# THE PREVENTION OF CYCLOPROPANE–EPINEPHRINE TACHYCARDIA BY DIETHYL ETHER *

J. W. Stutzman, Ph.D., C. R. Allen, Ph.D., and W. J. Meek, Ph.D.†

*Madison, Wis.*

Cyclopropane-epinephrine tachycardia is the ventricular tachycardia which occurs in the normal dog when epinephrine reaches a heart that is predisposed to irregularities during anesthesia with cyclopropane (1, 2). In studies of the mechanism by which this cardiac arrhythmia is produced it was noted that in dogs which had crossed circulations established under ether anesthesia ventricular tachycardia failed to occur when cyclopropane subsequently was administered and the test dose of epinephrine injected.

This is an investigation of the protective action of diethyl ether against cyclopropane-epinephrine tachycardia.

1. *Protection from Cyclopropane-epinephrine Tachycardia by Ether Premedication.*—To secure controls 21 unpremedicated dogs were anesthetized by rebreathing a cyclopropane-oxygen mixture from a 5 liter bag, intubated to insure an open airway, and then connected through a soda lime carbon dioxide absorber to a 100 liter rubber bag containing a 22 per cent mixture of cyclopropane in oxygen. After the animals had equilibrated on this constant mixture for thirty minutes, they were injected intravenously with 0.01 mg. of epinephrine per kilogram in 5 cc. of normal saline at a constant rate of 1 cc. per ten seconds. The duration of the resulting ventricular tachycardia was determined by constant observation of the beam of the electrocardiograph and by electrocardiograms (lead II) taken at short intervals throughout a five minute period beginning with the injection.

Several days later the dogs were anesthetized with diethyl ether by the open drop technic, intubated, and connected through a soda lime carbon dioxide absorber to an ether bottle. The concentration of oxygen in the inspired mixture was kept at a high level by a continuous flow of oxygen through a catheter which opened into the ether bottle. The animals were maintained in deep ether anesthesia with at least partial intercostal paralysis for fifteen minutes and then transferred to the 22 per cent cyclopropane-oxygen mixture. After thirty minutes of cyclopropane anesthesia the test dose of epinephrine was injected and the cardiac response determined as in the control experiments.

In table 1 it can be seen that, while each of the 21 dogs on its control had cyclopropane-epinephrine tachycardia which averaged forty-two

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† From the Department of Physiology, University of Wisconsin Medical School, Madison.

TABLE 1

PROTECTION FROM CYCLOPROPANE-EPINEPHRINE TACHYCARDIA WITH ETHER PREMEDICATION

| Dog No. | Duration of ventricular tachycardia following the injection of 0.01 mg./kg. epinephrine | | |
|---|---|---|---|
| | After 30 min. of 22% cyclo. in oxygen | After 15 min. ether followed by 30 min. of 22% cyclo. in oxygen | After 30 min. ether followed by 30 min. of 22% cyclo. in oxygen |
| 1 | 45 seconds | 10 seconds | 0 seconds |
| 2 | 60 " | 40 " | 0 " |
| 3 | 25 " | 0 " | |
| 4 | 20 " | 0 " | |
| 5 | 70 " | 12 " | 19 " |
| 6 | 30 " | 0 " | |
| 7 | 53 " | 64 " | 0 " |
| 8 | 67 " | 55 " | 55 " |
| 9 | 61 " | 0 " | |
| 10 | 34 " | 0 " | |
| 11 | 43 " | 0 " | |
| 12 | 30 " | 0 " | |
| 13 | 47 " | 0 " | |
| 14 | 30 " | 0 " | |
| 15 | 48 " | 0 " | |
| 16 | 40 " | 0 " | |
| 17 | 39 " | 0 " | |
| 18 | 50 " | 0 " | |
| 19 | 55 " | 0 " | |
| 20 | 48 " | 0 " | |
| 21 | 20 " | 0 " | |

seconds in duration, after fifteen minutes of deep ether anesthesia followed by thirty minutes of cyclopropane anesthesia 16 of the animals were completely protected against cyclopropane-epinephrine tachycardia. Of the remaining 5 animals, dogs 1 and 5 had ventricular tachycardia of forty-five and seventy seconds' duration, respectively, on the controls but only ten and twelve seconds after ether premedication. They were considered partially protected.

One week later the 5 dogs which had failed to be protected completely following fifteen minutes of ether premedication were given thirty minutes of ether anesthesia and tested for cyclopropane-epinephrine tachycardia as before. Dogs, 1, 2, and 7 were now completely protected, but there were no further effects on dogs 5 and 8. Thus, of 21 animals only 2 failed to be protected completely by thirty minutes or less of ether premedication.

2. *Protection from Cyclopropane-Epinephrine Tachycardia by the Addition of Ether to the Cyclopropane-Oxygen Mixture.*—While ether premedication is effective in protecting dogs from cyclopropane sensitization, objections to its practical use are that the premedication period requires fifteen to thirty minutes of deep ether anesthesia before cyclopropane can be employed and that the duration of protection is limited because the animal begins to lose ether as soon as it is transferred to

the cyclopropane-oxygen mixture. To determine if these objections might be removed by the addition of ether to the cyclopropane-oxygen mixture, controls were established by inducting 20 dogs with cyclopropane and oxygen and maintaining them on a 22 per cent mixture of cyclopropane in oxygen for fifteen minutes. The test dose of 0.01 mg. of epinephrine per kilogram was then injected. Several days later the same dogs were injected with the test dose of epinephrine after they had been anesthetized with a cyclopropane-oxygen mixture and then maintained for fifteen minutes on a mixture consisting of 22 per cent cyclopropane and 4.5 per cent ether in oxygen. This mixture was prepared by vaporizing 80 cc. of ether into 75 liters of 25 per cent cyclopropane in oxygen.

The protective action of ether in such a mixture may be seen in table 2. Ventricular tachycardia followed the injection of the control dose of epinephrine in every one of 20 experiments while the dogs were on the 22 per cent cyclopropane-oxygen mixture. When ether had been added to the mixture, the control epinephrine injection was followed by ventricular tachycardia in only 3 of the same 20 dogs. Cyclopropane-epinephrine tachycardias of sixty-five, twenty-four, and forty-five seconds' duration in dogs 27, 31, and 35, respectively, were reduced by the addition of ether to twenty-five, twenty and twenty seconds. Dogs 27 and 35 were therefore considered partially protected.

In addition to the series just discussed, 8 dogs, numbers 42 to 49 of table 2, were also subjected to 22 per cent cyclopropane plus 4.5 per cent ether in oxygen. In none of these did epinephrine produce ventricular tachycardia. The net result was that under cyclopropane plus ether only 3 of 28 animals showed cyclopropane-epinephrine tachycardia.

Since 22 per cent cyclopropane plus 4.5 per cent ether produces a deeper anesthesia than 22 per cent cyclopropane alone, it seemed desirable to make tests under a concentration of cyclopropane alone which gives a comparable level of deep surgical anesthesia, as evidenced by partial or complete intercostal paralysis. This was obtained by anesthetization with 30 per cent cyclopropane in oxygen. The results may be seen in column 3 of table 2. Fourteen animals were tested with the control epinephrine injection, and all showed ventricular tachycardia, one terminating in ventricular fibrillation.

Cyclopropane-epinephrine tachycardia readily occurs immediately after induction. To determine whether there is an early and rapid protection of the dog's heart by the cyclopropane-ether-oxygen mixture, 5 dogs were given 30 mg. of nembutal per kilogram intraperitoneally and artifically respired with 22 per cent cyclopropane in oxygen for five minutes. They were then injected with the control dose of epinephrine. From table 3 it can be seen that all responded with ventricular tachycardia. One week later these dogs were again given nembutal and

maintained on the cyclopropane-ether-oxygen mixture for five minutes. At the end of this period the injection of epinephrine was not followed by ventricular tachycardia. Protection had thus occurred within a five minute period.

TABLE 2

COMPARISON OF CYCLOPROPANE-EPINEPHRINE TACHYCARDIA IN DOGS UNDER LIGHT CYCLOPROPANE, LIGHT CYCLOPROPANE PLUS ETHER, AND DEEP CYCLOPROPANE ANESTHESIAS

| Dog No. | Duration of ventricular tachycardia after injection of 0.01 mg./kg. epinephrine | | |
|---|---|---|---|
| | After 22% cyclo. in $O_2$ for 15 min. | After 22% cyclo. plus 4.5% ether in $O_2$ for 15 min. | After 30% cyclo. in $O_2$ for 15 min. |
| 22 | 20 seconds | 0 seconds | |
| 23 | 48 " | 0 " | 78 seconds |
| 24 | 30 " | 0 " | |
| 25 | 40 " | 0 " | 65 " |
| 26 | 39 " | 0 " | 60 " |
| 27 | 65 " | 25 " | |
| 28 | 52 " | 0 " | |
| 29 | 18 " | 0 " | |
| 30 | 30 " | 0 " | |
| 31 | 24 " | 20 " | |
| 32 | 40 " | 0 " | |
| 33 | 35 " | 0 " | |
| 34 | 50 " | 0 " | |
| 35 | 45 " | 20 " | |
| 36 | 50 " | 0 " | |
| 37 | 35 " | 0 " | |
| 38 | 13 " | 0 " | |
| 39 | 18 " | 0 " | 55 " |
| 40 | 16 " | 0 " | 45 " |
| 41 | 40 " | 0 " | 55 " |
| 42 | | 0 " | 53 " |
| 43 | | 0 " | Ventricular fibrillation |
| 44 | | 0 " | 17 seconds |
| 45 | | 0 " | 27 " |
| 46 | | 0 " | 36 " |
| 47 | | 0 " | 46 " |
| 48 | | 0 " | 37 " |
| 49 | | 0 " | 66 " |

Nine unpremedicated dogs (table 3) were inducted with a mixture of 45 per cent cyclopropane and 9 per cent ether in oxygen and then transferred to the standard mixture of 22 per cent cyclopropane and 4.5 per cent ether in oxygen for five minutes. The epinephrine injection at this time was followed by no ventricular tachycardia in 7 of the dogs. This procedure of testing the protective mixture before doing the controls under cyclopropane alone was instituted so that any subsequent fibrillation in the controls would emphasize the ether protection. One week later, when these animals were injected with epinephrine after being inducted with a 45 per cent cyclopropane in oxygen mixture and then maintained for five minutes on a 22 per cent cyclopropane in oxygen

TABLE 3

COMPARISON OF CYCLOPROPANE-EPINEPHRINE TACHYCARDIA IN DOGS UNDER 22% CYCLOPROPANE IN OXYGEN WITH 22% CYCLOPROPANE PLUS ETHER IN OXYGEN AFTER ONLY 5 MINUTES OF ANESTHESIA

| Dog No. | Duration of ventricular tachycardia following injection of 0.01 mg./kg. of epinephrine | |
|---|---|---|
| | After 5 min. of 22% cyclo. in $O_2$ | After 5 min. of 22% cyclo. plus 4.5% ether in $O_2$ |
| | Premedicated with nembutal | Premedicated with nembutal |
| 25 | 50 seconds | 0 seconds |
| 26 | 57 " | 0 " |
| 27 | 56 " | 0 " |
| 28 | 54 " | 0 " |
| 29 | 55 " | 0 " |
| | Unpremedicated | Unpremedicated |
| 22 | 40 seconds | 5 seconds |
| 23 | 13 " | 0 " |
| 24 | Ventricular fibrillation | 0 " |
| 42 | 65 seconds | 24 " |
| 43 | 65 " | 0 " |
| 47 | 50 " | 0 " |
| 48 | 37 " | 0 " |
| 49 | 63 " | 0 " |
| 50 | Ventricular fibrillation | 0 " |

mixture, all animals showed ventricular tachycardia and 2 died of ventricular fibrillation.

## DISCUSSION

The criticism may be made that the ether concentration in the mixture is sufficient to produce anesthesia and that this study actually is concerned with ether anesthesia. The fact remains, however, that the mixture also contains an effective anesthetic concentration of cyclopropane which, in the absence of ether, is capable of sensitizing the heart to epinephrine so that cyclopropane-epinephrine tachycardia is readily produced.

From more than 100 anesthetizations of 70 dogs with the cyclopropane-ether-oxygen mixture it was noted that speed of induction and recovery are as rapid as with cyclopropane alone and that the moment to moment control also resembles cyclopropane. Abdominal relaxation appears to be as good as with ether at a comparable depth of anesthesia. The respiratory depression of cyclopropane alone is not so apparent with the mixture. In its failure to depress respiration and in its failure to sensitize the heart to epinephrine the cyclopropane-ether-oxygen mixture resembles ether rather than cyclopropane.

## CONCLUSIONS

Twenty-two per cent cyclopropane in oxygen plus sufficient diethyl ether to produce an anesthetic mixture, which will maintain unpre-

medicated dogs in deep surgical anesthesia with partial or complete intercostal paralysis, does not sensitize the heart of the dog to epinephrine.

This cyclopropane-ether-oxygen mixture appears to have many of the advantages of both cyclopropane and ether.

REFERENCES

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For the information of anesthesiologists who are contemplating application for certification by the American Board of Anesthesiology, Inc., or who are training physicians for the specialty, the following questions have been employed for Part I (written) examination in the past in *Pharmacology:*

1. How does anesthesia with each of the following affect the white blood count postoperatively? *a.* ether; *b.* cyclopropane; *c.* subdural procaine.
2. Name a barbituric acid derivative representative of each of the following classifications: *a.* long acting; *b.* medium acting; *c.* short acting; *d.* ultra-short acting. What factors other than their duration of action logically place these drugs in the designated classifications?
3. How are the blood sugar and the carbon dioxide combining power affected by surgical anesthesia with each of the following: *a.* ether; *b.* morphine; *c.* cyclopropane; *d.* pentothal; *e.* chloroform.
4. Discuss briefly the advisability of using *a.* spinal anesthesia in the presence of pernicious anemia; *b.* pentothal sodium intravenously in the presence of dyspnea.
5. List the toxic effects of each of the following: *a.* procaine hydrochloride; *b.* chloroform; *c.* metrazol; *d.* epinephrine.
6. Give the therapeutic dose of the following drugs when they are given separately to an average adult male, aged thirty: *a.* chloral hydrate, rectally; *b.* paraldehyde, orally; *c.* trional (sulphonethylmethane), orally; *d.* dilaudid, subcutaneously.
7. Define the term "secondary saturation" and give your opinion of its importance in the administration of nitrous-oxide.
8. What essential differences may be expected when using atropine or scopolamine in comparable doses for preanesthetic medication?
9. What is the effect of ethyl ether given for inhalation anesthesia on the gastro-intestinal tract?
10. What are the signs and symptoms of atropine poisoning? How should it be treated?