Effects of Halothane on Automaticity and Contractile Force of Isolated Blood-perfused Canine Ventricular Tissue

Keitaro Hashimoto, M.D., Masao Endoh, M.D., Tomohiko Kimura, B.S.
Koroku Hashimoto, M.D.

The effects of halothane on canine ventricular automaticity and contractility were studied in intact and isolated heart preparations in which the right anterior papillary muscle and sinoatrial node of a recipient dog were separately perfused with arterial blood from a donor animal. One percent halothane inhaled by the donor dog decreased blood pressure and heart rate in the donor animal and sensitized the ventricle of the donor dog to the arrhythmic effects of norepinephrine. One percent halothane inhaled by donor dogs also produced negative inotropic and chronotropic responses in the isolated, perfused sinoatrial and ventricular preparations, but had no effect on positive chronotropic or inotropic responses to norepinephrine or perivascular nerve stimulation. Norepinephrine administered to donor dogs produced no arrhythmia in either spontaneously beating or electrically paced recipient hearts even though producing ventricular fibrillation in the donor. The results suggest that re-entry mechanisms play an important role in halothane–catecholamine-induced arrhythmias. (Key words: Anesthesiology, volatile; Heart; arrhythmias; halothane–catecholamine; Sympathetic nervous system: norepinephrine.)

HALOTHANE is well known for its ability to sensitize the ventricle to adrenergic compounds. Recently, the authors proposed that decreased heart rate played an important role in production by epinephrine of bigeminal rhythm and multifocal ventricular tachycardia during halothane anesthesia.1,2 This was based on the finding that these types of arrhythmias, which Dresel and Sutter3 call “minimal ventricular arrhythmias,” were produced within a certain range of heart rate, and that the arrhythmias were prevented by driving the atrium at a rate higher than that which was attained by epinephrine in the absence of halothane. It was proposed1,2 that depression of the maximal chronotropic response of the sinoatrial node to epinephrine during halothane anesthesia resulted in a heart rate favorable for production of arrhythmias. Vick has also reported the important role of the heart rate in producing arrhythmias during chloroform anesthesia.4 He found that sustained ventricular arrhythmias were converted to a normal supraventricular rhythm by vagal stimulation which decreased the sinoatrial rate. Restoring the faster heart rate by pacing the atrium re-established arrhythmias even though the vagus was stimulated. These two studies suggest that “minimal ventricular arrhythmias” produced by a combination of anesthetics and adrenergic compounds require an optimal range of heart rate, and that either higher or lower rates could prevent arrhythmias. Both studies also suggested that ventricular pacemaker activity was not increased by anesthetics and that the ability of epinephrine to increase ventricular automaticity was not affected. It is, thus, of interest to determine the direct effects of anesthetics on ventricular automaticity and possible cellular mechanisms for the production of anesthetic–catecholamine-induced arrhythmias.

Reynolds et al.,5 using the canine Purkinje fiber perfused by Tyrode’s solution, and Logic and Morrow,6 using in-situ canine ventricle with vagal stimulation, found that halothane depressed ventricular automaticity and also depressed the stimulant action of epinephrine on automaticity. However, the results of these studies did not permit evaluating possible changes in ventricular...
automaticity produced by halothane at the time when the ventricles were sensitized to adrenergic compounds. Recently, we developed an experimental method in which isolated right anterior papillary muscles and sinoatrial nodes were perfused by arterial blood from a donor dog, thereby allowing simultaneous observation of ventricular automaticity and contractility in the isolated tissues and cardiovascular function in the donor animal. The isolated preparations are perfused with arterial blood via branches of the coronary artery, thus maintaining stable automaticity and contractility free of neural influences and free of the influence of changes in blood pressure and wall tension. The blood-perfused sinoatrial node preparation was also useful for comparing the automaticity of the ventricle with that of the sinoatrial node.

In the present study we examined: 1) the effects of halothane administered to the donor dog on both the isolated preparation and the donor dog; 2) the effects of halothane on norepinephrine-induced changes in automaticity and contractility; 3) the difference between responses to exogenously applied norepinephrine and to endogenously released norepinephrine following perivascular nerve stimulation; 4) the effects of electrical pacing on ventricular automaticity during administration of norepinephrine and halothane.

Methods

Fourteen mongrel dogs of either sex, weighing 6–12 kg, were anesthetized with sodium pentobarbital 30 mg/kg, iv. After an iv injection of sodium heparin, 200 U/kg, the heart was excised and plunged into oxygenated Tyrode’s solution at 4 C. The papillary muscle with underlying ventricular septum was isolated and perfused via the anterior septal artery (fig. 1, left) with arterial blood from a donor dog, as previously described. In seven experiments the right atrium with a part of the vena cava was isolated and perfused via the sinus node artery (fig. 1, right) as previously described. The isolated tissues were maintained in a moist chamber at 38 C.

Donor dogs, weighing 16–25 kg, were anesthetized with sodium pentobarbital, 30 mg/kg, iv. They were then vagotomized bilaterally at the midcervical level. The trachea was cannulated and the dogs respired with 100 per cent oxygen (20 ml/kg at a rate of 18/min) through a semiclosed anesthetic apparatus using a Harvard respirator. Sodium heparin, 300 U/kg, iv, was given to the donor dog at the beginning of perfusion and 100 U/kg were added at 1-hour intervals. Arterial blood was drawn from the carotid artery and the isolated preparations were perfused at a constant pressure of 100 mm Hg using a peristaltic pump and a pneumatic resistance placed in parallel to the perfusion system. The blood from the preparation and from the overflow through the pneumatic resistance was collected in a venous reservoir and returned to the donor dog through the jugular vein.

Bipolar silver wire recording electrodes were placed on the surface of the papillary muscle and the right atrial surface of the sinoatrial node preparation. The resulting electrograms were used to trigger cardiograph meters (Nihon Kohden RT-2) to record the rate of automaticity. The tendinous end of the papillary muscle was connected to a force–displacement transducer (Grass FT03B) by a thin thread so that the muscle remained under 1-g tension. Arterial blood pressure, ECG and cardiograph from the donor dog were recorded on an ink-writing oscillograph (San-ei Sokki) along with recordings from the isolated preparations.

Perivascular nerve stimulation of the papillary muscle was performed in five experiments by silver wire stimulating electrodes placed around the anterior septal artery, using an electronic stimulator (Nihon Kohden MSE-3R). This stimulator was also used to drive the papillary muscle through the stimulating electrodes at the base of the muscle.

Halothane administration to the donor dog was produced as previously described. One per cent halothane was vaporized in oxygen using a calibrated vaporizer (ACOMA TEC). Responses to norepinephrine or perivascular nerve stimulation were recorded during the control period and again 30 minutes or more after the start of halothane administration.
Halothane administration was terminated within 3 hours.

1-Norepinephrine hydrochloride dissolved in 0.9 per cent isotonic saline solution was injected either into the isolated preparation through the rubber tube close to the Y-shaped connector or intravenously into the donor dog. Intra-arterial injections into isolated preparations in volumes of 0.01 to 0.03 ml were made over a period of 4 seconds using a microsyringe (Jintan Terumo Micro Syringe); intravenous injections were made in volumes of 20 ml over a period of 50 seconds.

Statistical analysis was performed using Student’s t test for paired data.

Results

Blood pressure and heart rate of the donor dog remained constant during intra-arterial injections of norepinephrine into the isolated preparation. This was probably because even the highest dose of norepinephrine administered to the isolated preparation, 0.3 μg, became too diluted to show systemic effects in the donor dog. Norepinephrine administered intravenously to the donor dog increased both the blood pressure and the heart rate, but they returned to control values within 10 minutes even with a higher dose of 10 μg/kg.

Effects of Halothane on the Donor Dog (Table 1)

One per cent halothane significantly decreased both blood pressure and heart rate in donor animals. These decreases began soon after introduction of halothane, and within 30 minutes both values reached the level shown in table 1. These values remained constant as long as halothane was inhaled. Blood pressure and heart rate, both before and during halothane administration, were similar to those observed in dogs used in previous studies of halothane–epinephrine-induced arrhythmias.1,2

Recovery from halothane administration was studied in five experiments. Blood pressure and heart rate soon started to increase, and within an hour they stabilized at values close to control levels.

Effects of Halothane on the Isolated Papillary Muscle (Table 1)

At the beginning of the experiment, when perfusion with arterial blood of the donor dog
TABLE 1. Direct Effects of Halothane on the Donor Dog and on Isolated Sinoatrial Node and Papillary Muscle Preparations (Mean ± SE)

<table>
<thead>
<tr>
<th></th>
<th>Number of Experiments</th>
<th>Control</th>
<th>Halothane 1 Per Cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor dog</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>14</td>
<td>147 ± 8 mm Hg</td>
<td>97 ± 5 mm Hg</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>14</td>
<td>103 ± 7 mm Hg</td>
<td>71 ± 4 mm Hg</td>
</tr>
<tr>
<td>Heart rate</td>
<td>14</td>
<td>170 ± 6 beats/min</td>
<td>139 ± 5 beats/min</td>
</tr>
<tr>
<td>Papillary muscle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contractile force</td>
<td>14</td>
<td>2.0 ± 0.3 g</td>
<td>1.1 ± 0.2 g</td>
</tr>
<tr>
<td>Automaticity</td>
<td>14</td>
<td>48 ± 5 beats/min</td>
<td>41 ± 4 beats/min</td>
</tr>
<tr>
<td>Sinoatrial node</td>
<td>7</td>
<td>110 ± 4 beats/min</td>
<td>101 ± 3 beats/min</td>
</tr>
</tbody>
</table>

* P < 0.05.
† P < 0.01.

was started, the papillary muscle preparation showed a short period of fibrillatory activity, but usually the preparation stabilized within 30 minutes, although multifocal extrasystoles were occasionally observed and, in some preparations, bursts of rapid contractions. The contractile force tended to increase during the first 30 minutes. After that, as already reported, the values of the automatic rate and the contractile force remained constant for as long as 10 hours, if drugs or other experimental procedures were not employed.

In the present experiments, both rate and contractile force were transiently increased by intra-arterially and intravenously administered norepinephrine or by perivascular nerve stimulation, but they returned to control values within 4 minutes when 0.3 μg of norepinephrine was given intra-arterially to the isolated preparation and within 5 minutes when 3 μg/kg of norepinephrine were given to the donor dog. The use of norepinephrine was limited to four times for intra-arterial injections and three times for intravenous injections after the control period.

After control observations of the responses to norepinephrine in the absence of halothane, the same protocol for norepinephrine administration was repeated during halothane administration.

Halothane administered to the donor dog decreased both automaticity and the contractile force in the isolated preparation, but the depressant effect on contractile force was more pronounced. There were relatively rapid decreases in automaticity and contractile force during the first 30 minutes, after which they continued to decrease more slowly. Therefore, mean values of rate and contractile force were calculated 30 minutes and 60 minutes after halothane anesthesia, and were subsequently used for statistical evaluation.

After discontinuation of halothane administration, the automaticity and the contractile force of the papillary muscle remained at the depressed values even though the donor dog's blood pressure and heart rate recovered to control values.

**EFFECTS OF HALOTHANE ON THE ISOLATED SINOATRIAL NODE (TABLE 1)**

Soon after the beginning of perfusion with arterial blood of the donor dog, the sinoatrial node preparation started beating quite regularly, and within 30 minutes, the rate became stable. The average rate of seven preparations before halothane administration was 110 beats/min, significantly lower than the heart rate of the donor dog.

Halothane administration decreased the rate of the sinoatrial node preparation slightly but significantly (P < 0.05), compared with the larger decrease in the heart rate of the donor dog (P < 0.01).
Fig. 2. Effects of intravenous injection of norepinephrine into the donor dog during halothane administration. Three μg/kg produced bigeminal rhythm mixed with multifocal ventricular tachycardia at A. The heart rate recording picked up only R waves of the normal electrocardiogram, thus showing a slow rate during bigeminal rhythm. The numbers above the contractile force recording represent the rate of ventricular automaticity. In isolated preparations, positive chronotropic and inotropic effects of norepinephrine were apparent, but there were no arrhythmic contractions in the papillary muscle, even when ventricular fibrillation was induced by 10 μg/kg in the donor dog.

**Effects of Halothane on the Responses to Intravenous Norepinephrine (Fig. 2)**

Prior to halothane administration, norepinephrine, 1 to 10 μg/kg, iv, injected into the donor dog, increased both blood pressure and heart rate soon after the start of injection, reaching maximal values in about a minute and remaining at that level for about a minute. Both blood pressure and heart rate then decreased gradually to control values. Intravenous injection of norepinephrine caused sinus tachycardia in the donor dog and only slight changes in configuration of the ST and T waves.

After a delay of about 30–60 seconds (because of the circulation time of norepinephrine and tubing deadspace), automaticity and contractile force of the papillary muscle preparation and the rate of the sinoatrial node preparation increased for about 2 minutes.

The effects of intravenous injection of norepinephrine into the donor dog were compared with those of intra-arterial administration of norepinephrine to the isolated preparation. There was considerable variation in responses to norepinephrine among isolated preparations; 1 μg/kg and 3 μg/kg norepinephrine, iv, into the donor had essentially the same effects as 0.1 and 0.3 μg, respectively, norepinephrine administered intra-arterially to the isolated preparations, in increasing the rate and contractile force of the papillary muscle and the rate of the sinoatrial node. The duration of the response to intravenously injected norepinephrine was always longer than that to intra-arterially injected norepinephrine.
TABLE 2. Effects of Halothane on the Responses of the Isolated Sinoatrial Node and Heart Rate of the Donor Dog to Intravenous Norepinephrine (Mean ± SE)

<table>
<thead>
<tr>
<th></th>
<th>Heart Rate of Donor Dog</th>
<th>Sinoatrial Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Basal Rate (Beats/Min)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>1 μg/kg</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>3 μg/kg</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Halothane, 1 per cent</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>1 μg/kg</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>3 μg/kg</td>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

* Significant change from control, P < 0.01.
† Two dogs showed ventricular arrhythmia with 3 μg/kg.

After 30 minutes of administration of 1 per cent halothane, sensitization of the ventricular muscle to norepinephrine was observed in the donor dog. Intravenous injection of norepinephrine produced transitory increases of blood pressure and heart rate in the donor dog, and ventricular arrhythmias occurred at the time of maximal heart rate. Norepinephrine, 1 μg/kg, produced bigeminal rhythm or multifocal tachycardia in more than half the donor dogs, and 3 μg/kg produced arrhythmias in all dogs. In four of 14 dogs, ventricular fibrillation occurred (fig. 2).

In contrast to the response of the donor dog, the isolated preparation did not show arrhythmic contractions or irregular sinus rate even when the heart of the donor dog was fibrillating, as shown in figure 2. The automaticity and the contractile force of the papillary muscle were depressed by halothane, but the relative increase in contractile force after intravenous administration of norepinephrine to the donor dog was the same during halothane administration as before. These results were similar to those observed for intra-arterial administration of norepinephrine to the preparation, as described in the next section.

The responses of the heart rate of the donor dog and the automaticity of the sinoatrial node preparation to intravenous administration of norepinephrine were compared in five experiments (table 2). Halothane decreased the heart rate, but the percentage increase produced by norepinephrine was not depressed by halothane. This was also observed in the isolated preparation, in which the rate was depressed slightly by halothane, but the percentage changes induced by norepinephrine were not depressed.

**EFFECTS OF HALOTHANE ON THE RESPONSES OF THE PAPILLARY MUSCLE PREPARATION TO INTRA-ARTERIAL NOREPINEPHRINE AND PERIVASCULAR NERVE STIMULATION (FIGS. 3–5)**

**Contractile Force.** Norepinephrine administered directly to the preparation intra-arterially prior to halothane administration increased contractile force after a delay of 20–40 seconds (fig. 3). As already reported, the frequency-related increase in the contractile force was negligible up to 2 Hz, so increases in tension can be interpreted as being the direct positive inotropic effect of norepinephrine. The dose-related increase in contractile force was examined in five experiments (fig. 3). It is noteworthy that the increase in contractile force in the isolated preparation reached 300 per cent of the basal contractile force following 0.3 μg norepinephrine. Halothane decreased the basal contractile force, but the percentage increase, using norepinephrine, was not significantly changed (fig. 4).
Perivascular nerve stimulation increased the contractile force soon after the start of stimulation, as shown in the right panel of figure 3. A positive inotropic effect equal to that of 0.1 to 0.3 μg norepinephrine was produced by 15 to 30 seconds of stimulation at 4–15 V, 10–30 Hz, of 1 to 3 msec duration. Halothane did not change the response to perivascular nerve stimulation when expressed as percentage increase.

Automaticity. Intra-arterial administration of norepinephrine and perivascular nerve stimulation increased automaticity, but arrhythmias were not produced, even when the rates were maximal. The maximal increase in the rate averaged 45 per cent, i.e., 70 beats/min (fig. 5). Halothane did not affect the percentage increase in the rate produced by either intra-arterial administration of norepinephrine or perivascular nerve stimulation.

**Effects of Halothane on the Responses to Intra-arterial Norepinephrine in the Sinoatrial Node Preparation (Figs. 3 and 6)**

The automaticity of the sinoatrial node preparation increased after intra-arterial injection of norepinephrine prior to halothane administration, the maximal increase with 0.3 μg of norepinephrine being 68 per cent, i.e., 190 beats/min. The percentage increase in the rate during halothane administration following norepinephrine was slightly greater, although the difference was not statistically significant.
Fig. 4. Effects of halothane on the dose-dependent percentage increase in the contractile force of the papillary muscle. The slight shift of the curve caused by halothane is not statistically significant. Vertical bars represent SEM.

Fig. 5. Effect of halothane on the dose-dependent percentage increase in the rate of ventricular automaticity of the papillary muscle preparation. There was no significant change. Vertical bars represent SEM.

Fig. 6. Effect of halothane on the dose-dependent percentage increase in the rate of the isolated sinoatrial node. Halothane slightly shifted the curve to the left, but this was not statistically significant. Vertical bars represent SEM.

Rine was almost the same as that to norepinephrine, iv, as described in the preceding section.

Effects of Electrical Pacing on the Papillary Muscle Preparation during Halothane Administration (Fig. 7)

In the isolated spontaneously beating papillary muscle, norepinephrine or perivascular nerve stimulation did not produce arrhythmias even during halothane administration, so the preparation was electrically driven at twice the threshold voltage at various frequencies in an attempt to produce arrhythmias. In three experiments, the papillary muscle was driven during halothane administration at frequencies from 1.5 to 4 Hz while norepinephrine was injected intra-arterially into the preparation. The papillary muscle showed an increase in contractile force, but no irregular beats. In the same
experiments, norepinephrine was given intravenously, using an infusion pump (Harvard Apparatus), to the donor dog during halothane administration at a rate of 1 \( \mu \text{g/kg/min.} \) As shown in figure 7, the donor dog showed a stable bigeminal rhythm. The papillary muscle showed an increase in contractile force and automaticity, but no irregular beats. The papillary muscle was then driven at frequencies of 1 to 4 Hz; no arrhythmias of the papillary muscle were produced.

**Discussion**

The present study of isolated preparations of the heart shows that halothane has negative inotropic and chronotropic effects. The direct negative inotropic effect decreased the contractile force of the papillary muscle about 50 per cent. This is consistent with other reports in which rat heart, cat papillary muscle, and rabbit heart perfused with artificial salt solutions were used. Also, as reported by others, halothane decreased the rate of the isolated sinoatrial node only slightly. The heart rate of the donor dog was always higher than the rate of the sinoatrial node preparation, and the former decreased more than the latter during halothane administration. This may indicate that the sinoatrial node of the donor animal is influenced by the sympathetic nerve and that the decrease in heart rate in the whole animal is attributable not only to the direct effect of halothane on the sinoatrial node but also to the depressing effect of halothane on sympathetic nerve activity.

Recovery of contractile force and sinoatrial rate to the pre-halothane level was very slow after discontinuation of halothane administration in the donor dog, unlike the rapid return to control levels reported for preparations bathed in artificial salt solution. This
delayed recovery is attributed to the effect of halothane remaining in the donor animal. Halothane is known to be excreted very slowly from the body after discontinuation of anesthesia.\textsuperscript{19,20} However, in the donor dog, blood pressure and heart rate returned to control values steadily after halothane administration was terminated, probably by virtue of compensatory mechanisms such as autonomic neural activity.

The basal contractile force of the papillary muscle and automaticity of the sinoatrial node were decreased by direct negative inotropic and chronotropic effects of halothane, but positive inotropic and chronotropic effects of norepinephrine on contractile force and automaticity, expressed on a percentage basis, were not influenced by halothane administration. There has been a report to the contrary,\textsuperscript{14} namely, that halothane enhances the effects of norepinephrine on the contractile force of the cat papillary muscle and on the rabbit atrial rate.

In the isolated papillary muscle, we compared the effect of norepinephrine by injecting directly into the preparation and by stimulating the perivascular nerve to release norepinephrine endogenously. In both cases the chronotropic and inotropic effects were similar, and halothane did not change the response to either exogenous or endogenous norepinephrine.

One of the purposes of the present study was to determine whether increased automaticity or re-entry is the mechanism for halothane–catecholamine-induced arrhythmias. The blood-perfused canine papillary muscle preparation was stable enough to show changes of automaticity due to halothane and norepinephrine. Although the preparation is small, it contains the Purkinje system up to the bundle of His, and so the rate of automaticity of the preparation is almost the same as the ventricular rate of the dog heart with atroventricular block, as reported by Vick.\textsuperscript{4}

In the present study, ventricular automaticity was slightly depressed by halothane, as previously reported.\textsuperscript{5,6} However, the chronotropic response to exogenous or endogenous norepinephrine was not depressed by halothane when compared on a percentage basis. It has been reported that the effect of epinephrine on the isolated Purkinje fiber was greatly depressed by halothane\textsuperscript{6} and that halothane has an antiarrhythmic effect\textsuperscript{21} on some experimental arrhythmias, such as those produced by digitalis, the mechanism of which is thought to be increased automaticity.

During halothane administration, irregularities of rhythm were not produced in the papillary muscle preparation. The maximal rate attained by norepinephrine was about 70 beats/min, which was much less than the sinoatrial rate. It can thus be concluded that halothane–catecholamine-induced arrhythmias are not caused by an increase in ventricular pacemaker activity to a rate exceeding that of the sinoatrial node.

Therefore, it is unlikely that the mechanism of halothane–catecholamine-induced arrhythmia is increased automaticity, but there is still need for consideration of ventricular automaticity under the influence of electrical pacing. In Vick’s experiments\textsuperscript{4} using the dog heart with surgically produced atroventricular block in situ, chloroform–epinephrine-induced arrhythmias were produced only when electrical pacing was applied to the ventricle. There have been other reports that show driving can enhance automaticity.\textsuperscript{25–28}

In the present study, electrical pacing of the isolated papillary muscle did not produce arrhythmias.

Since changes in ventricular automaticity caused by halothane are an unlikely mechanism for halothane–catecholamine-induced arrhythmia, a re-entry mechanism must be involved. Re-entry excitation requires a certain size of tissue, in which the excitation wave travels until the first depolarized part of the tissue recovers its excitability. Comparing our study and Vick’s,\textsuperscript{4} the rates of ventricular automaticity are the same and the protocols for applying electrical pacing are similar, but arrhythmia occurred only in Vick’s intact ventricle. This may suggest that our preparation is too small for re-entry excitation to occur. In addition to this finding, electrophysiologic studies with halothane suggest favorable conditions for re-entry excitation.\textsuperscript{25,26} Therefore, although re-entry excitation has not been dem-
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onstrated, it would seem to be the most probable mechanism to account for halothane–catecholamine-induced arrhythmia.

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