Glibenclamide attenuates peaked T wave in early phase of myocardial ischemia 1

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Abstract

Objectives: ECG peaked T wave appears during the early phase of myocardial ischemia, but the underlying mechanisms remain unknown. The purpose of this study was to elucidate the role of ATP-sensitive K+ channel (KATP) in this ECG change. Methods: In 12 anesthetized, open-chest dogs, the sinus node was crushed and the right atrium was paced at a cycle length of 400 ms. The left anterior descending coronary artery was abruptly occluded for 60 s before (control) and 1.5 min after an intravenous infusion of vehicle (n = 6) or glibenclamide (1 mg/kg, n = 6), a blocker of KATP. Forty-eight epicardial electrograms were simultaneously recorded from the anterior surface of the left ventricle. The potentials at 40, 80 and 120 ms from the J point were measured, and these points corresponded to the early, middle and late phases of the T wave, respectively. Results: During the control occlusion, T wave increased time-dependently and the maximal T-wave change was noted at the end of 60 s of coronary occlusion. The extents of T-wave elevation at the early, mid and late T phases were 5.5 ± 0.5, 7.3 ± 0.8 and 11.7 ± 1.8 mV, respectively, and these T-wave elevations were significantly reduced by 33 ± 21%, 59 ± 12% and 63 ± 13%, respectively, after the pretreatment with glibenclamide but not with its vehicle. The % reductions of mid and late T by glibenclamide were significantly larger than that of early T wave (P < 0.05). Conclusions: An abrupt coronary occlusion accompanied peaked T wave as an early ECG wave change. As the extent of this T-wave elevation was attenuated by glibenclamide, the ischemia-induced alteration of ventricular repolarization can partly (60%) be explained by the modification of KATP activation.

Keywords: Potassium channel, ATP sensitive; Sulphonylureas; Myocardial ischemia; ECG

1. Introduction

It is important not to overlook early ECG abnormalities such as tall or peaked T wave for the prompt diagnosis of myocardial ischemia [1,2], because the peaked T wave frequently appears before the elevation of ST segment [3]. A mechanism of this immediate increase of T wave is assumed to be a shortening of action potential duration in the ischemic myocardium [4], but the underlying alterations of ionic channel remain unknown.

ATP-sensitive K+ channels (KATP) are activated when the myocardium becomes ischemic [5-9], and this leads to a shortening of the action potential duration [5-8]. Recently, we reported that in canine hearts this channel participates partly in the ST-segment elevation noted at 2 min of coronary occlusion [10]. The configuration of ST segment depends on alterations in phase 2 and/or resting potential of transmembrane action potential, and that of T wave depends on alterations in phase 3 [11]. Theoretically, a reduction of action potential duration should alter T-wave rather than ST-segment area, as the first ECG sign of ischemic ECG. It was postulated that the peaked T wave at the very early phase of ischemia should relate to the activation of KATP. In the present study, we analyzed early T-wave changes following coronary occlusion and studied the role of KATP in the emergence of peaked T wave using glibenclamide, a blocker of KATP [12].

2. Methods

This study conformed to the guiding principles of animal experiments in our institution. Twelve mongrel dogs 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. Arterial pressure, blood gases, and pH were monitored. The \( pO_2 \) and pH of the arterial blood were maintained at levels greater than 150 mmHg and between 7.35 and 7.45, respectively. The sinus node was crushed, and the right atrium was paced at a cycle length of 400 ms.

An abrupt 60-s occlusion of the left anterior descending coronary artery was repeated before (control occlusion) and 15 min after an intravenous infusion of vehicle (n = 6) or glibenclamide (1 mg/kg, n = 6) [13]. The \( K_{ATP} \) blocker, glibenclamide (Sigma Chemical Co, St. Louis, MO) was dissolved in a vehicle [14], consisting of 1 ml of sodium hydroxide (1 N), ethanol (100%) and polyethylene glycol (molecular weight, 200). The vehicle or drug-containing solution was diluted with 97 ml of 0.9% physiological saline solution before infusion.

An array of 48 unipolar electrodes was placed on the anterior surface of the left ventricle (Fig. 1). In Fig. 1, the numeral on the electrode array indicates the number of dogs which showed maximal T-wave change at that electrode site after LAD occlusion. Ao = aorta, PA = pulmonary artery, LAD = left anterior descending artery, LCx = left circumflex artery, RV = right ventricle, LV = left ventricle.

**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>early-T</th>
<th>mid-T</th>
<th>late-T</th>
</tr>
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<tbody>
<tr>
<td>Vehicle (n = 6)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>before</td>
<td>-0.1 ± 0.2</td>
<td>-0.4 ± 0.3</td>
<td>-3.2 ± 0.9</td>
</tr>
<tr>
<td>after</td>
<td>0.4 ± 0.3</td>
<td>-0.1 ± 0.4</td>
<td>-3.2 ± 1.1</td>
</tr>
<tr>
<td>Glibenclamide (n = 6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>before</td>
<td>0.6 ± 0.5</td>
<td>0.4 ± 0.5</td>
<td>3.7 ± 0.7</td>
</tr>
<tr>
<td>after</td>
<td>0.8 ± 0.6</td>
<td>0.6 ± 0.6</td>
<td>-2.9 ± 0.7</td>
</tr>
</tbody>
</table>

**3. Results**

Before occlusions, neither vehicle nor glibenclamide were influential on amplitude of early-T, mid-T and late-T (Table 1). Fig. 2 shows isopotential contour maps of delta early-T, mid-T and late-T at 60 s of occlusion before and after the intravenous administration of glibenclamide in a representative dog. The isopotential lines were drawn at every 2-mV interval. In the control maps, the area of positive delta T occupied the greater part of the map area and the most remarkable increase was noted at a site of lead D5. Both the peak magnitude and the size of the T-wave elevated area were attenuated after the administration of glibenclamide. Time-related changes in ST-T waves at the lead D5 during control occlusion (A) and occlusion after the pretreatment with glibenclamide (B) are superimposed in Fig. 3.

The sites of maximal T-wave increase during ischemia were located apparently in the central area of the ischemic region of the left ventricle in each dog (Fig. 1). For further analysis, we chose one electrogram representing the maximal T-wave level in each dog and plotted the time courses of the delta early-T, delta mid-T and delta late-T during a...
Fig. 2. Isopotential contour maps of delta early-T, delta mid-T and delta late-T at 60 s of coronary occlusion under control condition (control) and after pretreatment with glibenclamide (1 mg/kg i.v.) in a representative dog. Isopotential lines were drawn at 2 mV intervals. + indicates the site of maximum. Columns A to H and rows 1 to 6 represent the electrode sites which were shown in Fig. 1.

Fig. 3. Superimposed ST-T waves recorded at the ischemic region (lead D5 in Fig. 2) in 60-s coronary occlusion under control conditions (A) and after pretreatment with glibenclamide (1 mg/kg i.v., B). Arrows indicate the sites of early-T, mid-T and late-T, of which locations were 40, 80 and 120 ms from the J point, respectively.

Fig. 4. Mean values of maximal delta early-T, delta mid-T and delta late-T during a 60-s control occlusion. Values are expressed as mean ± s.d.

60 s control occlusion (Fig. 4). After the start of coronary occlusion, T wave rose progressively and the T-wave change was the peaked level at the end of occlusion. At 60 s, the mean value of the maximal delta late-T was 11.7 ± 1.8 mV, which was significantly larger than that of the maximal delta early-T (5.5 ± 0.5 mV, \( P < 0.01 \)) and that of the maximal delta mid-T (7.3 ± 1.8 mV, \( P < 0.05 \)).

The effects of the vehicle and glibenclamide on the delta Ts at 60 s after the initiation of the occlusion are summarized in Fig. 5. Glibenclamide but not the vehicle significantly reduced the increase of delta early-T, mid-T and late-T (\( P < 0.05, < 0.01 \) and \( < 0.01 \), respectively). The mean % reductions of delta early-T, mid-T and late-T were 33 ± 21, 59 ± 12 and 63 ± 13%, respectively. The reductions of delta mid-T and delta late-T were significantly larger than that of delta early-T (\( P < 0.05 \)).

Fig. 5. Effects of vehicle and glibenclamide on delta T at 60 s after the initiation of coronary occlusion. The mean values of the maximal delta early-T, mid-T and late-T before and after vehicle were 5.6 ± 1.4, 6.6 ± 2.4 and 9.3 ± 6.2 mV and 5.0 ± 1.9, 6.3 ± 2.9 and 8.3 ± 6.3 mV, respectively. These values before and after glibenclamide were 5.3 ± 2.1, 8.0 ± 3.4 and 14.0 ± 6.2 mV and 3.2 ± 1.1, 3.2 ± 1.2 and 5.0 ± 2.0 mV, respectively. There were no significant differences in delta early-T, mid-T and late-T between values before treatment (vehicle or glibenclamide i.v.). Values are expressed as mean ± s.d. C = control, V = vehicle, G = glibenclamide.
Accordingly, it seems likely that from the very early onset of myocardial ischemia activation of $K_{ATP}$ begins to produce repolarization changes which may culminate in ventricular reentrant arrhythmias.

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### References

