Effects of Intravenous Anesthetics, Thiopental, Fentanyl, and Morphine on Ventricular Delayed Activation in a Canine Myocardial Infarction Model

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We examined the effects of intravenous anesthetics (thiopental, fentanyl and morphine) on the ventricular activation in a canine myocardial infarction model. Thiopental at 5 and 10 mg/kg delayed or abolished the delayed activation in the infarcted zones with slight delay of activation of the normal zones. Fentanyl at 30 μg/kg slightly but significantly prolonged the activation time in both normal and infarcted zones. Morphine at 1 mg/kg did not produce any significant effect. Thiopental, but neither fentanyl nor morphine, inhibited ventricular stimulation-induced arrhythmias. Thus, thiopental, but not fentanyl nor morphine, markedly depressed the delayed activation in myocardial infarction, which may affect and probably inhibits the ventricular arrhythmias in myocardial infarction. It also should be kept in mind that thiopental may have arrhythmogenic effects in myocardial infarction.

Keywords thiopental; fentanyl; morphine; canine myocardial infarction; ventricular activation; ventricular arrhythmias

When an anesthetic is administered to patients with ischemic heart disease, it may affect not only the hemodynamics but also the electrophysiologic properties in the ischemic myocardium. Several investigators have examined the electrophysiologic effects of volatile anesthetics on normal and infarcted myocardium.2–10 Those such as halothane decreased the maximal rate of depolarization (\( V_{max} \)), depressed delayed conduction, and suppressed the induction of ventricular arrhythmias in a canine myocardial infarction model.10 For intravenous anesthetics, it has been reported that thiamylal depressed cardiac sodium channels in isolated rat ventricular cells,11 and that fentanyl prolonged the activation potential duration (APD) in isolated ventricular muscles.12 However, electrophysiologic effects of the intravenous anesthetics on the infarcted heart have not yet been clarified. In the present study, we examined the effects of thiopental, fentanyl, and morphine on the ventricular delayed activation in a canine myocardial infarction model. The delayed activation in infarcted myocardium is one of the important factors in initiation of reentrant tachyarrhythmias, and class I antiarrhythmic drugs such as lidocaine produce arrhythmogenic effects when the delayed activation is abolished.13,14 Thiopental is used for induction of anesthesia or for short time anesthesia, and fentanyl and morphine are used usually in combination with volatile anesthetics. We also compared the effect of these drugs to that of lidocaine.

Materials and Methods

Animal Preparation Ten mongrel dogs weighing between 8.0—13.0 kg were anesthetized with sodium pentobarbital, 30 mg/kg i.v. Each animal was intubated and ventilated with room air using a positive pressure respirator. A left thoracotomy was performed in the fourth intercostal space and the heart was exposed. After exposing the pericardium, the left anterior descending coronary artery (LAD) was occluded according to Harris,15 and then several branches of the LAD were also occluded. The chest was closed after the complete occlusion, and routine postoperative care was performed including prophylactic antibiotic therapy, i.e. intramuscular administration of cefotaxime every day during post-infarction convalescence.

Measurement of the Ventricular Activation Time We examined the effects of the drugs in eight animals which survived 5 to 8 d after the LAD occlusion. The animal was prepared as mentioned above. After the heart was cradled on the pericardium, bipolar stimulating electrodes were saturated on the left atrial appendage and right ventricle for atrial pacing and ventricular premature stimulation, respectively. Several bipolar electrodes (intra-electrode distance: 1 mm; length of each electrode: 3 mm) were also sutured on the epicardial surface of the left and the right ventricle for recording the ventricular activation. Usually one electrode was sutured on the normal zone in the right ventricle, and other two on the infarcted zone in the left ventricle. By monitoring the electrocardiograms in the risk areas, an area was located where delayed activation was observed, and one of the electrodes was sutured to the surface of the area. Another electrode in the infarcted zone was located at any point within the infarcted zone regardless of activation delay. The atrial pacing was performed at a fixed rate slightly above the sinus rhythm in a control state throughout the electrophysiologic study (160 ± 9 beats/min, n = 8). The effect of the drugs was examined during atrial pacing of sinus rhythm. Premature stimulation of the right ventricle was performed by a 5 ms rectangular pulse with stimulus strength of the triple diastolic threshold. In order to study the effect of the drug on the ventricular activation, the premature stimulation-induced ventricular activation was recorded from both normal and infarcted zones of the ventricle. The time interval from the artifact of the premature stimulation to a sharp and reproducible delayed deflection was measured on the epicardial bipolar electrocardiograms in the infarcted zone, and this value was taken as the activation time. When multiple delayed deflections were recorded, the time was measured in the most delayed activation. The activation time in the normal zone was the interval between the artifact of the stimulation and the largest deflection of the electrocardiogram of the normal zone. The premature stimulation was triggered by excitation of the normal zone. The coupling interval of the stimulation was changed usually between 300 and 140 ms. Effects of the four drugs were compared in the activation of the same area at a coupling interval of 180 ms. The bipolar electrocardiogram was amplified at a filter frequency of 30 to 1000 Hz. Lead II ECG, femoral arterial pressure and the epicardial bipolar electrocardiograms were recorded on an 8 channel polygraph recorder (Nihonkohden, Tokyo, Japan) at a paper speed of 100 mm/s. In each animal, effects of the four drugs were examined at a time interval of 60 to 90 min when the effect of a prior drug was negligible. At the end of the experiments, we confirmed that electrodes were located in normal and infarcted zones by histological examination as described previously.16

Drug Administration The doses of the drugs were 5 and 10 mg/kg of thiopental, 10 and 30 μg/kg of fentanyl, 1 mg/kg of morphine and 3 mg/kg of lidocaine. The measurements after the anesthetic were started at 5 min after the drug administration. The maximal clinical dose of thiopental is about 1 g, and the usual clinical dose of fentanyl and morphine is 5 to 10 μg/kg and 5 to 30 mg, respectively. The doses of these drugs may vary depending on individuals. Thus, the doses employed in the present study may not greatly differ from the clinical doses.

Statistical Analysis All data were expressed as arithmetic mean ± SEM. A statistical significance of changes in heart rate, blood pressure and ventricular activation time after drug administration was determined by paired t-test or Student’s t-test. The criterion for statistical significance was p < 0.05.

Drugs The following drugs were used: thiopental sodium (Tanabe

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Effects of the Anesthetics on Ventricular Activation

Representative electrocardiograms recorded from normal and infarcted zones of the ventricle are shown in Fig. 1 (control). At the basic cycle length, the electrocardiogram recorded from the normal zone consisted of deflections with duration of less than 50 ms, whereas most of the electrocardiograms recorded from the infarcted zone consisted of fractionated potentials, indicating delay of the activation in the infarcted area. The delayed activation was further delayed in the premature excitation induced by the premature stimulation. We recorded the delayed activation from an area where subepicardial thin muscle layers were observed by histological examination, which is consistent with previous observations. 17)

Figure 1 shows the effect of thiopental at 5 and 10 mg/kg on ventricular delayed activation. Thiopental prolonged the activation time of the delayed activation in the premature excitation in the infarcted zone in a dose-dependent fashion. This drug did not change the configuration of the electrocardiogram in the infarcted zone except for prolonging its duration. In the normal zone, thiopental did not show any obvious effect on the activation time of the premature excitation; these effects were also observed during the sinus rhythm. The effect of thiopental disappeared about 30 min after the administration. Figure 2 shows the effect of thiopental on seriously delayed activation in the infarcted zone: at 5 mg/kg it markedly prolonged and at 10 mg/kg abolished the delayed activation. Thiopental abolished the delayed activation in one and three of seven animals examined at 5 and 10 mg/kg, respectively.

The effect of thiopental was related to the coupling interval. A typical case is shown in Fig. 3. At a coupling
Fig. 2. Thiopental-Induced Block of Delayed Activation in the Infarcted Zone

L-II, standard limb lead II ECG. NZeg, IZeg, electrocardiograms of the normal and the infarcted zones. The upward and downward arrows indicate the premature stimulation with a coupling interval of 180 ms and delayed activation, respectively. The open arrow indicates the block of the delayed activation. Basic cycle length: 370 ms.

Table II. Effects of Thiopental and Lidocaine on Ventricular Activation Time (ms) in a Canine Myocardial Infarction Model

<table>
<thead>
<tr>
<th></th>
<th>Normal zone</th>
<th>Infarcted zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopental</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (P)</td>
<td>29 ± 6</td>
<td>100 ± 5</td>
</tr>
<tr>
<td>5 mg/kg (P)</td>
<td>36 ± 7</td>
<td>150 ± 18b</td>
</tr>
<tr>
<td>10 mg/kg (P)</td>
<td>36 ± 4a</td>
<td>197 ± 25b</td>
</tr>
<tr>
<td>10 mg/kg (SR)</td>
<td>45 ± 4b</td>
<td>235 ± 47b</td>
</tr>
<tr>
<td>Lidocaine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (P)</td>
<td>30 ± 5</td>
<td>93 ± 6</td>
</tr>
<tr>
<td>3 mg/kg (P)</td>
<td>35 ± 5</td>
<td>142 ± 16b</td>
</tr>
</tbody>
</table>

The values are mean ± SEM of seven animals. P, SR; values during atrial pacing and sinus rhythm, respectively. a, b) p<0.05 and 0.01 vs. control.

Table III. Increases in Ventricular Activation Time (ms) with Fentanyl and Thiopental in a Canine Myocardial Infarction Model

<table>
<thead>
<tr>
<th></th>
<th>Normal zone</th>
<th>Infarcted zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 µg/kg (SR)</td>
<td>19 ± 7a</td>
<td>16 ± 7a</td>
</tr>
<tr>
<td>10 µg/kg (P)</td>
<td>7 ± 2</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>30 µg/kg (SR)</td>
<td>38 ± 10a</td>
<td>28 ± 8a</td>
</tr>
<tr>
<td>30 µg/kg (P)</td>
<td>18 ± 6a</td>
<td>17 ± 5a</td>
</tr>
<tr>
<td>Thiopental</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg/kg (P)</td>
<td>24 ± 7a</td>
<td>100 ± 14a</td>
</tr>
</tbody>
</table>

The values are mean ± SEM of seven animals. SR, P; values during sinus rhythm and atrial pacing, respectively. a) Increases are statistically significant at p<0.05.

interval of 300 ms, thiopental at 10 mg/kg prolonged the activation time in infarcted area from 95 to 106 ms, while at 180 ms it prolonged the time from 121 to 189 ms.

Table II shows the effects of thiopental on seven animals in comparison with those of 3 mg/kg lidocaine. Lidocaine markedly prolonged the activation time in the infarcted zone without any significant effect in the normal zone, which is consistent with previous results.18) The effect of thiopental (5 mg/kg) was comparable to that of lidocaine (3 mg/kg). These data did not include the activation which was blocked by the drugs. Thiopental markedly prolonged the activation time of infarcted zones at a coupling interval of 180 ms, while it only slightly prolonged the activation time in the normal zones. A comparison of the effects of thiopental and fentanyl is shown in Table III. Fentanyl at 30 µg/kg slightly but significantly prolonged the activation time in both normal and infarcted zones to a similar extent. Its effect at 30 µg/kg was to a lesser extent than that of
Fig. 4. Effects of Morphine at 1 mg/kg on the Ventricular Activation
L-II; standard limb lead II ECG. NZeg, IZeg; electrocardiograms of the normal and the infarcted zones. The upward arrows indicate the premature stimulation with a coupling interval of 180 ms. Basic cycle length: 360 ms. The downward arrows are delayed activations. The times of the delayed activations in the infarcted zone were 141 and 146 ms in control and after the administration of morphine (1 mg/kg), respectively.

Fig. 5. Effect of Thiopental at 10 mg/kg on the Premature Stimulation-Induced Ventricular Arrhythmias
L-II; standard limb lead II ECG. NZeg, IZeg; electrocardiograms of the normal and the infarcted zones. Coupling interval: 140 ms. Basic cycle length: 360 ms. The upward arrows are the premature stimulations.

Thiopental at 10 mg/kg. Fentanyl at 10 μg/kg prolonged the activation time during sinus rhythm in both normal and infarcted zones, but did not produce any significant effect during atrial pacing.

Figure 4 shows a typical effect of morphine at 1 mg/kg. This drug did not produce any significant effect in infarcted or normal zones.

In three of seven animals, the stimulation-induced premature beat was followed by seriously delayed activation, which resulted in ventricular ectopic beats (Fig. 5). The coupling intervals of the stimulation which produced the arrhythmias in these animals were between 160 and 140 ms. These ventricular ectopic beats did not occur during anesthesia with 10 mg/kg of thiopental. Fentanyl did not affect these arrhythmias.

Discussion
The present study showed that thiopental depressed the delayed activation in infarcted zones of canine ventricles. These effects were selective to the activation in the infarcted zone, while the effect of activation of the normal zone was slight. Class I antiarrhythmic drugs also selectively depressed the delayed activation (Table II).16,19 It has been shown that halothane decreased the $V_{\text{max}}$ and slowed the conduction in the isolated Purkinje fibers of infarcted hearts but did not decrease the $V_{\text{max}}$ of Purkinje fibers of non-infarcted zones.9 By a previous report showed that thiamylal, a barbiturate, reduced the sodium currents,12 it is probable that depression of the delayed activation by thiopental may be caused by its inhibition of sodium channels. On the other hand, Terrar and Victory showed that halothane inhibits a cell-to-cell electrical coupling.20 In addition, Ozaki et al. reported that halothane and enflurane reduced the conduction velocity in guinea pig papillary muscles without any significant reduction of $V_{\text{max}}$.21 Spray and Burt showed that a variety of lipophilic molecules and myoplasmic acidification reduced cell-to-cell electrical coupling.22 Therefore, it cannot be denied that a depression of cell-to-cell electrical coupling may also contribute to the supression of delayed activation in the infarcted zone by thiopental. In contrast to thiopental, fentanyl prolonged the activation time in both normal and infarcted zones to a similar extent. It has been shown that fentanyl did not reduce the $V_{\text{max}}$ in canine cardiac Purkinje fibers.12 Although the electrophysiologic effects of fentanyl have not been fully examined in vitro, different mechanisms may be involved in the depressant effects of thiopental and fentanyl on delayed activation. The effect of morphine on ventricular activation or arrhythmias was negligible. It is unlikely that the depressant effect of the anesthetics on the ventricular acti-
vation is a secondary effect caused by the reduction in blood pressure, because the blood pressures after administration of the three anesthetics were not significantly different.

Thiopental abolished a seriously depressed activation in the infarcted zones in some cases. A markedly delayed activation may lead to reentrant arrhythmias, and abolition of the activation with antiarrhythmic drugs prevents the arrhythmias. In the three animals examined in the present study, ventricular arrhythmias were induced by the premature stimulation, and were suppressed by thiopental. The antiarrhythmic effects of enflurane and halothane in canine myocardial infarction have been reported previously, and may be caused partly by the drug's selective suppression of delayed activation in the infarcted zone. The antiarrhythmic effect of thiopental may also be caused by a suppressing the delayed activation in the infarcted zone.

The depressant effect of the anesthetics on the delayed activation was coupling interval-related. A similar effect was observed with class I antiarrhythmic drugs, and may be due to a time-dependent inhibition of sodium channels. According to Ikemoto et al., halothane and thiamyal delayed recovery of sodium channels from inactivation, but these drugs did not produce the use-dependent block of sodium channels. They suggested that the mechanism of sodium channel inhibition by these drugs may be different from that of local anesthetics such as class I antiarrhythmic drugs. As for the mechanism involved with the effect of fentanyl, it is also probable that the prolongation of APD by this anesthetic contributed to the depression of the delayed activation at a short coupling interval.

Several authors have reported that class I antiarrhythmic drugs have proarrhythmic effects. Although premature stimulation did not produce ventricular arrhythmias after the administration of thiopental in the present study, it should be kept in mind that this anesthetic may have proarrhythmic effects, because it and others tested delayed the ventricular activation in the infarcted zone as do antiarrhythmic drugs.

In conclusion, thiopental selectively depressed the delayed activation in the infarcted zones, which may affect and probably inhibit the ventricular arrhythmias in myocardial infarction. The effect of fentanyl was less than that of thiopental, and that of morphine was negligible.

References and Notes
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