Comparison of the Arrhythmic Doses of Epinephrine during Forane,* Halothane, and Fluoroxyne
Anesthesia in Dogs

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The effect of Forane on epinephrine-induced cardiac arrhythmias was tested in dogs by comparing it with halothane and fluoroxyne. The dose of epinephrine necessary to produce two or more premature ventricular contractions at 1.25 and 2.0 MAC and at Pao₂'s of 20, 40, and 80 torr were determined. Only 14 to 22 per cent as much epinephrine as in the awake state was needed to produce arrhythmias during halothane anesthesia. The amounts of epinephrine which induced arrhythmias during fluoroxyne and Forane anesthesia did not differ from the values in awake animals. With Forane, production of arrhythmias required progressively more epinephrine as Pao₂ increased. With halothane and fluoroxyne, the same trend was present, but it was not significant. As depth of anesthesia increased, more epinephrine was needed to produce arrhythmias with all agents tested. (Key words: Halothane; Fluoroxyne; Forane; Epinephrine-induced arrhythmias; Premature ventricular contraction; Pao₂.)

Several commonly used inhalated anesthetics sensitize the myocardium to the arrhythmic properties of epinephrine.¹ A significant advantage of any new inhalation anesthetic would be its lack of this sensitizing property and, even more, its ability to prevent epinephrine-induced arrhythmias. A recently developed inhalation anesthetic, Forane (Com- pound 469; 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether), was purported not to sensitize the myocardium to epinephrine-induced arrhythmias.² To study this property, we modified the classic technique of Meek, Hathaway and Orth.³ They compared the types and durations of arrhythmias after injection of a standard intravenous dose of epinephrine (10 µg/kg in 5 ml saline solution over one minute) into the same dog awake and anesthetized. However, because their technique permits neither construction of a dose–response curve nor determination of the threshold dose of epinephrine that causes arrhythmias, we modified it to overcome these limitations and included control of carbon dioxide levels and depth of anesthesia.

We compared the doses of epinephrine needed to produce arrhythmias in awake dogs and in dogs anesthetized with Forane, halothane, and/or fluoroxyne. We chose halothane because it represents a sensitizing agent,¹ and fluoroxyne because it represents a nonsensitizing agent.²

Methods
Twenty-nine unanesthetized mongrel dogs of either sex weighing between 8.2 and 23.2 kg were anesthetized with the anesthetic studied in oxygen only. The trachea was intubated with a cuffed tube, through which a fine nylon catheter was inserted to allow sampling of anesthetic gas. Alveolar anesthetic concentrations were measured by a Beckman LB-1 infrared gas analyzer. End-tidal gas was sampled continuously from a needle in the endotracheal tube for measurement of Pao₂ with a second Beckman LB-1 infrared gas analyzer. An esophageal thermistor probe was inserted and connected to a Yellow Springs Telether-
mometer. Esophageal temperature was maintained between 36.5 and 39°C. A femoral arterial catheter allowed continuous pressure measurement and intermittent blood-gas analysis. \( \text{Paco}_2 \) was measured with a Severinghaus electrode, oxygen tension with a modified Clark electrode, and pH with a Radiometer electrode. A catheter (PE190, 36-inch, volume 0.85 ml) was advanced through a femoral vein until a right ventricular pressure pattern was observed. The catheter was then withdrawn until the ventricular pattern just disappeared, at which position the tip was assumed to be in the right atrium. In two instances a common carotid artery and external jugular vein were catheterized in a similar manner because previous manipulations had obliterated both femoral veins and arteries. A \( \text{Paco}_2 \) level of approximately 20, 40, or 80 torr was established by hyperventilation or addition of CO\(_2\) to the inspired gas mixture. A MAC level of 1.25 or 2.0 was established. (MAC is defined as the minimum alveolar concentration of anesthetic required to prevent movement in 50 per cent of animals when painfully stimulated.'). These equivalents in the dog are: fluroxene 6.0 per cent; halothane 0.87 per cent; Forane 1.48 per cent. Cardiac rhythm was monitored by lead II of the electrocardiogram. Arterial pressure, right atrial pressure, ECG, and \( \text{Paco}_2 \) were recorded continuously on a Grass Model 7 polygraph.

When the desired alveolar anesthetic concentration and \( \text{Paco}_2 \) had been established, an arterial blood gas sample was obtained to determine \( \text{Paco}_2 \) and calculate base deficit. When the base deficit was 5 mEq or greater, sodium bicarbonate (1/6 base deficit \( \times \) kg body weight) was given intravenously until base deficit was less than 5 mEq. The epinephrine challenge was delayed until \( \text{Paco}_2 \) had returned to baseline.

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**Fig. 1.** The mean (± SE) arrhythmic dose of epinephrine awake and at each MAC with each agent. Arterial carbon dioxide tension equals 40 torr.
A predetermined dose of epinephrine based on body weight, diluted with physiologic saline solution to 5 ml, was administered through the right atrial catheter over a 60-second period by a Harvard infusion pump, followed immediately by a 2-ml physiologic saline solution flush through the same catheter. When two or more premature ventricular contractions did not occur within five minutes, a larger dose of epinephrine was given. The next infusion was delayed until arterial pressure had returned to control and at least five additional minutes had elapsed. When the arrhythmia did occur, anesthetic depth or P_{a\text{CO}_2} was changed and the epinephrine challenge repeated, starting with the low dose. In this manner, epinephrine challenges continued until arrhythmias were obtained at each P_{a\text{CO}_2} and at each anesthetic level. Each dog was studied in the same manner using one of the other agents or while awake after a minimum of a week. Sequences of anesthetic agent, carbon dioxide tensions, and anesthetic concentration were randomized.

The awake control measurements were obtained as follows. The dog was anesthetized with either Forane or halothane for placement of arterial and right atrial catheters. The dog awakened (duration of anesthesia was 20 minutes or less) and was placed upright in a restraining sling. After a two-hour wait, during which arterial pressure and P_{a\text{CO}_2} were

![Graph](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931577/)

**Fig. 2.** Increases in mean arterial pressure following administration of epinephrine and during arrhythmias. Values represent mean percent change (± SE) from pre-epinephrine challenge pressures.
repeatedly measured and found to be stable, we proceeded with the epinephrine challenge as described above.

Five animals survived studies of all anesthetics and the awake control. Twenty-four animals died during the course of the study, either from ventricular fibrillation or of intercurrent disease. No effort was made to salvage animals who developed ventricular fibrillation. All data were analyzed with Student's t test; paired analysis was performed where possible.

**Results**

The mean arrhythmic dose of epinephrine in awake animals and at each MAC during normocapnia with each agent is shown in figure 1. Significantly less epinephrine was needed to produce arrhythmias at 1.25 and 2.0 MAC halothane than in nonanesthetized animals. The arrhythmic dose was not significantly altered by Forane or fluroxene. With Forane, a significantly greater dose of epinephrine was needed to produce arrhythmias at 2.0 MAC than at 1.25 MAC.

Increases in mean arterial blood pressure after epinephrine as per cent of the prechallenge pressure at each MAC with each agent are compared in figure 2. The increase of mean arterial pressure during arrhythmias was significantly less during halothane anesthesia than during either Forane or fluroxene anesthesia. With all agents greater increases in mean arterial pressure occurred at 2.0 MAC than at 1.25 MAC; these were associated with the larger doses of epinephrine needed for arrhythmias at this level.
The heart rate at the time of arrhythmias did not differ significantly from the awake value with any of the agents.

The effect of \( P_{\text{aCO}_2} \) on mean arrhythmic dose of epinephrine with each anesthetic is shown in figure 3. The results of each \( P_{\text{aCO}_2} \) include pooled values at both MAC levels for each agent. With Forane, arrhythmias were significantly more difficult to produce as \( P_{\text{aCO}_2} \) increased from 20 to 40 and from 40 to 80 torr. During halothane anesthesia, hypercarbia significantly increased the arrhythmic dose of epinephrine. With fluoroence, an increase in \( P_{\text{aCO}_2} \) from 20 to 40 torr protected against arrhythmias, whereas a further increase to 80 torr did not. At each \( P_{\text{aCO}_2} \) the arrhythmic dose was significantly less during halothane anesthesia than during Forane or fluoroence anesthesia. The mean arrhythmic dose of epinephrine measured at each MAC level with each agent at each \( P_{\text{aCO}_2} \) is given in table 1.

### Table 1. Arrhythmic Doses of Epinephrine

<table>
<thead>
<tr>
<th>( P_{\text{aCO}_2} ) (torr)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>1.23 MAC</td>
<td>2.0 MAC</td>
<td>1.23 MAC</td>
<td>2.0 MAC</td>
<td>1.23 MAC</td>
<td>2.0 MAC</td>
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<td>13</td>
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<td>4</td>
<td>3</td>
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<tr>
<td>Mean arrhythmic dose (µg/kg)</td>
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<td>6</td>
<td>13</td>
<td>22</td>
<td>19</td>
<td>19</td>
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<tr>
<td>Standard error</td>
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<td>1</td>
<td>3</td>
<td>8</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Number of animals</td>
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<td>18</td>
<td>11</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Mean arrhythmic dose (µg/kg)</td>
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<td>8</td>
<td>22</td>
<td>37</td>
<td>43</td>
<td>48</td>
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<tr>
<td>Standard error</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>9</td>
<td>16</td>
<td>11</td>
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<tr>
<td>Number of animals</td>
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<td>13</td>
<td>18</td>
<td>14</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Mean arrhythmic dose (µg/kg)</td>
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<td>34</td>
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<td>26</td>
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</tbody>
</table>

The mean arrhythmic dose of epinephrine we found in awake animals and during halothane anesthesia agrees with that reported by Raveotes.\(^9\) As with Forane, we found no epinephrine sensitization during fluoroence anesthesia. While the mean arrhythmic epinephrine dose during fluoroence anesthesia has not been reported, White\(^10\) did not see arrhythmias following administration of 20 µg/kg epinephrine to dogs during fluoroence-nitrous oxide anesthesia.

The protection afforded by elevated \( P_{\text{aCO}_2} \) is both consistent and in conflict with results of others. Ueda,\(^11\) working with pentobarbital-anesthetized dogs, found that the addition of \( \text{CO}_2 \) to expired gases increased the dose of epinephrine necessary to induce arrhythmias. Virtue\(^12\) found that dogs were more sensitive to epinephrine-induced arrhythmias during cyclopropane anesthesia with respiratory alkalosis than with respiratory acidosis. In man, hypercarbia may cause arrhythmias during cyclopropane anesthesia.\(^13\) The direct effect of elevated \( P_{\text{aCO}_2} \) on the heart is depression of contractility, with minimal effects on rhythm.\(^14\) It may be that the reflex response to hypercarbia differs among animal species. The response may reflect species differences in endogenous release of catecholamines or in response to elevated catecholamine levels. Anesthetic agents differ in the cardiac rhythm disturbances seen during hy-
perfoaquam. Arrhythmias occur at lower $P_{CO_2}$ levels during cyclopropane anesthesia than during halothane anesthesia. Also, as cyclopropane concentration increases, arrhythmias occur at lower $P_{CO_2}$ levels. Such relationship is not seen regularly with halothane.

Meek, Hathaway and Orth noted increased myocardial sensitivity to epinephrine-induced arrhythmias as cyclopropane concentration increased. This contrasts with our forane results and with the tendency we saw with halothane and fluoroxiene. One reason for the difference may be the differences between patterns of arterial pressure with various anesthetics. Blood pressure is elevated with cyclopropane, in contrast to forane and halothane. Fluoroxiene behaves in an intermediate fashion. Moe and Dresel have shown that elevation of arterial pressure is necessary for induction of arrhythmias with epinephrine. The differences between agents may reflect dissimilarity in endogenous catecholamine levels associated with the various agents. Smaller additional increases may be needed to produce arrhythmias during cyclopropane anesthesia. The difference may reflect dissimilarity in depression of ectopic foci, which prevents emergence of aberrant rhythms with the nonsensitizing agents. Conversely, the differences may reflect dissimilar properties of the various anesthetics to allow sinus and atrioventricular nodes and the ventricular conduction systems to respond to increased rate and automaticity and thereby prevent emergence of ectopic foci.

The anesthetic-epinephrine-arrhythmia relationship may bear on two additional, common intra-anesthetic circumstances. One is the likelihood of arrhythmias in response to administration of atropine. The nonsensitizing agents may be associated with fewer arrhythmias when vagal blockade with unopposed sympathetic activity is produced. The other is the likelihood of arrhythmias from $CO_2$ elevation alone. Occurrence of arrhythmias is common with cyclopropane and halothane but not with forane or fluoroxiene.

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