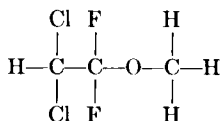# EFFECT OF EPINEPHRINE ON THE DOG HEART DURING METHOXYFLURANE ANESTHESIA

BETTY J. BAMFORTH, M.D., KARL L. SIEBECKER, M.D.
RICHARD KRAEMER, O. SIDNEY ORTH, M.D., PH.D.

DURING cyclopropane anesthesia, the myocardium of the dog is sensitized to epinephrine with production of ventricular tachycardia and fibrillation. Meek, Hathway and Orth [1] demonstrated that a dose of epinephrine can be determined for each dog which will consistently produce ventricular tachycardia during cyclopropane anesthesia. The reproducibility of this phenomenon makes it a useful standard test for comparing the effects of other anesthetic agents regarding cardiac sensitization.

Methoxyflurane (Penthrane) is one of a series of fluorinated hydrocarbons introduced by Artusio and Van Poznak [2, 3] and has the structural formula:

$$H-\overset{\displaystyle Cl}{\underset{\displaystyle Cl}{\overset{\textstyle |}{\underset{\textstyle |}{C}}}}-\overset{\displaystyle F}{\underset{\displaystyle F}{\overset{\textstyle |}{\underset{\textstyle |}{C}}}}-O-\overset{\displaystyle H}{\underset{\displaystyle H}{\overset{\textstyle |}{\underset{\textstyle |}{C}}}}-H$$

Its anesthetic properties are being intensely investigated by a number of workers.

The present study was undertaken to compare the effect of epinephrine on the dog heart during methoxyflurane anesthesia with that seen with cyclopropane anesthesia.

METHOD

Twenty dogs were used in these experiments. Without premedication, each was anesthetized for thirty minutes with cyclopropane by to-and-fro absorption technique. Then, using the standard technique of Meek,[1] epinephrine, 0.01 mg./kg. of body weight, diluted to 5 ml. in normal saline solution, was administered intravenously at a constant

rate of 1.0 ml. per ten seconds. The electrocardiogram was recorded continuously by means of a Sanborn Twin Viso Recorder or a Gilson Polygraph. In some experiments the electroencephalograph was used to determine depth of anesthesia and in others the systemic blood pressure was monitored by means of a cannula in the femoral artery and a Statham pressure transducer. If ventricular tachycardia was not produced, the administration of epinephrine was repeated using 0.02 mg./kg. of body weight, diluted to 5 ml.

Several days after the cyclopropane anesthesia, with production of ventricular tachycardia by administration of epinephrine, the same dogs were anesthetized with methoxyflurane. After anesthesia had been established for thirty minutes, epinephrine was administered intravenously in the same manner and dosage. If ventricular tachycardia did not then occur, 0.02 mg./kg. of body weight of epinephrine was diluted to 5 ml. and administered as before at a constant rate of 1.0 ml. per ten seconds. Again if ventricular tachycardia was not produced, 0.05 mg./kg. of body weight of epinephrine was diluted and administered in the same manner.

To assure adequate pulmonary ventilation, respiration was usually assisted manually, but was not controlled. Arterial blood samples were drawn on several occasions and the pH was determined with a Beckman Model G glass electrode pH meter.

RESULTS

During the control anesthetization with cyclopropane, 0.01 mg./kg. of body weight of epinephrine produced ventricular tachycardia in 16 of the 20 dogs. The other 4 animals required a dose of 0.02 mg./kg. of body weight to produce ventricular tachycardia.

After anesthetization with methoxyflurane

and the administration of 0.01 mg./kg. of body weight of epinephrine, ventricular tachycardia was seen only in 3 animals. The most common arrhythmia, seen in 9 of the 20 administrations was complete atrio-ventricular block. A typical electrocardiogram is shown in figure 1. Atrio-ventricular nodal rhythm occurred five times and sino-auricular tachycardia twice.

Fifteen animals were then given a dose of 0.02 mg./kg. of body weight of epinephrine after a 15-minute rest period. Ventricular

tachycardia was produced in 2 animals and one of them had ventricular fibrillation. Seven of the dogs had complete atrio-ventricular block, 3 had a sino-auricular tachycardia, one had atrio-ventricular nodal rhythm and in another there was sino-auricular rhythm.

In 10 of the animals a dose of 0.05 mg./kg. of body weight of epinephrine was then administered. This produced ventricular tachycardia in one dog and ventricular fibrillation in another. There were three instances

Dog number 13

Cyclopropane anesthesia   Epinephrine 0.01 mgm./kilo. body wt.

Ventricular tachycardia

Methoxyflurane anesthesia   Epinephrine 0.02 mgm./kilo. body wt.
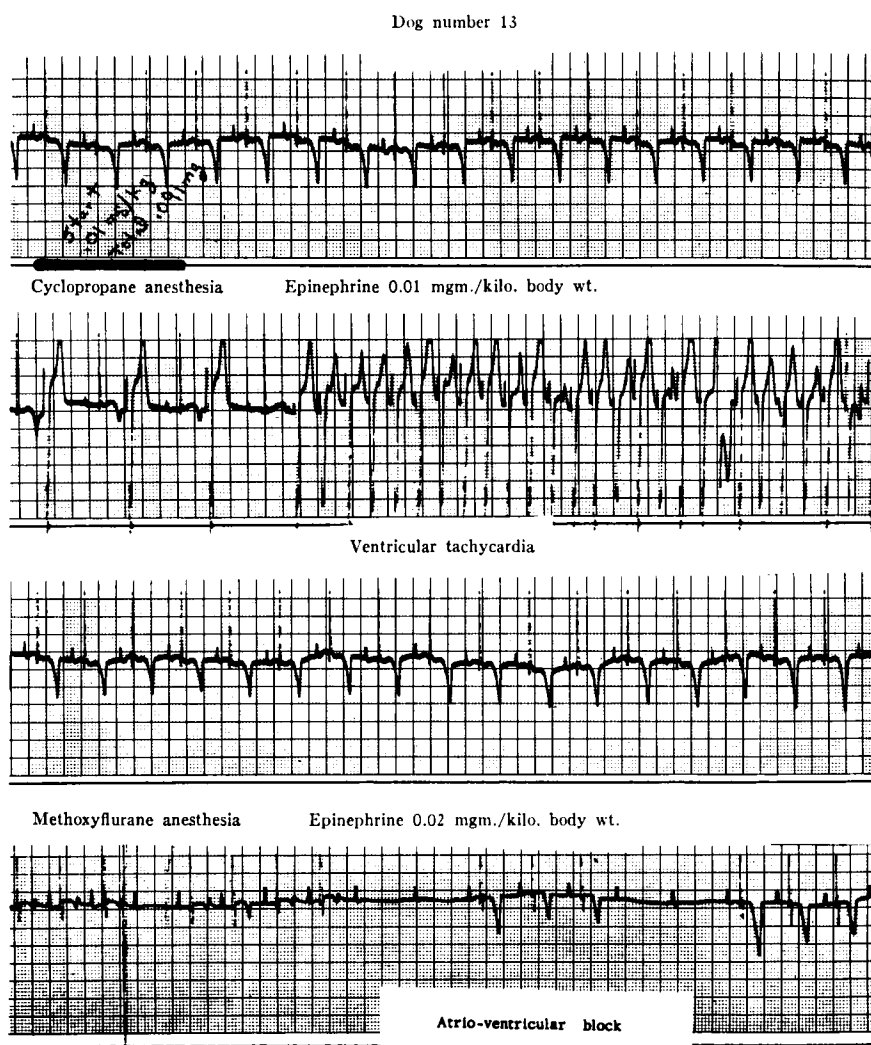
Atrio-ventricular block

FIG. 1. Typical electrocardiogram showing the most common arrhythmia, complete atrio-ventricular block, seen after administration of epinephrine during methoxyflurane anesthesia.

TABLE 1

ARRYTHMIAS DURING CYCLOPROPANE AND METHOXYFLURANE ANESTHESIA PRODUCED BY EPINEPHRINE

Dog and Weight (kg.)	Cyclopropane Anesthesia Dose Epinephrine (mg./kg. body wt.)	Control Result (rhythm and duration)	Methoxyflurane Anesthesia Dose Epinephrine (mg./kg. body wt.)	Result (rhythm and duration)
1–11	0.01	Ventricular tachycardia 20 seconds	0.01	Atrio-ventricular nodal rhythm
2–8.5	0.01	Ventricular tachycardia 40 seconds	0.01	Complete atrio-ventricular block
3–7	0.01	Ventricular tachycardia 70 seconds	0.01 0.02	Atrio-ventricular nodal rhythm Complete atrio-ventricular block
4–6	0.01	Ventricular tachycardia 26 seconds	0.01 0.02	Sino-auricular tachycardia Sino-auricular tachycardia—occasional premature ventricular contraction
5–8.2	0.01 0.02	2 : 1 block atrio-ventricular rhythm Ventricular tachycardia 84 seconds	0.01 0.02	Atrio-ventricular nodal rhythm Ventricular fibrillation
6–10.5	0.01	Ventricular tachycardia 120 seconds	0.01	Ventricular tachycardia
7–8.6	0.01	Ventricular tachycardia 112 seconds	0.01	Atrio-ventricular block and multifocal ventricular premature contractions
8–9.1	0.01	Ventricular tachycardia 200 seconds	0.01 0.02 0.05	Complete atrio-ventricular block Complete atrio-ventricular block Sino-auricular rhythm
9–9.0	0.01	Ventricular tachycardia 45 seconds	0.01 0.02 0.05	Atrio-ventricular nodal rhythm with multi-focal premature ventricular contractions Atrio-ventricular nodal rhythm Ventricular fibrillation
10–9.2	0.01 0.02	Complete atrio-ventricular block Ventricular tachycardia 90 seconds	0.01 0.02 0.05	Atrio-ventricular nodal rhythm Complete atrio-ventricular block Complete atrio-ventricular block
11–5.2	0.01	Ventricular tachycardia 120 seconds	0.01 0.02 0.05	Complete atrio-ventricular block Complete atrio-ventricular block Complete atrio-ventricular block
12–7.7	0.01	Ventricular tachycardia 82 seconds	0.01 0.02 0.05	Complete atrio-ventricular block Complete atrio-ventricular block plus multifocal ventricular premature con-tractions Complete atrio-ventricular block plus multifocal ventricular premature con-tractions
13–10.2	0.01	Ventricular tachycardia 260 seconds	0.01 0.02 0.05	Complete atrio-ventricular block Complete atrio-ventricular block Sino-auricular tachycardia plus ventricular premature contractions
14–5.9	0.01	Ventricular tachycardia	0.01	Ventricular tachycardia—135 seconds fol-lowed by atrio-ventricular nodal rhythm (rate 40)
15–9.6	0.01 0.02	Complete atrio-ventricular block Ventricular tachycardia 120 seconds	0.01	Ventricular tachycardia —170 seconds
16–10.5	0.01	Ventricular tachycardia 28 seconds	0.01 0.02 0.05	Complete atrio-ventricular block Complete atrio-ventricular block plus a few premature ventricular contractions Ventricular tachycardia—90 seconds
17–19.9	0.01	Ventricular tachycardia 190 seconds	0.01 0.02	Complete atrio-ventricular block Ventricular tachycardia—100 seconds
18–6.8	0.01	Ventricular tachycardia 180 seconds	0.01 0.02 0.05	Complete atrio-ventricular block Sino-auricular tachycardia Sino-auricular tachycardia
19–13.7	0.01	Ventricular tachycardia 90 seconds	0.01 0.02 0.05	Sino-auricular tachycardia Sino-auricular tachycardia Sino-auricular tachycardia
20–6.5	0.01 0.02	Ventricular rhythm (rate 110) Ventricular tachycardia (rate 320) 100 seconds	0.01 0.02 0.05	Sino-auricular tachycardia Sino-auricular tachycardia Sino-auricular tachycardia

TABLE 2

A rrythmias During Methoxyflurane Anesthesia Produced by Epinephrine Intravenously*

Dose Epinephrine (mg./kg. body wt.)	No. of Dogs	Cardiac Rhythm					
		Sinus Nodal	Atrio-Ventricular Nodal	Atrio-Ventricular Block (complete)	Sinus Nodal Tachycardia	Ventricular Tachycardia	Ventricular Fibrillation
0.01	20	1	5	9	2	3	0
0.02	15	1	1	7	3	2	1
0.05	10	2	0	3	3	1	1

* Ventricular tachycardia produced on a previous day during cyclopropane anesthesia in all 20 dogs.

of atrio-ventricular block and three of sino-auricular tachycardia. Two continued to have sino-auricular rhythm. In several of these animals there were marked changes indicative of coronary insufficiency following administration of epinephrine. The pH values of the arterial blood samples were well within the normal range of 7.38–7.42 except on three occasions, when the pulmonary ventilation was inadvertently allowed to become inadequate. This did not appear to affect the results, but the total number of pH determinations is not sufficient to draw definite conclusions.

DISCUSSION

In evaluating the effect of epinephrine on the heart during anesthesia, it is important to have a standard for comparison. In this study, we have first determined the dose of epinephrine which would cause ventricular tachycardia during cyclopropane anesthesia. In most dogs, ventricular tachycardia can be produced during cyclopropane with 0.01 mg./kg. of body weight of epinephrine, although occasionally a larger challenge dose is needed. Rarely, a dog will not have cyclopropane-epinephrine tachycardia. We found it necessary to discard observations from one animal in this study because no reasonable dose of epinephrine would result in ventricular tachycardia during cyclopropane anesthesia. Very large doses of epinephrine may produce electrocardiographic changes of myocardial ischemia or infarction, and occasionally death occurs during recovery. Sixteen of these dogs required a dose of 0.01

mg./kg. of body weight and four 0.02 mg./kg. of body weight of epinephrine to produce ventricular tachycardia during cyclopropane anesthesia.

Adherence to a technique such as that described by Meek, Hathaway and Orth[1] is essential since this will produce consistent results. The concentration of epinephrine in the blood with this method is probably somewhat greater than one would expect to find under conditions of stress such as operation and anesthesia.[4] Increasing the dose of epinephrine greatly, injecting closer to the heart with massive doses or injecting more rapidly, as some investigators have reported, will produce entirely different effects from that obtained with the original technique. The use of cyclopropane anesthesia as a control is considered to be essential.

Our experiments show that the effect of epinephrine on the dog heart during methoxyflurane anesthesia is similar to that of chloroform as shown by Orth and associates.[5] The hazard of epinephrine administration during methoxyflurane anesthesia should contraindicate such a combination in clinical practice.

SUMMARY

After induction of anesthesia with cyclopropane, the dose of epinephrine administered intravenously needed to produce ventricular tachycardia was determined in twenty dogs anesthetized with cyclopropane. On a subsequent day the same dogs were anesthetized with methoxyflurane, and the challenging dose of epinephrine and/or an increased dose

was administered. Methoxyflurane was found to be similar to chloroform in sensitization of the heart to epinephrine, but not as potent as cyclopropane in this regard.

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ANESTHESIA IN NEWBORNS Pentobarbital was more toxic to new-born than to adult rabbits and rats, produced a longer righting reflex in new-born animals but did not anesthetize them effectively in less than toxic doses. Urethane did not anesthetize new-born animals in doses which anesthetized adults. Ether produced loss or righting reflex at lower concentrations for new-born than for adults, but the new-born animals became anesthetized more slowly. (*Weatherall, J. A. C.: Anesthesia in New-Born Animals, Brit. J. Pharmacol. 15: 454 (Sept.) 1960.*)

VETERINARY ANESTHESIA The problems confronting the veterinary anesthetist when dealing with large animals such as horses and cattle are twofold: control of movement and relief of pain. Time-honored methods of man-handling an animal are tending to become outmoded and replaced to a greater extent by tranquillizers and sedatives. For major surgery on the horse, recumbency and restraint are essential. One method of inducing recumbency is the intravenous administration of succinylcholine chloride.

Within 45 to 60 seconds the limbs flex and the animal falls quietly to the ground. The levels of cholinesterase in equine plasma are high, consequently the effect of the relaxant wears off rapidly, the duration of apnea not exceeding 30 to 60 seconds and artificial ventilation rarely being necessary. Anesthetic procedures fall into three types: regional anesthesia, narcosis, and general anesthesia. In contrast to the equine, the bovine temperament is more placid, and handling and restraint do not present the problems associated with the horse. However, because of the multiple ruminant stomach, ruminal regurgitation followed by inhalation pneumonia is a distinct hazard. For this reason, if general anesthesia is necessary, the animal should be intubated with a cuffed endotracheal tube. Dimensions of tubes are large: 1 to 2 cm. internal diameter and 60 to 90 cm. in length. Rebreathing bags of 25 to 35 liters capacity are necessary, and carbon dioxide absorbers must contain up to 3.5 kg. of soda lime. (*Tavernor, W. D.: Anaesthetic Procedures in Larger Domesticated Animals, Proc. Roy. Soc. Med. 53: 717 (Sept.) 1960.*)