Comparison of the Arrhythmic Doses of Epinephrine during Forane, Halothane, and Fluroxene 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 fluroxene. The doses of epinephrine necessary to produce two or more premature ventricular contractions at 1.25 and 2.0 MAC and at Pa_{CO_2}'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 fluroxene and Forane anesthesia did not differ from the values in awake animals. With Forane, production of arrhythmias required progressively more epinephrine as Pa_{CO_2} increased. With halothane and fluroxene, 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; Fluroxene; Forane; Epinephrine-induced arrhythmias; Premature ventricular contraction; Pa_{CO_2}.)

SEVERAL commonly used inhaled 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 (Compound 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 fluroxene. We chose halothane because it represents a sensitizing agent[4] and fluroxene because it represents a nonsensitizing agent.[5]

Methods

Twenty-nine unpremedicated 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 Pa_{CO_2} with a second Beckman LB-1 infrared gas analyzer. An esophageal thermistor probe was inserted and connected to a Yellow Springs Telether-

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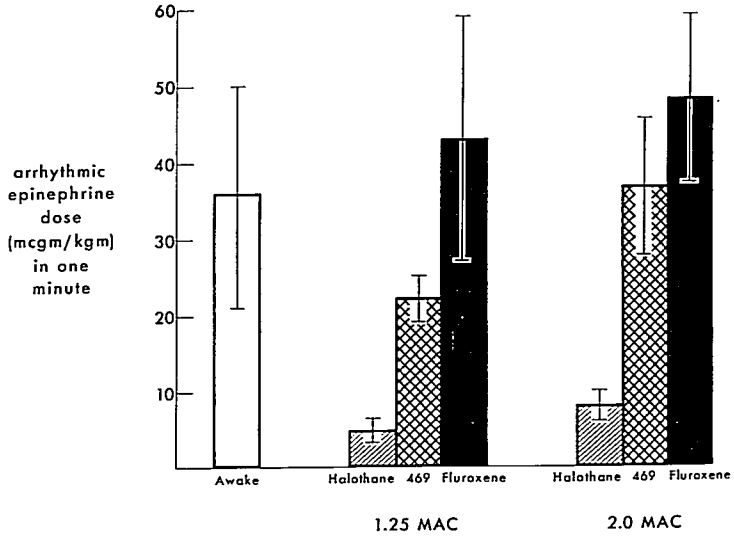

FIG. 1. The mean (± SE) arrhythmic dose of epinephrine awake and at each MAC with each agent. Arterial carbon dioxide tension equals 40 torr.

mometer. Esophageal temperature was maintained between 36.5 and 39 C. A femoral arterial catheter allowed continuous pressure measurement and intermittent blood–gas analysis. Pa_{CO_2} was measured with a Severinghaus electrode, oxygen tension with a modified Clark electrode, and *p*H 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 Pa_{CO_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.[6]). These equivalents in the dog are: fluroxene 6.0 per cent[7]; halothane 0.87 per cent[7]; Forane 1.48 per cent.[8] Cardiac rhythm was monitored by lead II of the electrocardiogram. Arterial pressure, right atrial pressure, ECG, and Pa_{CO_2} were recorded continuously on a Grass Model 7 polygraph.

When the desired alveolar anesthetic concentration and Pa_{CO_2} had been established, an arterial blood gas sample was obtained to determine Pa_{CO_2} and calculate base deficit. When the base deficit was 5 mEq or greater, sodium bicarbonate (1/6 base deficit × kg body weight) was given intravenously until base deficit was less than 5 mEq. The epinephrine challenge was delayed until Pa_{CO_2} had returned to baseline.

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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 Pa_{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 Pa_{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 Pa_{CO_2} were

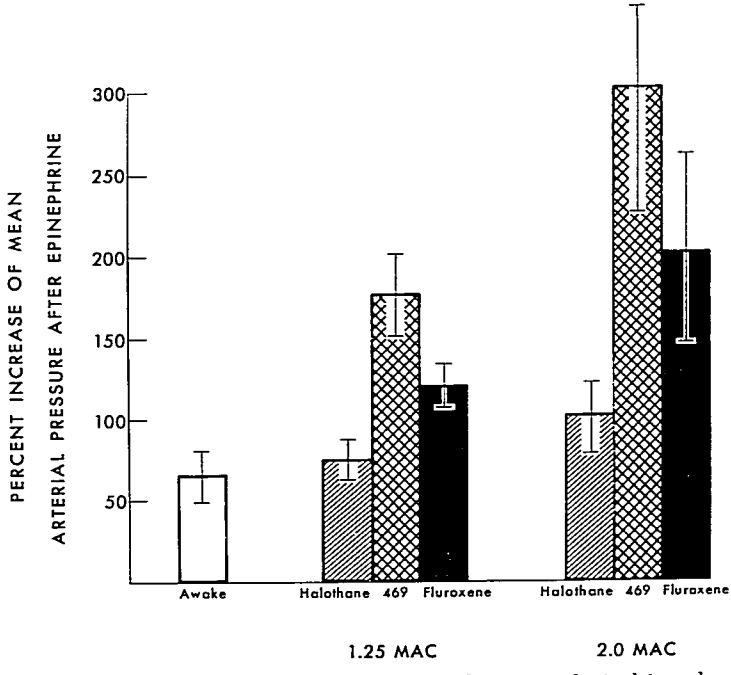

FIG. 2. Increases in mean arterial pressure following administration of epinephrine and during arrhythmias. Values represent mean per cent change (± SE) from pre-epinephrine challenge pressures.

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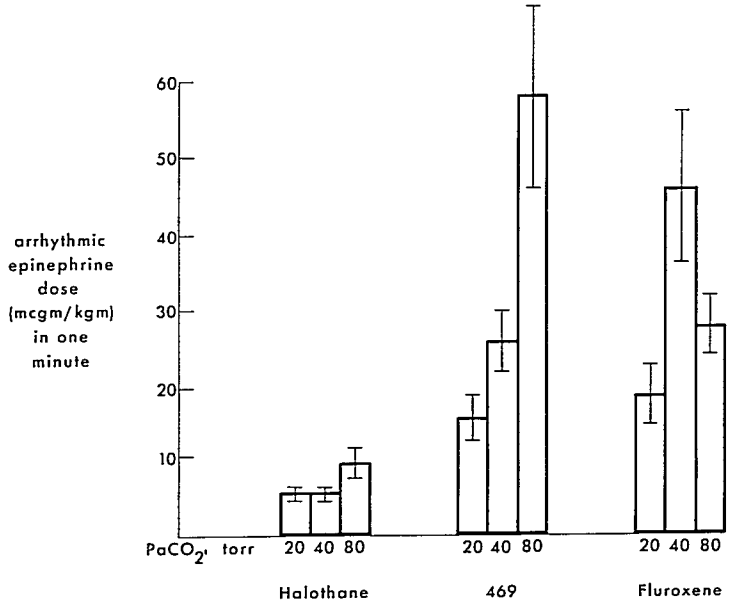

FIG. 3. Effects of arterial carbon dioxide tension on arrhythmic doses of epinephrine. Value (mean ± SE) at each P_{CO_2} includes results at both 1.25 and 2.0 MAC.

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.

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TABLE 1. Arrhythmic Doses of Epinephrine

	Halothane		Forane		Fluroxene		Control
	1.25 MAC	2.0 MAC	1.25 MAC	2.0 MAC	1.25 MAC	2.0 MAC	
Pa_{CO_2} 20 torr							
Number of animals	13	13	19	8	4	3	—
Mean arrhythmic dose (μg/kg)	5	6	13	22	19	19	—
Standard error	1	1	3	8	8	4	—
Pa_{CO_2} 40 torr							
Number of animals	13	12	18	11	5	5	7
Mean arrhythmic dose (μg/kg)	5	8	22	37	43	48	36
Standard error	1	2	3	9	16	11	15
Pa_{CO_2} 80 torr							
Number of animals	13	13	18	14	4	3	—
Mean arrhythmic dose (μg/kg)	7	14	66	77	23	34	—
Standard error	2	4	20	26	5	14	—

The heart rate at the time of arrhythmias did not differ significantly from the awake value with any of the agents.

The effect of Pa_{CO_2} on mean arrhythmic dose of epinephrine with each anesthetic is shown in figure 3. The results of each Pa_{CO_2} include pooled values at both MAC levels for each agent. With Forane, arrhythmias were significantly more difficult to produce as Pa_{CO_2} increased from 20 to 40 and from 40 to 80 torr. During halothane anesthesia, hypercarbia significantly increased the arrhythmic dose of epinephrine. With fluroxene, an increase in Pa_{CO_2} from 20 to 40 torr protected against arrhythmias, whereas a further increase to 80 torr did not. At each Pa_{CO_2} the arrhythmic dose was significantly less during halothane anesthesia than during Forane or fluroxene anesthesia. The mean arrhythmic dose of epinephrine measured at each MAC level with each agent at each Pa_{CO_2} is given in table 1.

Discussion

In the present study halothane sensitized the myocardium to epinephrine-induced arrhythmias, whereas Forane and fluroxene did not. Our data suggest that it is safer to use Forane or fluroxene than halothane when epinephrine is to be injected or released (*e.g.*, pheochromocytoma). Forane and fluroxene did not protect against epinephrine-induced arrhythmias, however.

The mean arrhythmic dose of epinephrine we found in awake animals and during halothane anesthesia agrees with that reported by Raventos.[9] As with Forane, we found no epinephrine sensitization during fluroxene anesthesia. While the mean arrhythmic epinephrine dose during fluroxene anesthesia has not been reported, White[10] did not see arrhythmias following administration of 20 μg/kg epinephrine to dogs during fluroxene–nitrous oxide anesthesia.

The protection afforded by elevated Pa_{CO_2} is both consistent and in conflict with results of others. Ueda,[11] working with pentobarbital-anesthetized dogs, found that the addition of CO_2 to respired 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 Pa_{CO_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-

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percapnia. Arrhythmias occur at lower P_{CO_2} levels during cyclopropane anesthesia than during halothane anesthesia.[15] 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 [3] 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 fluroxene. 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. Fluroxene behaves in an intermediate fashion. Moe [16] and Dresel [17] 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 fluroxene.

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