THE EFFECT OF ETHER ON CYCLOPROPANE–EPINEPHRINE ARRHYTHMIAS *

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It is well established that ether reduces or prevents irregularities of the heart under cyclopropane-oxygen anesthesia, whether spontaneous (1, 2) or induced by injection of epinephrine (3, 4). This study was undertaken to determine the blood concentration of the anesthetic at which the latter, that is, the irregularities produced by injections of epinephrine, occurred. Many investigators have studied cardiac irregularities, which occur so frequently under cyclopropane-oxygen anesthesia, since the advent of the first report (5) on cyclopropane, in which it was pointed out that missed beats appeared on the blood pressure tracing.

Method

Mongrel dogs, weighing from 20 to 25 kg., were narcotized with intravenous 2 per cent sodium thiopental, using 1 ml. (20 mg.) per kilogram of body weight, which was usually sufficient to last through the preliminary preparation and induction period of cyclopropane. Immediately after the injection of the barbiturate, the trachea was cannulated and strain gauges connected to catheters placed in the root of the aorta and pulmonary artery. Fluoroscopic confirmation was used. Three unipolar electrocardiographic leads were arranged for recording. An oscillographic record, in addition, of one lead was used as a monitor to show the presence or absence of arrhythmias. The aortic and pulmonary artery pressures and the three electrocardiograms were recorded on the same bromide paper.

When satisfactory records under sodium thiopental narcosis were obtained, arterial (femoral) and mixed venous (pulmonary artery) blood samples were drawn. Cyclopropane-oxygen anesthesia was then begun, using the Connell machine. A flow of approximately 1 liter of oxygen per minute was maintained throughout the remainder of the experiment. The flow of cyclopropane was maintained between 100 and 200 ml. per minute, according to the needs of the individual dog. The aim was to hold the animal in the first or second

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plane of the third stage of anesthesia, the upper limit of which Robbins and Baxter (6) found to be at a blood concentration of approximately 17 mg. per 100 cc. In order to prevent accumulation of carbon dioxide, fresh soda lime was used for each experiment, and a free airway was assured by the cannulation of the trachea.

After approximately fifty minutes under cyclopropane-oxygen anesthesia, records were taken and a trial dose of epinephrine was injected, while recording continuously. It was considered a satisfactory dose when runs of premature contractions or a bigeminal rhythm ensued. The range of the required amount of epinephrine was found to vary from 0.9 to 8.5 micrograms per kilogram of body weight in the group of dogs studied. That the first dose was not always satisfactory is shown by the fact that ventricular fibrillation resulted from the first injection of epinephrine in 15 dogs. Epinephrine was administered by femoral vein, in less than one second, in a concentration of 1:10,000 solution freshly diluted with isotonic sodium chloride. Once the satisfactory dose was determined, it remained constant for that animal. When the trial dose proved satisfactory, arterial and venous blood samples were drawn as soon as the previous rhythm of the heart reappeared; this was usually in less than two minutes.

After this, ether was added, usually without changing the rate of flow of cyclopropane. The range of ether flow varied in different experiments from 10 to 72 drops per minute; in the Connell machine used, 27 drops were equal to 1 ml. After approximately thirty minutes, records were begun, and epinephrine again was injected, while recording continuously. If irregularities were absent or greatly reduced, blood samples were drawn and the experiment terminated. If irregularities appeared, the administration of ether-cyclopropane-oxygen was continued for ten to twenty minutes longer, and the above procedure repeated.

RESULTS

Sixty-three dogs were used in this study. Of this group, ventricular fibrillation was produced by the first injection of epinephrine in 15 dogs. Thirty experiments had to be discarded because of spontaneous cardiac irregularities under cyclopropane, damage to the heart during catheterization, blocking of a catheter, unsatisfactory records or uncontrollable hemorrhage. Of the remaining 18, cardiac irregularities attributable to epinephrine were successfully prevented by administration of ether in 13 experiments, while in 5 the irregularities were only delayed in onset or shortened in duration.

Blood Analyses

Determinations of blood oxygen and carbon dioxide content were made in certain experiments. The blood drawn under sodium thiopental served as a blank for nitrogen in the determinations of cyclo-

propane and ether. Dr. Kety (7) and his laboratory assistants developed a method for the determination of nitrous oxide and ether in the presence of each other; our method for the determination of cyclopropane and ether in the presence of each other is a modification of theirs. Cyclopropane is determined at approximately 1 C. and ether at about 41 C., in the same sample.

Oxygen Content

The oxygen content was determined in arterial blood in 23 experiments. As compared with the preliminary period under sodium thiopental, the oxygen content increased during the administration of cyclopropane-oxygen anesthetic. In the experiments in which blood

TABLE 1

OXYGEN AND CARBON DIOXIDE CONTENT OF ARTERIAL BLOOD

	Oxygen, volumes per cent			Carbon Dioxide, volumes per cent (whole blood)		
	Minimum	Maximum	Average*	Minimum	Maximum	Average*
16 dogs; breathing spontaneously after sodium thiopental	12.8	18.9	15.2	29.7[a]	45.5	38.8
After 40 min. on cyclopropane-oxygen	15.0	25.2	20.1	27.3	48.8	38.6
After 30 min. on ether-cyclopropane-oxygen	15.7	23.8	20.3	29.1	42.8	38.0
7 dogs requiring artificial respiration for a part of the time	12.0	26.6[a]	17.8	35.0	58.3[a]	42.8
After 40 min. on cyclopropane-oxygen	16.3	26.5	20.6	29.8	58.5	44.7
After 30 min. on ether-cyclopropane-oxygen	14.5	25.6	19.1	31.5	57.5	44.1

* Averages given are simple averages (arithmetic means) obtained by dividing the sum of the observations by the number of observations.

gases were determined, 16 dogs breathed spontaneously throughout and 7 had to be given artificial respiration (by means of the Connell machine) during some part of the experiment. The minimal, maximal and average oxygen contents under sodium thiopental, after forty minutes under cyclopropane-oxygen and after thirty minutes under ether-cyclopropane-oxygen anesthesia, for each group, are shown in table 1.

Carbon Dioxide Content

The carbon dioxide content of whole blood showed a wide range in the initial values under sodium thiopental narcosis. In some dogs the narcosis lightened before the preliminary preparations were completed, and hyperventilation occurred before the induction of

cyclopropane-oxygen anesthesia. In other dogs, undue depression of the respiratory center accompanied the narcotic state, and these animals showed higher carbon dioxide contents than the preceding animals. In general, the carbon dioxide content remained practically unchanged in any one animal during the course of the experiment, as shown by the minimal, maximal and average carbon dioxide contents in table 1. We thought that we ruled out accumulation of carbon dioxide by maintaining a free airway, giving artificial respiration when required and filling the canister with fresh soda lime before each experiment.

Cyclopropane

In the 13 dogs in which cardiac irregularities were produced by injection of epinephrine under cyclopropane-oxygen anesthesia and

TABLE 2

CYCLOPROPANE AND ETHER CONCENTRATIONS IN ARTERIAL BLOOD

	Concentration of cyclopropane in blood at time of first injection of epinephrine; mg. %			Concentration of cyclopropane in blood at time of last injection of epinephrine; mg. %			Concentration of ether in blood at time of last injection of epinephrine; mg. %		
	Min.	Max.	Av.*	Min.	Max.	Av.*	Min.	Max.	Av.*
Arrhythmias prevented; 13 dogs	7.43	15.77	11.60	5.16	16.62	11.64	18.74	124.20	58.49
Duration of administration in minutes	18	123	43.8	13	63	31.8	13	63	31.8
Arrhythmias not prevented; 5 dogs	5.52	17.59	11.80	6.59	13.04	10.72	29.8	87.8	46.9
Duration of administration in minutes	20	75	48	18	78	42.7	18	78	42.7
Ventricular fibrillation after first injection; 15 dogs	7.04	14.58	11.84						
Duration of administration in minutes	32	156	59.7						

* Averages given are simple averages (arithmetic means) obtained by dividing the sum of the observations by the number of observations.

subsequently prevented by the administration of ether, the range of cyclopropane concentration in the blood was 7.43 to 15.77 mg. per 100 cc., with an average of 11.60. The average duration of cyclopropane administration was 43.8 minutes. At the time of the last injection of epinephrine, when the irregularities were successfully prevented by ether, the range of cyclopropane concentration in the blood was 5.16 to 16.62 mg. per 100 cc., and the average 11.64. The average duration of ether-cyclopropane-oxygen administration was 31.8 minutes. This, together with the time of cyclopropane-oxygen anesthesia before the first injection of epinephrine, gives an average total time of 75.6 minutes during which cyclopropane was administered.

The minimal, maximal and average concentrations for this group, for the group of 5 dogs in which ether did not entirely prevent the epinephrine arrhythmias and for the group in which ventricular fibrillation followed the first injection of epinephrine are shown in table 2.

Ether

In the 13 experiments in which ether prevented the appearance of arrhythmias after epinephrine, the concentration of ether in the blood ranged from 18.74 to 124.20 mg. per 100 cc., with an average of 58.49. The duration of administration of ether-cyclopropane-oxygen averaged 31.8 minutes. The minimal, maximal and average concentrations

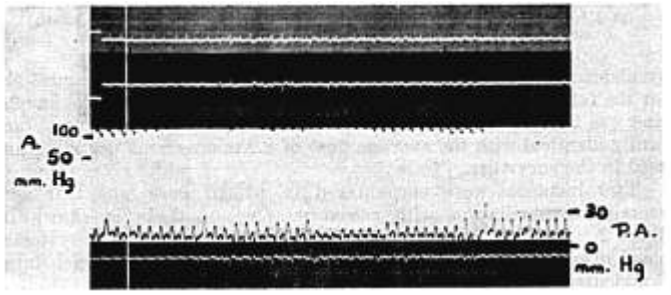

FIG. 1 *a*. Effect of epinephrine during cyclopropane-oxygen administration. Records from top to bottom, Vf, Vl, aortic pressure, pulmonary artery pressure, Vr. Vertical black lines on Vl are ten second timer. Epinephrine injected at millivolt signal, approximately ten seconds of record omitted indicated by white bar through all records. Arrhythmia shown in larger section to right of white bar. Cyclopropane, in arterial blood, 7.03 mg. per 100 cc. after forty-one minutes.

for this group and for the group of 5 dogs in which ether was not effective in preventing arrhythmias are shown in table 2.

The cardiovascular records for a typical experiment in which the injection of epinephrine produced arrhythmias under cyclopropane-oxygen anesthesia are shown in figure 1 *a*. The absence of such arrhythmias when ether was given, after the second injection of epinephrine, is evident in figure 1 *b*.

Fibrillation

It has been stated that 15 cases of ventricular fibrillation after the first injection of epinephrine were encountered. The concentration of cyclopropane in the blood was not higher in this group than in the group of survivors, as shown in table 2. However, the average duration of administration of cyclopropane-oxygen anesthesia was greater

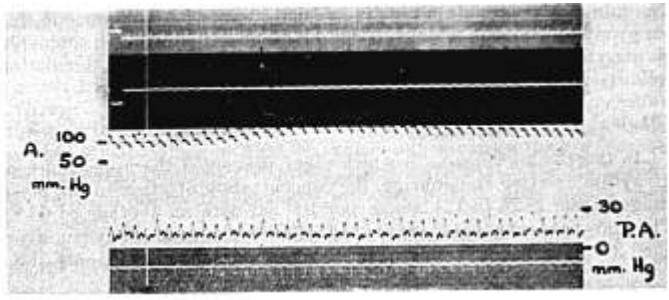

FIG. 1 *b*. Same as 1 *a*, after ether for thirty-five minutes. Cyclopropane in arterial blood, 9.46 mg. per 100 cc., ether in arterial blood, 35.40 mg. per 100 cc.

by about sixteen minutes; we do not believe that this is responsible for the fatal outcome in these animals. The average dose of epinephrine was 2.4 micrograms per kilogram of body weight, which is practically identical with the average dose of 2.2 micrograms per kilogram used in the survivors.

Two instances were encountered in which there was transient ventricular fibrillation with recovery. One of these is shown in figure 2. During the brief bout of ventricular fibrillation the systemic blood pressure fell toward zero. Three of the 15 dogs in which fatal ventricular fibrillation occurred showed spontaneous bigeminal rhythm

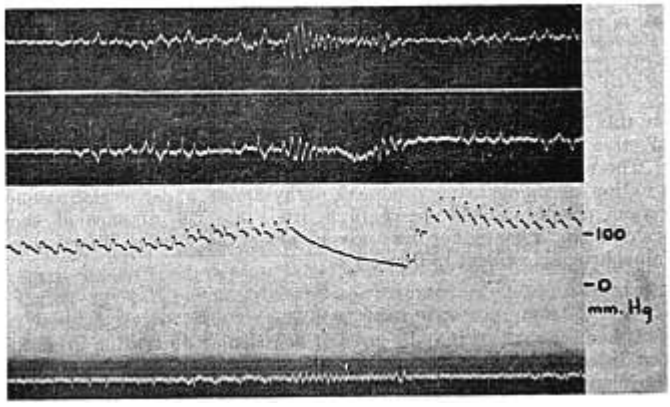

FIG. 2. Records from above downward, Vf, Vl, pressure in root of aorta and Vr. Transient fibrillation following the injection of epinephrine ten seconds previously.

during the administration of cyclopropane-oxygen, before epinephrine was injected.

Type of Irregularity

The commonest irregularity noted after epinephrine was a bigeminal rhythm. This consisted of a normal beat followed by a ventricular premature systole. It was noted that during the ventricular systole of ectopic origin the pressure developed in the right ventricle opened the pulmonary semilunar valve, but that in the left ventricle was insufficient to open the aortic semilunar valve. This is illustrated in figure 3. The bradycardia often noted in the peripheral pulse during cyclopropane-oxygen anesthesia may be due to this. Thus, the ventricular systoles which normally followed the discharge of the pacemaker ejected larger quantities of blood, as is shown by the higher

TABLE 3

Area in which beat originated for 3 simultaneous unipolar leads Vr, Vl, Vf	Area represented on epicardium	Cases	
		Number	Per cent
PPD	Upper anterior right ventricle	19	51.4
PDD	Posterior right ventricle	6	16.2
DDP	Apex and posterior left ventricle	4	10.8
All others	7 Different areas	8	21.6
Total		37	100.0%

systolic pressure. This mechanical alternans was not accompanied by unusual rises in pulmonary venous pressure.

Origin of Arrhythmias

The origin of ectopic beats was determined by the method of Nahum *et al.* (8), using three simultaneous unipolar leads. Analysis of the records indicated that the first ectopic beat of a bout of arrhythmias, following the first injection of epinephrine, originated in the upper anterior right ventricle in 19 of 37 cases, in the posterior right ventricle in 6 and in the apex and left posterior ventricle in 4; the remaining 8 originated in 7 different areas. The data are presented in table 3.

Of the dogs in which arrhythmias developed after both the first and second injection of epinephrine, 11 of 26 showed that the first ectopic beat after the second injection arose in the same area as after the first injection. Fifteen of 26 showed the origin of the first ectopic beat after the second injection of epinephrine to be in a different focus from that after the first injection.

When multifocal premature contractions were produced by the

first injection of epinephrine, it was difficult to suppress them by the subsequent administration of ether. The first focus to discharge ectopic beats after the second injection of epinephrine routinely differed from that after the first injection. In many cases the ectopic beats which originate in the anterior upper right ventricle have only a short downward displacement of the beam in Vr and Vl, and only a short upward one in Vf. After these short initial strokes there is a longer stroke in the opposite direction in all three unipolar leads; this is shown in figure 3. This means that although these beats originate

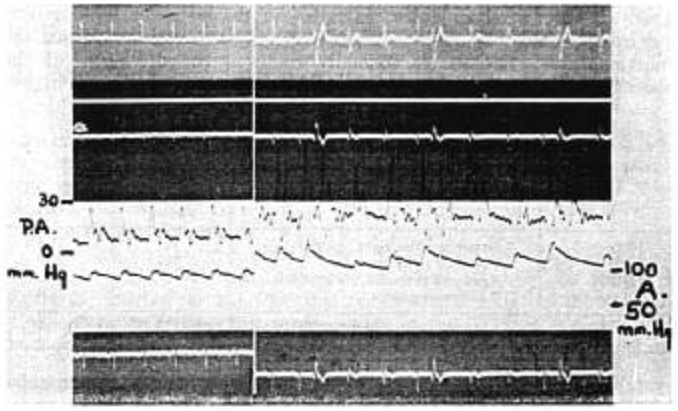

FIG. 3. Records from above downward, Vf, Vl, pulmonary arterial pressure (under damped), pressure at root of aorta and Vr. Control period at left; at right, fourteen seconds after injection of epinephrine. Both pulmonary and systemic pressures are elevated. The number of pressure pulses in pulmonary artery is greater than in aorta. First ectopic is P (proximal) and D (distal) for Vr, Vl, and Vf, respectively, which indicates its origin in upper anterior right ventricle. Note short initial movement of beam with longer beam movement in opposite direction indicating spread of impulse to opposite zone. Activity in proximal zones produces a downward movement of the beam and vice versa.

as indicated, the focus is very near the boundary and spreads quickly to the opposite zone, which most often is the lower anterior right ventricle.

DISCUSSION

Both hypoxia and accumulation of carbon dioxide may be important factors in the production of arrhythmias induced by the injection of epinephrine under cyclopropane-oxygen anesthesia (9, 10). We believe that both of the factors have been ruled out in our experiments, as shown by the analyses of blood gases. The determinations of the blood gases, in our opinion, are more reliable in indicating accumulation of carbon dioxide than analysis of mask gas.

The rate of induction of anesthesia by an anesthetic gas depends upon its solubilities in blood and various tissues, especially fat (11). Ether is carried away rapidly from the lungs and depends upon recirculation for equilibration. Although subanesthetic concentrations of ether in the blood are effective in preventing epinephrine-induced arrhythmias under cyclopropane anesthesia, it is not surprising that the tissues are unsaturated, since the concentration of ether in the alveolar air and hence in arterial blood rises slowly under the conditions of our experiments. The wide range of concentration of ether in the blood found in our dogs is in part dependent upon the variable muscle-fat mass in different animals.

It is believed by some investigators (12) that impulses are initiated from receptors in the mesentery; these reach the central nervous system and eventually are discharged by way of the sympathetic supply to the heart to produce arrhythmias when epinephrine is injected under cyclopropane anesthesia (13). This is vigorously opposed by Moe *et al.* (14) and Rennick *et al.* (15), who believe that the arrhythmias are secondary to the pressor effects of epinephrine.

Another reflex mechanism has been suggested as playing a part in the protective effect of ether. Since ether is an irritating vapor it stimulates receptors in the air passages and sets up pulmocardiac reflexes which inhibit ectopic foci in the ventricle (9), but the consensus is that the vagi do not supply ventricular muscle.

It has been pointed out that depression of the sinus and atrioventricular nodal pacemakers by the vagus nerves and the simultaneously enhanced activity of idioventricular pacemakers are essential factors in the production of ventricular tachycardia (16) and that vagotomy or injection of atropine prevents ventricular tachycardia (17).

As stated before, bradycardia may occur under cyclopropane anesthesia (18). We found that ectopic ventricular beats frequently failed to open the aortic valves but did open the pulmonary valves. This agrees with the finding of a diminished work capacity of the heart under cyclopropane (19).

SUMMARY AND CONCLUSIONS

Pulmonary arterial and aortic blood pressures were recorded simultaneously with electrocardiograms by three unipolar leads before, during and after the injection of epinephrine under cyclopropane-oxygen and ether-cyclopropane-oxygen anesthesia.

The concentration of cyclopropane and ether in blood in the presence of each other, was determined.

In some experiments, oxygen content and carbon dioxide content of whole blood were determined.

The epinephrine-induced arrhythmias were not apparently at-

tributable to either hypoxia or accumulation of carbon dioxide in the blood.

In 13 of the 18 experiments, the epinephrine-induced arrhythmias were prevented by the administration of ether.

The first ectopic beat after injection of epinephrine was found to originate most frequently in the upper anterior right ventricle.

Ectopic beats induced by epinephrine under cyclopropane-oxygen anesthesia often develop pressures which are great enough to open the pulmonic valves, but not the aortic valves. The electrocardiogram shows a faster heart rate than the peripheral pulse when this situation prevails.

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