FURTHER STUDIES ON THE PRODUCTION OF CYCLOPROPANE–EPINEPHRINE TACHYCARDIA * †

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A dose of epinephrine which is insufficient to produce ventricular tachycardia in a normal unanesthetized dog will do so in the same animal under cyclopropane anesthesia (1, 3). This study was undertaken to determine the site of action of cyclopropane in sensitizing the heart to injected epinephrine.

Procedure and Results

The technics of maintaining a constant level of anesthesia and testing for cyclopropane-epinephrine tachycardia have been described previously (1). The test dose of epinephrine which was injected intravenously varied from 0.005 to 0.01 mg. per kilogram but remained constant for any one experiment. In each case the dose was sufficient to produce fifteen to eighty-five seconds of ventricular tachycardia in the intact anesthetized dog. In experiments in which cyclopropane was to be restricted in its site of action, it was necessary to carry out surgical procedures with the animal under an anesthetic other than cyclopropane. Since it is known that nembutal does not interfere with cyclopropane-epinephrine tachycardia (4), this agent was selected as the preliminary anesthetic for the following procedures designed to eliminate cyclopropane from the cerebral or body circulation.

First, preparations were made in which the body but not the brain was exposed to cyclopropane. This was accomplished by clamping the brachiocephalic and left subclavian arteries and the superior vena cava in 6 dogs anesthetized with nembutal. Since occlusion of cerebral circulation was limited to five minutes, the hypothalamus remained functional and could mediate reflexes during that time.

Second, three crossed circulation experiments were carried out so that cyclopropane might be restricted either to the brain or to the remainder of the body. These animals were anesthetized with nembutal, and 100 mg. per kilogram of the anticoagulant pontamine fast pink

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BL were injected into the donor. The peripheral end of the brachiocephalic artery of the recipient was connected by a paraffin-lined rubber tube to the central end of the left common cartoid artery of the donor. The superior vena cava of the recipient was joined to the left external jugular vein of the donor. Less than seven minutes were required to complete such preparations, and during this period the brain of the recipient was supplied by the vertebral branch of the left subclavian artery which was not ligated until the crossed circulation was established. The isolation of the cerebral circulation was verified by the absence of india ink in the cerebral vessels following its injection into the heart of the recipient. Furthermore, occlusion of the blood supply to the brain for thirty minutes resulted in an anemic decerebration as evidenced by cessation of contraction of the respiratory muscles.

TABLE 1

DURATION OF CYCLOPROPANE-EPINEPHRINE TACHYCARDIA IN CLAMPING AND CROSSED CIRCULATION EXPERIMENTS

Dog No.*	Before Decerebration		After Decerebration
	Cyclo. and Epinephrine Restricted to Body Circulation	Cyclo. in Entire Animal. Epinephrine Restricted to Body	Cyclo. and Epinephrine Restricted to Body Circulation
	Seconds	Seconds	Seconds
1	20		0
2	40	38	0
3	50		0
4	Ventricular fibrillation		
5	Ventricular fibrillation		
6	Ventricular fibrillation		
7†		15	0
8	47		0
9	50	50	0

* Dogs 1–6 were clamping experiments; dogs 7–9, crossed circulation experiments.

† When cyclopropane was restricted to the cerebral circulation, injection of epinephrine into either the cerebral or body circulation did not result in ventricular tachycardia.

The results of the experiments made possible by these preparations are summarized in table 1. In the first 6 animals both cyclopropane and epinephrine were restricted to the body circulation by clamping the cerebral blood supply. Each of these animals had ventricular tachycardia, and in 3 cases this immediately passed into ventricular fibrillation. Cyclopropane and epinephrine were likewise restricted to the body circulation of the recipient in crossed circulation experiments on dogs 8 and 9. Again ventricular tachycardia was at once produced. Cyclopropane was allowed to reach the entire animal while epinephrine was restricted to the body circulation in dogs 2, 8 and 9. This also resulted in ventricular tachycardia.

In 3 of the animals which had previously had temporary occlusion of the cerebral circulation and in the 3 recipients of the crossed circu-

lation experiments an anemic decerebration was induced by occluding the cerebral blood flow for thirty minutes. Cyclopropane and epinephrine were then restricted to the body circulation. In contrast to previous experiments ventricular tachycardia was no longer produced. It was also found that there was no ventricular tachycardia with epinephrine injection when cyclopropane was allowed to circulate only in the cerebral circulation of the recipient.

From the results of these experiments it is evident that for the production of cyclopropane-epinephrine tachycardia cyclopropane and epinephrine do not have to reach the cerebral circulation but certain brain centers must be intact and functioning. Furthermore, the addition of cyclopropane to the cerebral circulation does not alter the duration of the cardiac irregularity. In view of these results and the fact that the cardiac sympathetics must be intact (3), it appears that the heart is reflexly sensitized by cyclopropane.

In an attempt to locate the afferent pathway of such a reflex the spinal cord was cut below the main cardiac sympathetic outflow. A cord section between the sixth and seventh intercostal nerves in 4 dogs abolished cyclopropane-epinephrine tachycardia. In two of these animals an initial section one segment posteriorly afforded no protection from the arrhythmia. These experiments suggest that afferent impulses entering the cord below T 6 are involved in reflex sensitization of the heart.

Bilateral supradiaphragmatic splanchnicotomy and sympathetic chain resection from T 9 to L 1 were done in 15 dogs. This procedure afforded complete protection from ventricular tachycardia in 13 of the animals. In the remaining 2, a cord section at T 11 resulted in protection. It was found that bilateral adrenalectomy alone does not interfere with the production of ventricular tachycardia.

In the next group of experiments various nerves were cut below the diaphragm in an attempt to abolish cyclopropane-epinephrine tachycardia. The results of experiments on 63 dogs are summarized in table 2. In some animals partial visceral denervation was sufficient to prevent ventricular tachycardia. However, in others, bilateral splanchnicotomy and resection of 6 cm. of sympathetic chain were necessary to abolish the cardiac irregularities.

The effect of excluding cyclopropane from the region innervated by these nerves was tested. The visceral circulation in 6 nembutalized dogs was completely occluded with rubber-shod hemostats. After the animals were given cyclopropane for fifteen minutes, an epinephrine injection resulted in no ventricular tachycardia. The hemostats were removed and cyclopropane allowed to enter the visceral circulation for fifteen minutes. The clamps were then replaced, and epinephrine injection immediately thereafter caused ventricular tachycardia in 5 of the animals and ventricular fibrillation in the sixth. These experiments

indicate that cyclopropane stimulates receptors located in the mesentery or abdominal viscera.

Partial eviscerations were done in an attempt to localize these receptors. Removal of the gastro-intestinal tract and 2 to 3 cm. of adjacent mesentery from pylorus to rectum afforded complete protection from cyclopropane-epinephrine tachycardia in 19 of 21 dogs. The cardiac irregularities were abolished in the other two by removing the superior mesenteric and celiac arteries at their origins. In 4 additional animals removal of the pylorus, duodenum, first 10 cm. of ileum, and

TABLE 2

SUBDIAPHRAGMATIC DENERVATIONS NECESSARY FOR PROTECTION FROM CYCLOPROPANE-EPINEPHRINE TACHYCARDIA

Initial Procedure	Dogs Protected	Dogs Not Protected	Additional Denervations Necessary for Protection on Dogs Not Protected by Initial Procedure
Subdiaphragmatic splanchnicotomy and removal of first 6 cm. of abdominal sympathetic chain on 16 animals	16	0	
Removal of celiac and superior mesenteric ganglia and plexuses on 14 animals	14	0	
Section of nerves around base of superior mesenteric and celiac arteries on 4 animals	4	0	
Section of nerves around base of superior mesenteric artery on 20 animals	12	8	Removal of celiac and superior mesenteric ganglia and plexuses
Section of preaortic nerves 2 cm. caudad to superior mesenteric artery on 9 animals	7	2	Removal of celiac and superior mesenteric ganglia and plexuses

the colon was sufficient for protection. In 6 animals the gastro-intestinal tract was removed from pylorus to rectum but the circulation of the mesentery to the ileum and jejunum was left intact. This was accomplished by making numerous ligations between the anastamosing mesenteric radicles and the intestine. After this procedure injection of epinephrine still resulted in ventricular tachycardia. Fifteen minutes later the peripheral 3 cm. of mesentery were clamped and removed. Epinephrine injection immediately thereafter caused no ventricular tachycardia.

CONCLUSIONS

Cyclopropane reflexly sensitizes the heart of the dog to injected epinephrine. The receptors are distributed for the most part throughout the peripheral 3 cm. of mesentery. Impulses travel by visceral

afferent fibers through the celiac and superior mesenteric plexuses, splanchnics, and spinal cord to a brain center above the pons. Efferent impulses then pass to the heart by way of the cardiac sympathetics and increase the irritability of the heart.

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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 *Pathology:*

1. Give the effects on the left ventricle of the following conditions:
   (a) Aortic stenosis.
   (b) Mitral insufficiency.
2. You are called to administer an anesthetic for an abdominal operation upon a patient with typhoid fever. State the anesthetic agent and method you would use, taking into consideration the pathological changes in the liver, kidneys, respiratory organs and circulatory apparatus.
3. (a) Name two causes of nasal obstruction.
   (b) What deformities of the chest may be the result of chronic nasal obstruction?
4. (a) Define acidosis. (1) Name three conditions in which it is commonly present.
   (b) Define alkalosis. (1) What is the most frequent cause of alkalosis?
5. Name three types of blood transfusion reactions. Give the symptoms or findings by which you would identify each type.
6. State ways in which pernicious anemia is significant in anesthesiology.