Electrophysiologic Effects of Nitrous Oxide, a Volatile Anesthetic, in Dogs Following Myocardial Infarction in Comparison with Other Anesthetics

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The present study was undertaken to examine the electrophysiologic effects of nitrous oxide in the dog heart after inducing myocardial infarction, and to compare these with those of other anesthetics. Myocardial infarction was produced by two-stage ligation of the left anterior descending coronary artery in dogs. Seven days after ligation, bipolar electrodes were sutured on the ventricular surface of the infarcted and normal regions for applying electrical stimulation or recording ventricular activation. Ventricular activation time and QT interval on the bipolar electrocardiogram and PQ interval from the standard limb lead II were measured during atrial pacing. Nitrous oxide 80% did not significantly prolong ventricular activation time, PQ interval or QT interval. However, halothane 1 minimum alveolar concentration (MAC), thiopental 5 and 10 mg/kg and fentanyl 30 μg/kg did prolong ventricular activation time; thiopental and fentanyl prolonged the QT interval. Nitrous oxide did not potentiate the effects of fentanyl. Therefore, electrophysiologic effects of nitrous oxide are much weaker compared with those of thiopental, fentanyl or halothane.

Key words: nitrous oxide; anesthetics; heart; electrophysiology; myocardial infarction

Many studies have shown that anesthetics affect electrophysiologic properties of the ischemic and nonischemic myocardium. 1–5) Turner et al. examined the effects of halothane on the electrical activity of Purkinje fibers from normal and infarcted canine hearts. 6) They showed that halothane decreased the maximal rate of depolarization and slowed conduction in the infarcted zone. Our previous studies showed that halothane and sevoflurane delayed or blocked ventricular activation in the infarcted zone of dog hearts. 7) A similar effect was also observed with thiopental. 8) Nitrous oxide is a popular volatile anesthetic and may be used in patients with ischemic heart disease. However, the electrophysiologic effects of nitrous oxide on ischemic hearts have not been investigated. In the present study, we examined the effects of nitrous oxide on the activation and QT interval of the ventricle and the PQ interval of the standard limb lead II electrocardiogram (ECG) in a canine myocardial infarction model, and compared these with those of other anesthetics.

MATERIALS AND METHODS

Animal Preparation Myocardial infarction was produced in 15 mongrel dogs weighing 7 to 20 kg by a two-stage ligation of the left anterior descending coronary artery during anesthesia with pentobarbital 30 mg/kg i.v. according to the procedure described previously. 7) After surgery, the dogs recovered from anesthesia and were returned to their quarters for postoperative care. Seven days after surgery, the animals were submitted to the electrophysiological investigation.

Measurement of the Ventricular Activation Time Animals were reanesthetized with pentobarbital 20 mg/kg i.v. and their body temperature was maintained at 36–37°C with a heating-pad (American Pharseal Co., U.S.A.). Each animal was intubated and ventilated 12 times/min with 100% O2 at a tidal volume of 15 ml/kg. Left thoracotomy was performed, and the pericardium was opened. After cradling the heart on the pericardium, a bipolar stimulating electrode was sutured on the left atrial appendage and right ventricle for atrial pacing and applying premature stimulation, respectively. Electrical stimulation of the ventricle was performed using a 5 ms rectangular pulse with an electrical stimulator (SEN-7103, Nihon Kohden). The stimulus strength was kept at twice the diastolic threshold, and atrial pacing was performed at a cycle length of 350–400 ms throughout the electrophysiological investigation. For recording ventricular activation, three bipolar electrodes were sutured on the infarcted region of the left ventricle and a normal region of the right ventricle.

To study the effects of the drug on ventricular activation, we measured the activation time in both normal and infarcted regions of the ventricle after premature ventricular stimulation of the normal region. The time interval from the artifact of the premature stimulation to the most delayed measurable wave was measured on the epicardial bipolar ECGs and this value was taken as the activation time. The coupling interval of the ventricular stimulation was varied between 300 and 160 ms. Lead II ECG, femoral arterial blood pressure, and epicardial bipolar ECGs were recorded on a multichannel thermal-array recorder (WS-682G, Nihon Kohden) at a paper speed of 100 mm/s.

Drug Administration The doses of the drugs were 5 and 10 mg/kg thiopental, 10 and 30 μg/kg fentanyl, 1 minimum alveolar concentration (MAC) of halothane (1.2%) and 80% nitrous oxide (nitrous oxide: O2 = 4:1). The dosages of anesthetics were selected based on the recommended human dosages. In the study of thiopental and fentanyl, the drug was administered cumulatively via the femoral vein at 7 min intervals, and measurements were started 5 min after drug administration. In the study of halothane and nitrous oxide, measurements were started 30 min after the start of inhalation. To examine the effect of a combination of nitrous oxide and fentanyl, © 1997 Pharmaceutical Society of Japan
nitrous oxide was first inhaled and its effects were monitored. Then fentanyl was administered during inhalation of nitrous oxide, and the effects of the combination of the two drugs were examined. The number of animals used to study thiopental, fentanyl and nitrous oxide was eight, and seven were used to study halothane.

**Statistical Analysis** All data are expressed as arithmetic means ± standard deviation (S.D.). Comparison between control and drug values of epicardial activation time and ECG values was performed by a one-way analysis of variance followed by Dunnett’s test. The criterion for statistical significance was \( p < 0.05 \).

**RESULTS**

Representative ECGs recorded from normal and infarcted regions are shown in Fig. 1. At the basic cycle length, the ECG from a normal region consisted of a deflection with duration of less than 50 ms, whereas most of the ECGs from the infarcted region exhibited a fractionated potential, indicating that activation in the infarcted region was delayed. The delayed activation was exacerbated during premature excitation induced by premature stimulation.

Typical effects of thiopental and nitrous oxide on ventricular activation are shown in Fig. 1. Thiopental, 10 mg/kg, further prolonged the activation time of delayed activation in the infarcted region. The activation of the normal region was unaffected by thiopental. In one of the eight animals, exacerbation of the delayed activation by thiopental resulted in a ventricular ectopic beat (Fig. 2). As shown in our previous study, thiopental produced a block of the delayed activation of the infarcted region in two of eight animals.\(^9\) Nitrous oxide had no obvious effect on the delayed activation.

![Diagram](image)

**Fig. 1.** Effects of Thiopental (10 mg/kg) and Nitrous Oxide (\( N_2O, 80\% \)) on Ventricular Activation

L-II, standard limb lead II ECG. NZeg, IZeg, ECGs of normal and infarcted regions. The upward arrows indicate premature electrical stimulation with a coupling interval of 300 ms. The basic cycle length was 360 ms. The downward arrows indicate delayed activation. The numbers are the activation time. The IZegs were recorded from different areas, and the effects of drugs are also monitored in these two areas.

![Diagram](image)

**Fig. 2.** A Ventricular Ectopic Beat Induced by Premature Stimulation after Administration of Thiopental 10 mg/kg.

L-II, standard limb lead II ECG. NZeg, IZeg, ECGs in normal and infarcted regions. The upward arrows indicate premature stimulation. The asterisk indicates a ventricular ectopic beat. After thiopental, continuous delayed activations in the infarcted region (in the two IZegs) were followed by the ventricular ectopic beat.

Table 1 summarizes the results of fifteen animals. Thiopental, 10 mg/kg, significantly prolonged the activation time in the infarcted region to a greater extent at
Table 1. Prolongation of Ventricular Activation Time by Thiopental, Fentanyl and Nitrous Oxide (N₂O) in Dog Hearts Following Myocardial Infarction

<table>
<thead>
<tr>
<th></th>
<th>Infarcted region</th>
<th>Normal region</th>
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<tbody>
<tr>
<td></td>
<td>Coupling interval (ms)</td>
<td>Coupling interval (ms)</td>
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<tr>
<td></td>
<td>160</td>
<td>300</td>
</tr>
<tr>
<td>Basal values</td>
<td>131±38</td>
<td>10±38</td>
</tr>
<tr>
<td>Thiopental (5 mg/kg)</td>
<td>14±11*</td>
<td>4±6</td>
</tr>
<tr>
<td>Thiopental (10 mg/kg)</td>
<td>34±14*</td>
<td>9±8*</td>
</tr>
<tr>
<td>Basal values</td>
<td>132±43</td>
<td>98±42</td>
</tr>
<tr>
<td>N₂O (80%)</td>
<td>1±5</td>
<td>3±6</td>
</tr>
<tr>
<td>Basal values</td>
<td>131±41</td>
<td>131±24</td>
</tr>
<tr>
<td>Fentanyl (10 µg/kg)</td>
<td>7±4</td>
<td>2±3</td>
</tr>
<tr>
<td>Fentanyl (30 µg/kg)</td>
<td>12±5**</td>
<td>3±4</td>
</tr>
<tr>
<td>Fentanyl + N₂O</td>
<td>10±5*</td>
<td>2±3</td>
</tr>
<tr>
<td>Basal values</td>
<td>126±22</td>
<td>115±22</td>
</tr>
<tr>
<td>Halothane (1 MAC)</td>
<td>46±22*</td>
<td>14±9*</td>
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</tbody>
</table>

Values (ms) are means ± S.D. of 8 (thiopental, N₂O, fentanyl) or 7 (halothane) experiments. Basal values represent the activation time before the drug, and values for each drug represent prolongation of the activation time after drug. Fentanyl + N₂O; fentanyl (30 µg/kg) + N₂O (80%). * p < 0.05 vs. basal value. ** p < 0.01, 0.05 vs. thiopental.

Table 2. Prolongation of the PQ and QT Intervals by Thiopental, Fentanyl and Nitrous Oxide (N₂O) in Dog Hearts Following Myocardial Infarction

<table>
<thead>
<tr>
<th></th>
<th>PQ interval</th>
<th>QT interval</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Basal values</td>
<td>Thiopental (5 mg/kg)</td>
</tr>
<tr>
<td></td>
<td>68±7</td>
<td>7±8</td>
</tr>
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<td></td>
<td>180±29</td>
<td>9±11</td>
</tr>
</tbody>
</table>

Values (ms) are means ± S.D. of 8 experiments. Basal values represent the PQ or QT intervals before the drug, and values for each drug represent prolongation of the PQ or QT intervals after drug. Fentanyl + N₂O; fentanyl (30 µg/kg) + N₂O (80%). * p < 0.05, 0.01 vs. basal value.

The cardiac effects of nitrous oxide have been studied by many investigators. 11-16 Nitrous oxide increases cardiac output in vivo, 11 but depresses myocardial contractility in vitro. 13,15 Stowe et al. suggested that nitrous oxide may be a mild cardiac depressant drug, especially in the presence of other cardiac depressants. 16 The effects of nitrous oxide on cardiac conduction have also been examined. 15 Nitrous oxide does not delay atrioventricular (AV) conduction but produces AV dissociation, probably by increasing sympathetic nerve activity. 15 The effect of nitrous oxide on conduction in the ischemic heart has not been investigated. The present study shows that nitrous oxide does not significantly affect ventricular activation, the PQ interval or the QT interval. Therefore, nitrous oxide has only a minimum electrophysiological effect on the heart following myocardial infarction.

A synergistic interaction between anesthetics and antiaarrhythmic drugs, such as class I antiaarrhythmics, has been reported. 17,18 Gallagher et al. have reported an electrophysiological interaction between halothane and quinidine. 17 Our previous study showed that halothane potentiates the inhibitory effects of lidocaine and procainamide on ventricular delayed activation. 18 A combination of fentanyl and nitrous oxide is frequently used for anesthesia. The present results indicate that nitrous oxide and fentanyl exhibit no significant electrophysiological interactions.

In conclusion, electrophysiological effects of nitrous oxide on the heart following myocardial infarction are less marked compared with other volatile or intravenous anesthetics.
REFERENCES