of in situ hearts in open-chest pigs was similar to that reported previously. Eleven domestic swine of either sex and weighing 20–30 kg were anesthetized with sodium pentobarbital (25 mg/kg), and this was followed by \(\alpha\)-chloralose, as needed. Mechanical ventilation and oxygen supplementation were provided via an endotracheal tube attached to a Harvard respirator. Arterial blood gases were monitored, and appropriate ventilator adjustments were made to maintain arterial...
PO$_2$ at >80 mmHg and pH at 7.35–7.45. Catheters were placed in the femoral artery for blood pressure monitoring and blood sampling and in the femoral vein for blood sampling and administration of fluids and drugs. Core temperature was monitored continuously with a temperature probe (Yellow Springs Instrument Co., Yellow Springs, OH, USA). A heating blanket was used to maintain each animal’s body temperature at 36–37°C. The heart was exposed via median sternotomy and suspended in a pericardial cradle. A site midway along the length of the LAD was selected for cannulation and dissected from surrounding tissue. The epicardial margin between ischemic and non-ischemic tissues was identified by brief occlusion of the vessel at this site, and 3–4 K$^+$-selective electrodes were selected for cannulation and dissected from surrounding tissue. The epicardial margin between ischemic and non-ischemic tissues was identified by brief occlusion of the vessel at this site, and 3–4 K$^+$-selective electrodes were placed at various locations in the mid-myocardium in the center of the ischemic zone, defined as the region >10 mm inside the visible cyanotic border. A single K$^+$-selective electrode was placed in the normal (non-ischemic) zone for measuring [K$^+$]$_{i}$, and an intravascular K$^+$-selective electrode was placed in the great cardiac vein via the right external jugular vein for measurement of venous [K$^+$]$_{ve}$ (Fig. 1).

After electrode placement, systemic heparin (10,000 U bolus followed by 2,000 U/hr) was administered. A carotid artery-to-LAD shunt was created, as previously described. Placement of the shunt in the LAD took approximately 2–3 minutes, but the LAD flow was stopped for 5 minutes because successive occlusions produced similar metabolic and electrical changes. This carotid-coronary shunt was routed through a constant-flow roller pump, which permitted a controlled reduction in flow from a control value of 1.2–1.5 mL/kg body weight/min (30–50 mL/min) to zero. Heparin (3,000 U bolus followed by 7,000 U/hr) was administered to ensure cannula patency. Atrial pacing was used to maintain heart rate at 100–120 beats/min. Arterial blood pressure and the lead II electrocardiogram were recorded continuously during each experiment with a 12-channel Graphtec Linear recorder (Graphtec, Yokohama, Japan).

The care of animals used in this study conformed to the Position of the American Heart Association on Research Animal Use and was done in accordance with accepted guidelines for the care and treatment of experimental animals at the University of North Carolina. Approval for the study was obtained from the University of North Carolina at Chapel Hill’s Institutional Animal Use and Care Committee.

**Ion-selective electrodes:** Ion-selective plunge electrodes were fashioned and calibrated by methods described previously. Briefly, one end of a Teflon-coated silver wire (0.007 in diameter) was chloridized by soaking it in sodium hypochlorite. The end was then covered with a cellulose acetate-titanium dioxide sponge. K$^+$-selective electrodes were made by covering the sponge with a polyvinylchloride-valinomycin-based membrane. Reference electrodes were fashioned in an analogous manner but lacked the ion-selective membrane. One K$^+$-selective electrode along with a single reference electrode constituted an electrode pair (Fig. 2, left). Electrodes were calibrated before each experiment in standard solutions of 3 and 10 mmol/L KCl. Only electrodes that showed baseline stability to <1 mV/hr drift and 95–105% of the predicted Nernstian slope (56- to 62-mV shift per decade change in K$^+$ activity at room temperature) were used. The electrodes were threaded into a 19-gauge hypodermic needle, which was used to insert the pair into the mid-myocardium to a depth of 4–6 mm. The needle was then withdrawn, leaving the electrodes embedded in the myocardium. Up to 4 electrode pairs were used in each experiment. After insertion, *in-vivo* performance of the K$^+$-selective electrodes was tested by methods described previously.

An intravascular K$^+$-selective electrode was fashioned and calibrated by methods described previously. In brief, a disk from the valinomycin matrix membrane was placed on the tip of the medical grade polyvinyl chloride tubing which had an outer diameter 1.5 mm and an inner diameter of 1.0 mm, and then fused to it by application of 1 or 2 drops of tetrahydrofuran to the perimeter of the disk. The electrode was dried in air for 10–15 minutes and then filled with 0.5 KCl saturated with silver chloride. A chloridized silver wire was inserted into the lumen of the tubing and to a silicone rubber collar (Fig. 2, right). The collar also housed a metal connector for the cable leading to the recording device. A standard Ag-AgCl electrode containing 3 M KCl saturated with AgCl and having an outer diameter of 1.0 mm was
used for the reference electrode. At the end of each experiment, the electrodes were removed from the heart and re-tested in vitro to confirm stable function throughout the experiment.

**Experimental protocol:** The in-situ heart preparations were allowed to stabilize for at least 60 minutes after placement of the K⁺-selective electrodes. In 8 of the 11 hearts, coronary blood flow through the roller pump was reduced in a stepwise fashion at 5-minute intervals as follows: 40, 30, 20, 15, 10, 5, 2.5, and 0 mL/min. This graded reduction was followed by a return to the control flow rate. Our criteria for threshold flow change in [K⁺]ₑ was an increase in [K⁺]ₑ > 0.3 mM. In 3 of the 11 hearts, we increased the atrial pacing rate at the threshold flow rate, i.e., the flow rate at which [K⁺]ₑ increased >0.3 mM from the baseline [K⁺]ₑ level. In 4 of the 11 hearts, verapamil was administered intravenously at a loading dose of 0.2 mg/kg followed by 6.5 μg/kg/min after the first reduction in coronary flow, and in 3 other hearts, propranolol was administered intravenously at a loading dose of 0.4 mg/kg followed by 3 μg/kg/min after the first reduction in coronary flow. In 1 of the 11 heart, coronary flow was reduced in a graded manner twice, with each series of reductions separated by 50 minutes for examining the reproducibility of [K⁺]ₑ and [K⁺]ᵝcv during successive coronary flow reduction.

**Data collection and analysis:** The amplified signals from all electrodes, along with the lead II electrocardiogram, were digitized (Phoenix Data analog-to-digital converter, Middle town, PA, USA) and simultaneously sampled (1,000 samples per second) every 15 seconds during myocardial ischemia by a MicroVAX II/GPX computer (Digital Equipment Corp., Maynard, MA, USA). The millivolt (mV) readings from the K⁺-sensitive electrodes were converted to [K⁺]ₑ and [K⁺]ᵝcv.

**Statistical Analysis**

Data are presented as mean ± SEM unless otherwise indicated. Differences in the threshold coronary flow for initial change in each parameter were analyzed by Mann-Whitney U test. All statistical analyses were performed with StatView 5.0 software (SAS Institute, Cary, NC, USA), and P < 0.05 was considered significant.

**Results**

Changes in [K⁺]ₑ and [K⁺]ᵝcv with graded reductions in coronary flow: The changes in [K⁺]ₑ and [K⁺]ᵝcv with the reductions in coronary flow in a representative case are graphed in Fig. 3.

In the 8 hearts first subjected to stepwise reductions
in coronary flow. As shown in Fig. 4, the $[K^+]_{e}$ concentration in the ischemic zone began to increase at a flow rate of 20 mL/min, and it increased further with decreases in the flow rate to 0 mL/min. $[K^+]_{gcv}$ also began to increase at a flow rate of 15 mL/min, and it also increased with decreases in the flow rate until a rate of 2.5 mL/min was reached. The increases in $[K^+]_{gcv}$ were small, and despite the further increases

| Table 1  | Comparison of intramyocardial extracellular and great cardiac vein K⁺ during graded coronary flow reduction |
|-------------------------------|-------------------------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Coronary flow (mL/min) | 40 | 30 | 20 | 15 | 10 | 5 | 2.5 | 0 | Reflow |
| $[K^+]_{e}$ (mM) | 4.14 | 4.14 | 4.36* | 4.89 | 5.64 | 8.35 | 10.16 | 11.80 | 11.75 |
| (0.15) | (0.13) | (0.12) | (0.21) | (0.33) | (0.34) | (0.58) | (0.76) | (0.76) |
| $[K^+]_{gcv}$ (mM) | 4.14 | 4.14 | 4.19 | 4.32† | 4.44 | 4.73 | 4.89 | 4.98 | 6.76 |
| (0.15) | (0.13) | (0.13) | (0.10) | (0.13) | (0.18) | (0.20) | (0.37) |

$[K^+]_{e}$: intramyocardial extracellular K⁺, $[K^+]_{gcv}$: K⁺ in the great cardiac vein, number in parentheses shows standard deviation, *: $P = 0.003$ versus coronary flow of 30 mL/min, †: $P = 0.008$ versus coronary flow of 20 mL/min

| Table 2  | Effects of heart rate on the intramyocardial extracellular and great cardiac vein K⁺ |
|-------------------------------|-------------------------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Coronary flow (mL/min) | 40 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| Heart rate (beats/min) | 100 | 100 | 120 | 140 | 160 | 120 | 120 | 140 |
| $[K^+]_{e}$ IZ (mM) | 3.80 | 4.00 | 4.61 | 4.63 | 4.49 | 3.60 | 3.78 | 4.64 |
| $[K^+]_{gcv}$ (mM) | 3.80 | 3.80 | 4.10 | 4.18 | 4.10 | 3.60 | 3.60 | 3.81 |
| $[K^+]_{e}$ NZ (mM) | 3.80 | 3.80 | 3.87 | 3.87 | 3.95 | 3.60 | 3.60 | 3.74 |
| Coronary flow (mL/min) | 50 | 15 | 15 | 15 | 15 | 15 |
| Heart rate (beats/min) | 120 | 140 | 120 | 140 | 120 | 140 | 120 | 140 |
| $[K^+]_{e}$ IZ (mM) | 3.60 | 3.78 | 4.64 | 3.60 | 3.60 | 3.81 | 3.60 | 3.74 |
| $[K^+]_{gcv}$ (mM) | 3.60 | 3.60 | 3.60 | 3.60 | 3.60 | 3.60 | 3.60 | 3.60 |
| $[K^+]_{e}$ NZ (mM) | 3.60 | 3.60 | 3.60 | 3.60 | 3.60 | 3.60 | 3.60 | 3.60 |

$[K^+]_{e}$ IZ: intramyocardial extracellular K⁺ at ischemic zone, $[K^+]_{e}$ NZ: intramyocardial extracellular K⁺ at non-ischemic zone, $[K^+]_{gcv}$: K⁺ in the great cardiac vein

In coronary flow. As shown in Fig. 4, the $[K^+]_{e}$ concentration in the ischemic zone began to increase at a flow rate of 20 mL/min, and it increased further with decreases in the flow rate to 0 mL/min. $[K^+]_{gcv}$ also began to increase at a flow rate of 15 mL/min, and it also increased with decreases in the flow rate until a rate of 2.5 mL/min was reached. The increases in $[K^+]_{gcv}$ were small, and despite the further increases
Fig. 6  Representative experiment of the effect of verapamil on the changes in intramyocardial K$^{+}$ ([K$^{+}$]$_{im}$) and great cardiac venous K$^{+}$ ([K$^{+}$]$_{gcv}$) during graded coronary flow reduction.

Fig. 7  Representative experiment of the effect of propranolol on the changes in intramyocardial K$^{+}$ ([K$^{+}$]$_{im}$) and great cardiac venous K$^{+}$ ([K$^{+}$]$_{gcv}$) during graded coronary flow reduction.

Fig. 8  Comparison of changes in intramyocardial K$^{+}$ ([K$^{+}$]$_{im}$) and great cardiac venous K$^{+}$ ([K$^{+}$]$_{gcv}$) during 2 successive graded coronary flow reduction. CBF: coronary blood flow

Fig. 9  Comparison of changes in intramyocardial K$^{+}$ ([K$^{+}$]$_{im}$) and great cardiac venous K$^{+}$ ([K$^{+}$]$_{gcv}$) during graded coronary flow reduction at baseline (left panel) and after administration of verapamil (right panel). CBF: coronary blood flow
Table 3. Effects of verapamil and propranolol on $[\text{K}^+]_{\text{e}}$ and $[\text{K}^+]_{\text{gcv}}$ during graded coronary flow reduction

<table>
<thead>
<tr>
<th>Coronary flow (mL/min)</th>
<th>40</th>
<th>30</th>
<th>20</th>
<th>15</th>
<th>10</th>
<th>5</th>
<th>2.5</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control $[\text{K}^+]_{\text{e}}$ (mM)</td>
<td>3.80</td>
<td>3.80</td>
<td>4.59</td>
<td>6.21</td>
<td>7.50</td>
<td>8.08</td>
<td>8.88</td>
<td>10.33</td>
</tr>
<tr>
<td>Control $[\text{K}^+]_{\text{gcv}}$ (mM)</td>
<td>3.80</td>
<td>3.80</td>
<td>3.95</td>
<td>4.26</td>
<td>4.59</td>
<td>4.86</td>
<td>4.77</td>
<td>4.77</td>
</tr>
<tr>
<td>Control $[\text{K}^+]_{\text{e}}$ (mM)</td>
<td>3.90</td>
<td>3.90</td>
<td>4.62</td>
<td>6.02</td>
<td>7.41</td>
<td>8.62</td>
<td>8.85</td>
<td>11.01</td>
</tr>
<tr>
<td>Control $[\text{K}^+]_{\text{gcv}}$ (mM)</td>
<td>3.90</td>
<td>3.90</td>
<td>3.90</td>
<td>3.97</td>
<td>4.54</td>
<td>4.89</td>
<td>5.08</td>
<td>5.48</td>
</tr>
<tr>
<td>Control $[\text{K}^+]_{\text{e}}$ (mM)</td>
<td>3.90</td>
<td>3.90</td>
<td>3.90</td>
<td>3.95</td>
<td>4.40</td>
<td>5.33</td>
<td>6.51</td>
<td>8.21</td>
</tr>
<tr>
<td>Control $[\text{K}^+]_{\text{gcv}}$ (mM)</td>
<td>4.03</td>
<td>4.03</td>
<td>4.03</td>
<td>4.03</td>
<td>4.03</td>
<td>4.28</td>
<td>5.19</td>
<td>5.21</td>
</tr>
<tr>
<td>Control $[\text{K}^+]_{\text{e}}$ (mM)</td>
<td>4.10</td>
<td>4.26</td>
<td>4.43</td>
<td>4.74</td>
<td>6.02</td>
<td>9.30</td>
<td>9.46</td>
<td>11.46</td>
</tr>
<tr>
<td>Control $[\text{K}^+]_{\text{gcv}}$ (mM)</td>
<td>4.10</td>
<td>4.16</td>
<td>4.16</td>
<td>4.28</td>
<td>4.86</td>
<td>4.86</td>
<td>5.09</td>
<td>5.55</td>
</tr>
</tbody>
</table>

†: $P < 0.001$ versus control, *: $P < 0.01$ versus control, ‡: $P < 0.001$ versus control, ††: $P < 0.0001$ versus control

Table 4. Indices of ischemia and the coronary flow triggering their initial changes

<table>
<thead>
<tr>
<th>$[\text{K}^+]_{\text{e}}$ (mM)</th>
<th>ph_e</th>
<th>$[\text{K}^+]_{\text{gcv}}$ (mM)</th>
<th>Activation time</th>
<th>$\Delta$TQ-ST</th>
<th>$\Delta$MAPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 0.3 mM</td>
<td>&gt; 0.03</td>
<td>&gt; 0.3 mM</td>
<td>&gt; 2 msec</td>
<td>1 mV</td>
<td>&gt; 10 msec</td>
</tr>
<tr>
<td>15.0 ± 5.5</td>
<td>15.9 ± 4.4</td>
<td>10.8 ± 5.9*</td>
<td>8.3 ± 3.6*</td>
<td>7.5 ± 2.6*</td>
<td>4.3 ± 2.4†</td>
</tr>
</tbody>
</table>

$[\text{K}^+]_{\text{e}}$ indicates mid-myocardial extracellular $\text{K}^+$; pH_e, mid-myocardial extracellular pH; $[\text{K}^+]_{\text{gcv}}$, great cardiac venous $\text{K}^+$; Activation time, intra-myocardial conduction time; $\Delta$TQ-ST, change in the epicardial TQ-ST segment; $\Delta$MAPD, change in the epicardial monophasic action potential duration.

* $P < 0.01$ vs. $[\text{K}^+]_{\text{e}}$, and pH_e; † $P < 0.01$ vs. $[\text{K}^+]_{\text{e}}$, pH_e, and $\Delta$TQ-ST; ‡ $P < 0.02$ vs. Activation time.

(unpublished data from previous study [reference 24])
coronary flow reduction. Changes in representative cases are graphed in Figs. 6 and 7. In the heart in which coronary flow was reduced in the same stepwise fashion twice in succession, the changes in \([K^+]\) and \([K^+]_{gcv}\) were similar (Fig. 8, Table 3). The changes in \([K^+]\) and \([K^+]_{gcv}\) are graphed in Figs. 9 and 10, and it can be seen in these graphs that the changes in \([K^+]\) are reflected by the changes in \([K^+]_{gcv}\) (Table 3).

**Discussion**

In a previously reported study, we compared the threshold coronary flows associated with the initial changes in ionic, electrical, and hemodynamic indices of ischemia in in-situ pig hearts, and we showed that the changes in mid-myocardial \([K^+]_{e}\), \(pHe\), and TQ-ST segment provide the most sensitive means of detecting myocardial ischemia.\(^{24}\) In an unpublished sub study, we compared the threshold coronary flow for the initial changes in \([K^+]_{gcv}\), and we found that \([K^+]_{gcv}\) was less sensitive than mid-myocardial \([K^+]_{e}\), and \(pHe\) but more sensitive than the electrical indices of ischemia (Table 4).

Harris et al. were the first group of investigators to appreciate that coronary artery occlusion is followed by an increase in potassium in the extracellular space of the area deprived of circulation.\(^{26,30}\) Later, it was shown that acute coronary occlusion leads to a fall in extracellular \(\text{pH}\) and a rise in extracellular \(\text{pCO}_2\).\(^{31,32}\) Development of catheter-tip potassium-selective electrodes by Treasure et al.\(^{27}\) and Hill et al.\(^{28}\) led to clinical measurement of coronary sinus potassium levels during coronary angioplasty, which showed a transient increase in coronary sinus potassium after deflation.\(^{33,34}\) In a clinical study in which serial coronary sinus and arterial blood sampling was performed during pacing to determine the effects of ischemia and alterations in heart rate on myocardial potassium, investigators found a significantly greater loss of myocardial potassium in patients with ischemia than in those without ischemia.\(^{35}\) Subsequent to that study, however, there was no investigation of intramyocardial extracellular potassium or the potassium concentration in the great cardiac vein during graded coronary flow reduction nor of the effect of increasing heart rate on the intramyocardial extracellular potassium and great cardiac venous potassium concentrations.

We showed in the present study that the potassium concentration in the great cardiac vein increases with severe coronary flow reductions up to 5–2.5 mL/min and that it does not increase further at zero flow. Furthermore, in 3 experiments, with increases in heart rate, \([K^+]_{gcv}\) increases at the threshold flow for the initial increase in intramyocardial \(K^+\). However, an increase in heart rate also results in a small increase in the intramyocardial potassium concentration in the normal non-ischemic zone. Ibebekk et al. also reported an increase in the coronary sinus blood potassium concentration with an increase in heart rate by 50 beats/min above the sinus rate.\(^{36}\) Therefore, the increase in the great cardiac vein/coronary sinus potassium concentration with an increase in heart rate during ischemia may be, in part, influenced by physiological change in the intramyocardial potassium concentration.

We have shown that calcium channel blocker, verapamil decreases the rise in \([K^+]_{e}\), and attenuates the fall in \(pHe\) during no-flow and low-flow ischemia.\(^{25,37}\) Another calcium channel blocker, nisoldipine also demonstrated to protection against myocardial ischemia assessed by valinomycin \(K^+\)-sensitive microelectrodes.\(^{38}\) We also showed that ATP-sensitive \(K^+\) channel opener, pinacidil decreases the rise in \([K^+]_{e}\) during no-flow ischemia.\(^{39}\) However, \(\beta\)-adrenergic-blocking agent propranolol does not affect the rise in \([K^+]_{e}\), or the fall in \(pHe\) during no-flow and low-flow ischemia when the heart rate is held constant.\(^{25,40}\) We showed that micromyocardial \([K^+]_{e}\), \(pHe\), and TQ-ST change were the most sensitive marker of myocardial ischemia than other electrical and mechanical indexes of ischemia, but these parameters were impossible to measure clinically.\(^{24}\) Furthermore, changes in TQ-ST segment became unreliable marker in the progression of ischemia because of cellular uncoupling leading to paradoxical lessening of TQ segment depression, and drugs which affect intramyocardial conduction of the ischemic myocardium affect ST segment elevation, i.e., verapamil aggravate ST segment elevation and propranolol ameliorate ST segment elevation at the same \([K^+]_{e}\) level.\(^{41,42}\) In the present study, \([K^+]_{gcv}\) may have been the best marker of ischemia.

**Conclusion:** We conclude that \([K^+]_{gcv}\) is a sensitive marker of myocardial ischemia except at very low coronary flow.

**Acknowledgments**

This research was supported by National Institutes of Health grants HL-27430 and HL-07470.

**Conflict of Interest Disclosure**

Ichiro Watanabe: None
Leonard S. Gettes: None

**References**


