Mechanism of constant μ-volt level T-wave alternans – role of intracellular calcium cycling regulated by sarcoplasmic reticulum–

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ABSTRACTS
μ-Volt level T-wave alternans (μ V-TWA), which is provoked by constant high heart rate, has recently been exposed to attention as an index of the lethal ventricular arrhythmia. Alternans of action potential after abrupt cycle length shortening was abolished by caffeine and, therefore, was attributed to intracellular Ca cycling by sarcoplasmic reticulum (SR). We examined whether the alternans of action potential induced by constant high heart rate could also attributed to alternans of intracellular Ca.

Monophasic action potential (MAP) alternans was induced in dog beating heart by constant high heart rate. MAP alternans tended to appear with shorter the CL and lower the body temperature. Caffeine decrease MAP alternans in the dose dependent manner. It was concluded that μ V-TWA induced by constant high heart rate could be attributed to intracellular Ca cycling by sarcoplasmic reticulum.

INTRODUCTION
Alternans of T-wave and/or ST segment of surface ECG has been reported to be associated with various conditions such as long QT syndrome, ischemic heart disease, electrolyte abnormalities, low body temperature, administration of antiarrhythmics or sudden change of driving cycle length, and was frequently followed by ventricular tachyarrhythmias. Although the cause of T-wave alternans (TWA) was presumably attributed to the alternans of both duration and shape in ventricular action potential, precise mechanism of action potential alternans has not been completely elucidated yet.

We previously showed that alternans of the action potential duration after abrupt shortening of driving cycle length in dog Purkinje fiber was regulated by electrical restitution. On the other hand, alternans of action potential shape after abrupt shortening of driving cycle length has been attributed to the alternans of intracellular calcium concentration governed by sarcoplasmic reticulum. These results could be applied to the alternans of monophasic action potential, LV pressure or T-wave alternans induced by abrupt cycle length shortening in intact beating heart.

μ-Volt level T-wave alternans (μ V-TWA) has recently been exposed to attention as an index of the lethal ventricular arrhythmia. μ V-TWA is provoked by constant high heart rate over 105/min without abrupt change of driving cycle length. Constant high heart rate is attained by either cardiac pacing, drugs or exercise in clinical evaluation of μ V-TWA. However, it is not known whether μ V-TWA could be attributed to alternans of action potential. If it was the case, what is the mechanism
of action potential alternans induced by constant high heart rate?

PURPOSES

The purpose of this study is firstly to examine whether the microscopic alternans of both action potential and T-wave could be induced by constant high heart rate in intact beating heart. Secondly, to clarify the role of the SR, which played critical role in the genesis of alternans after abrupt cycle length shortening, in microscopic MAP alternans in relation to V-TWA under the condition of constant high frequency pacing.

METHOD

Twenty-four adult mongrel dogs of either sex were anesthetized by sodium pentobarbital 30mg/kg IV and midsternal incision was made in each. The dogs were ventilated with a respirator (Shinano Inc, Tokyo, Japan). Heart of each dog was suspended in pericardial cradle. Arterial pH and PCO2 were measured periodically and maintained at stable levels by adjusting ventilatory volume.

Suction electrodes with flexible silicone legs and monopolar electrodes were applied on epicardium in the areas of LV base and of LV apex using the technique described previously. MAP was also recorded from endocardium in the LV apex using Franz catheter simultaneously with LV pressure (LVP).

The heart is driven for 90 beats with constant CL of 500, 400, 300, 275, 250, 225 and 200msec by bipolar electrode placed on LV apex with cooling the body temperature (36°C, 34°C, and 32°C). The area under each waveform is calculated by 10 msec width strips from its upstroke. The areas of consecutive 2 waveforms in the same timing from their upstroke are made to be A and B, and

\[ \frac{(A-B)}{B} \times 100 \] (where, A>B) is defined as alternans amplitude (TWA-A, MAP-A and LVP-A).

MAP duration (MAPD) is defined as the time from the upstroke to the end of MAP as intersection of the maximum slope tangent and base line. Caffeine, which is thought to abolish Ca cycling by the SR, is administered in the dosage of 10, 20 and 30mg/kg.

RESULTS

In seven dogs, we examined the relation between TWA and MAP alternans. Positive alternans was arbitrarily defined as amplitude greater than 0.2%.

Alternans of such magnitude couldn't be detected by eye at all. MAP alternans tended to appear with the shorter the CL and lower the body temperature. The MAP-A was greater in the base than apex. TWA showed the similar characteristics with MAP alternans, however, required both shorter CL and lower body temperature than MAP alternans.

In seventeen dogs, we examined the effect of caffeine on alternans of both MAP and LVP. Although caffeine dose not change MAPD in any dosage, both MAP-A and LVP-A are made to decrease by caffeine in the dose dependent manner. (The data measured at the timing of 60% of MAPD in CL of 200msec are shown in the table).

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>10mg/kg</th>
<th>20mg/kg</th>
<th>30mg/kg</th>
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<tbody>
<tr>
<td>MAP-A</td>
<td>29 ± 11</td>
<td>13 ± 4*</td>
<td>7 ± 2**, 2 ± 1***</td>
<td></td>
</tr>
<tr>
<td>LVP-A</td>
<td>38 ± 14</td>
<td>19 ± 12*</td>
<td>12 ± 5***, 4 ± 3***</td>
<td></td>
</tr>
<tr>
<td>LVP</td>
<td>76 ± 13</td>
<td>83 ± 12</td>
<td>74 ± 14, 59 ± 10*</td>
<td></td>
</tr>
</tbody>
</table>

(\*P < 0.05, **P < 0.01, ***P < 0.001)

DISCUSSION

Although certaine magnitude of MAP-A was necessary for the appearance of TWA, we did not find TWA without MAP alternans. Therefore, constant TWA could be attributted to MAP alternans greater than certaine magnitude. In addition, MAP alternans showed spatial heterogeneity in its amplirude. The heterogeneity of MAP alternans might affect amplitude of TWA and explain the arrhythmogenecity of TWA.

Constant alternans in both MAP and LVP were decreased by caffeine in dose dependent manner. It was suggested that constant microscopic MAP alternans could be attributed, at least in part, to intracellular Ca cycling regulated by SR as like as action potential alternans induced by abrupt CL shortening.

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