Effect of Apomorphine on the Canine SA Node

Shigetoshi CHIBA, M.D., Hiroshi ONO, M.D.,
and Kazuhiko IWATSUKI, Ph.D.

SUMMARY

A constant pressure perfusion of the sinus node artery was performed in 10 in situ and in 3 isolated SA node preparations. The selective administration of apomorphine caused a negative chronotropic effect which was not blocked by treatment with atropine. The sinus deceleration was usually produced by apomorphine, 10–300 µg, while sinus irregularity and finally atrioventricular nodal rhythm in the in situ preparation or sinus arrest in the isolated one resulted from doses above 1 mg. In the in situ preparation at a higher dose from 300 µg to 1 mg, a slight sinus acceleration was occasionally induced following sinus deceleration. In this time, a fall in blood pressure was usually observed. This acceleration response to apomorphine was inhibited by propranolol.

From these results, it is concluded that apomorphine induces direct depressive action on the SA node and, in extremely high doses, a slight sinus acceleration may be induced by reflex mechanism.

Additional Indexing Words:
Apomorphine Sinus node artery SA node

It has been reported that apomorphine produced a hypotensive effect with reflex acceleration of the sinus rhythm but a marked bradycardia at a higher dose in the different species of experimental animals. Finch and Haeusler had considered that effect of apomorphine might involve the parasympathetic nervous system, because their electrophysiological studies showed that apomorphine increased both frequency and amplitude of discharges in the efferent vagal nerve.

In the present study, we made an attempt to evaluate direct effect of apomorphine on the canine SA node, using a direct perfusion technique of the sinus node artery in the in situ preparation and in the isolated atrium preparation.
METHODS

In the in situ preparations, 10 mongrel dogs of either sex, weighing 10 to 15 Kg, were anesthetized with sodium pentobarbital, 30 mg/Kg, intravenously. Artificial respiration was maintained with a Harvard respirator. The chest was opened at the right 4th intercostal space. Both vagi were cut at the mid-cervical level. The direct perfusion technique of the sinus node artery in these experiments was originally devised by James and Nadeau and modified by Hashimoto et al. The sinus node artery was cannulated and perfused at a constant pressure of 100 mmHg.

In 3 experiments, the isolated, blood-perfused SA node preparation of the dog was used as reported in a previous paper.

Drug solution was injected in a volume of 0.01 to 0.05 ml for a period of 4 sec by a microinjector (Terumo Co) into the perfusion system to the sinus node artery. Drugs used were apomorphine hydrochloride (Siegfried, Switzerland), atropine sulfate (Takeda), acetylcholine chloride (Daichi), norepinephrine hydrochloride (Sankyo), and propranolol hydrochloride (Sumitomo Chemicals).

RESULTS

Effect of apomorphine on the SA node (Fig. 1, Table I)

When apomorphine was injected into the sinus node artery in the in situ SA node preparation, a deceleration of sinus rate was usually observed. The threshold dose for inducing sinus deceleration was 10 µg of apomorphine. A marked sinus deceleration was usually produced with 30 to 100 µg of apomorphine and atrioventricular rhythm due to sinus suppression occasionally with 300 µg and with 1 mg in all 6 dogs. When more than 300 µg was given into the sinus node artery, it lowered the systemic arterial blood pressure by approximately 10–20 mmHg lasting 1 to 2 min. Such a large dose of apomorphine occasionally caused a slight sinus acceleration following a profound sinus deceleration.

![Graph showing response patterns of the SA node to increasing doses of apomorphine.](Image)

Fig. 1. Response patterns of the SA node to increasing doses of apomorphine injected into the sinus node artery. SBP: systemic blood pressure. HR: heart rate.
Table I. Chronotropic Responses of the Canine SA Node to Apomorphine

<table>
<thead>
<tr>
<th>Dose (µg)</th>
<th>No. of exps</th>
<th>Initial sinus rate (beats/min)</th>
<th>Chronotropic response to apomorphine</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Minimum sinus rate (beats/min)</td>
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<td></td>
<td></td>
<td></td>
<td>Decrease in sinus rate (%)</td>
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<td></td>
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<td>Incidence of sinus acceleration</td>
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</table>

In the *in situ* preparations

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<tbody>
<tr>
<td>3</td>
<td>4</td>
<td>133±7.5</td>
<td>133±7.5</td>
<td>0</td>
<td>0/4</td>
</tr>
<tr>
<td>30</td>
<td>6</td>
<td>130±8.2</td>
<td>125±8.7</td>
<td>4±1.6</td>
<td>0/6</td>
</tr>
<tr>
<td>300</td>
<td>6</td>
<td>130±8.2</td>
<td>118±10.0</td>
<td>10±8.5</td>
<td>0/6</td>
</tr>
<tr>
<td>300</td>
<td>6</td>
<td>130±8.2</td>
<td>105±11.5</td>
<td>19±4.5</td>
<td>0/6</td>
</tr>
<tr>
<td>300</td>
<td>6</td>
<td>130±8.2</td>
<td>91±8.6*</td>
<td>32±5.4</td>
<td>1/6</td>
</tr>
<tr>
<td>1,000</td>
<td>6</td>
<td>130±8.2</td>
<td>74±4.3**</td>
<td>46±1.7</td>
<td>2/6</td>
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In the isolated preparations

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<tr>
<td>10</td>
<td>3</td>
<td>102±6.5</td>
<td>102±6.5</td>
<td>0</td>
<td>0/3</td>
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<tr>
<td>300</td>
<td>3</td>
<td>102±6.5</td>
<td>97±6.2</td>
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<tr>
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<td>-</td>
<td>-</td>
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</tr>
</tbody>
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* Nodal rhythm appeared in one of 6 dogs.
** Nodal rhythm appeared in all experiments.
*** Atrial arrest appeared in all 3 isolated preparations.
The values are the mean±S.E.

In *in 3 isolated atrium preparations*, apomorphine induced dose-dependently sinus deceleration and never induced secondarily sinus acceleration. These results are summarized in Table I.

**Effect of atropine and propranolol on apomorphine-induced chronotropic responses** (Fig. 2)

The negative chronotropic response to apomorphine was not prevented by
treatment with atropine. A deceleration response to 100 μg of apomorphine was not modified by 10 μg of atropine and effect of 0.1 μg of acetylcholine was completely inhibited by 10 μg of atropine as shown in Fig. 2.

On the other hand, a slight positive chronotropic effect induced by 1 mg of apomorphine was abolished by treatment with 1 μg of propranolol in 2 in situ preparations. This dose of propranolol completely blocked a positive chronotropic response to 0.01 μg of norepinephrine injected into the sinus node artery.

DISCUSSION

It has been observed that apomorphine caused a bradycardia in different species. It was considered that effect of apomorphine might involve the parasympathetic nervous system when administered intravenously. In the present study, sinus deceleration induced by local injection of apomorphine was not influenced by atropine treatment. Therefore, it is indicated that apomorphine has a direct depressive action on the SA nodal pacemaker activity and does not modify the peripheral parasympathetic nervous system when given intraarterially to the local region of the SA node.

It has been also reported that apomorphine produced the pressor responses in pithed preparations, after bilateral vagotomy or after pretreatment with atropine. In this study, in 2 cases out of 6 in situ preparations, a large amount of apomorphine induced hypotensive effect and sinus acceleration. It is considered that the pressor responses might be due to catecholamine release by apomorphine, because the acceleration response to apomorphine in this study was blocked by propranolol which blocks adrenergic beta-receptors. However, in 3 isolated SA node preparations, apomorphine never induced sinus acceleration. Therefore, in the in situ preparation, sinus acceleration induced by apomorphine may be due to reflex mechanism.

In a previous paper, it was demonstrated that morphine induced a biphasic chronotropic response at higher doses when injected into the sinus node artery both in the in situ SA node preparation and isolated one. Apomorphine is derived from morphine. In this study, the response patterns to apomorphine were similar to that of morphine on the canine SA node. However, a negative chronotropic response induced by apomorphine was much greater than that by morphine at the same dose levels. And in a positive chronotropic response, apomorphine was less potent than morphine.

From these results, it is concluded that apomorphine has a direct depressant effect on the canine SA node and also an effect of catecholamine release at extremely large dose levels in the in situ preparation.
ACKNOWLEDGEMENTS

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REFERENCES