THE EFFECT OF CYCLOPROPAPE ON CARDIAC WORK CAPACITY* †‡

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The production of cardiac irregularities by epinephrine during cyclopropane anesthesia has been the subject of numerous investigations, but less information is available concerning the action of this anesthetic gas upon cardiac contractility. Robbins and Baxter (1), utilizing the Fick principle, found that cardiac output increased in dogs under moderate surgical anesthesia, but returned to normal or below under deep anesthesia. Volpitto, Woodbury and Hamilton (2) reported increases of venous pressure during surgical procedures under cyclopropane anesthesia in human subjects. No attempt was made to interpret this observation. Bennett, Bassett and Beecher (3) compared the effects of ether, cyclopropane and sodium evipal on the circulation under normal and shock conditions in dogs, and found that cyclopropane caused a greater increase of right auricular pressure than the other agents. They referred to unpublished studies by Krayer and Beecher (4) in which cyclopropane was observed to cause an increase of auricular pressure in the dog heart-lung preparation. Bracke, Scherf and Spire (5) reported dilatation of the heart in dogs under pentobarbital anesthesia when exposed to high concentrations of cyclopropane (50 to 75 per cent) for brief periods. Lee, Orth, Wangerman and Meek (6) perfused isolated hearts of turtles, rabbits, cats and dogs with Ringer’s solution or blood equilibrated with various concentrations of cyclopropane and oxygen, and reported decreased amplitude of contractions. The action was not abolished by atropine nor potentiated by physostigmine, and was therefore assumed to be a direct effect on the myocardium.

Observation of increased venous pressure suggests but does not prove a negative inotropic action of cyclopropane on the heart, since elevation of right auricular pressure could result from increased cardiac work, or from increased intrapleural pressure. Observation of

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increased cardiac output does not prove the absence of a negative inotropic effect, nor would the occurrence of a decline of cardiac output conclusively prove the presence of such an effect, for the level of cardiac output alone cannot be used as an index of cardiac reserve. The studies referred to, however, point toward a depression of cardiac work capacity by cyclopropane. A series of experiments, therefore, was planned to determine the effect of cyclopropane on cardiac reserve. In these experiments the heart was subjected to an increased work load either by raising the arterial pressure or the cardiac output or both, and the degree of sufficiency was estimated from the venous pressure response.

Methods

Experiments were performed on intact dogs and on dog heart-lung preparations. In both series cyclopropane was administered in a closed system from a Foregger anesthesia apparatus. In the intact dog pressure-loading of the heart was accomplished by elevating the pressure in a stabilizer attached to the abdominal aorta (7). Arterial pressure was recorded with a mercury manometer, and right auricular pressure with a bromoform or water manometer attached to a cannula inserted through the right external jugular vein into the auricle. In this preparation elevation of the pressure in the reservoir increases the arterial pressure of the animal by increasing cardiac output; consequently, if peripheral resistance remains constant a 50 per cent increase of arterial pressure must produce a 50 per cent increase of cardiac output, or an increase of 125 per cent in left ventricular work. Since carotid sinus reflexes may be expected to induce a compensatory vasodilatation, cardiac output must actually be increased somewhat more than 50 per cent to give a total work increment of more than 125 per cent. The work of the two ventricles is probably increased by approximately the same proportion, and right auricular pressure will, therefore, reflect in a qualitative way the response of both sides of the heart.

To rule out the effects of respiratory depression at high concentrations of cyclopropane, artificial respiration was maintained throughout with a Starling pump. To eliminate the influence of intrathoracic pressure changes on right auricular pressure, an opening was made in the right chest wall. To prevent clotting, all glass surfaces were silicone treated,* and connecting tubes were of transflex plastic tubing. Heparin was administered by continuous infusion.

In the heart-lung preparation [prepared as described by Krayen and Mendez (8)], the work load of the heart was altered by increasing the height of the venous reservoir to increase cardiac output at constant arterial pressure, or by increasing the arterial resistance. Aortic

* Dow-Corning "200 Fluid," kindly supplied by the Dow Corning Corporation, Midland, Michigan.
pressure was recorded with a mercury manometer, right auricular pressure by means of a water manometer and left auricular pressure with a bromoform manometer. Cardiac output was measured by means of a Stolnikow strohmur.

Cyclopropane concentrations in blood and air were estimated by the iodine-pentoxide method described by Robbins (9). Control determinations of the solubility of cyclopropane in water and of the distribution of the gas between inspired air and arterial blood checked closely with the values reported by Robbins.

Results

**Intact Animals.**—Seven experiments were performed with the pressure stabilizer. Anesthesia was induced with a single intravenous dose of thiopental (15 to 20 mg. per kilogram). The trachea was exposed immediately and attached to the anesthesia apparatus to permit introduction of cyclopropane and oxygen as the animals recovered from the barbiturate. After the abdominal aorta was cannulated and attached to the stabilizer, heparinized blood from a donor animal was administered through a cannula in a femoral or jugular vein and allowed to pass into the stabilizer reservoir.

After recovery from the effects of thiopental, the animals were exposed to a mixture of oxygen with sufficient cyclopropane to maintain adequate anesthesia, and artificial respiration was begun. In all experiments the system was frequently flushed out with the gas mixture to insure a relatively constant blood level. Arterial pressure was increased from the control level in steps of 20 mm. of mercury until a marked elevation of right auricular pressure occurred. Pressure was then returned to the control level, and the cyclopropane concentration was doubled. After an equilibration period of twenty minutes, step-wise elevation of arterial pressure was repeated. This level of cyclopropane caused severe depression of respiration, but not complete arrest (as determined by briefly stopping the respiration pump). After the effects of the higher concentration of cyclopropane were recorded, administration of the gas was discontinued and the system flushed with oxygen repeatedly for thirty minutes. As the level of anesthesia lightened, sodium pentobarbital was administered in small doses until a total of 10 to 30 mg. per kilogram had been given. At this time the venous pressure response to elevation of the arterial pressure was again determined, and again after administration of additional pentobarbital to a total dose of 30 to 45 mg. per kilogram.

Blood levels of cyclopropane were determined in only three of the seven experiments, but the results in all experiments were similar: sufficient cyclopropane to produce adequate anesthesia caused a significant reduction of cardiac reserve, and a concentration of cyclopropane causing moderate to severe respiratory depression resulted in severe impairment of cardiac work capacity. Typical responses
to pressure loading in one of the experiments are illustrated in figure 1. In the first segment, at a cyclopropane blood level of 10 mg. per 100 cc., elevation of arterial pressure from 86 to 108 mm. of mercury (work increment of approximately 60 per cent) increased the right auricular pressure from 50 to 96 mm. of water. During this period spontaneous respiratory efforts, both intercostal and diaphragmatic occurred synchronously, with the strokes of the respiration pump. Lid and corneal reflexes were present. In the second segment, at a blood level of 20.5 mg. per 100 cc., a comparable increase of cardiac work load increased the auricular pressure from 69 to 173 mm. of water. At this time spontaneous respiratory activity was present.

![Graphs](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931713/)

**Fig. 1.** Exp. 1–24–49. Dog 10.3 Kg. Pressure stabilizer attached to abdominal aorta. Tracings, top to bottom: arterial pressure, scale at right in millimeters of mercury; right auricular pressure, scale at left in millimeters of water; signal; time, 10 seconds. Figures after "Cyclo" refer to cyclopropane concentration in jugular venous blood. Pento = pentobarbital sodium. Between B and C, cyclopropane discontinued, followed by frequent flushing for twenty minutes.

but much weaker, and the lid reflex was abolished. Thirty minutes after the administration of cyclopropane was stopped, and after the injection of 10 mg. per kilogram of pentobarbital sodium, the record of segment 3 was taken. Although the concentration of cyclopropane in the blood was still more than 4 mg. per 100 cc., the response of the heart to an increased work load was much improved. The initial auricular pressure was only 23 mm. of water at an arterial pressure of 86 mm. of mercury, and was increased to only 68 mm. of water when arterial pressure was elevated to 134 mm. of mercury, an increment of nearly 150 per cent of cardiac work. Spontaneous respiratory efforts and lid and corneal reflexes were present. Further adminis-
tration of pentobarbital to a level which abolished spontaneous respiratory activity resulted in little further impairment of cardiac work capacity.

Heart-Lung Preparations.—In the experiments on the intact animals it was impossible to compare the response of the heart to increased work load under cyclopropane with the response in the unanesthetized animal. Furthermore, induction with thiopental was necessary to permit dissection with the cautery prior to heparinization. In the heart-lung preparations the blood was drawn from a donor animal under local anesthesia, and at the beginning of these experiments the control response of the heart could be determined in an environment almost free of anesthetic drugs.

Five experiments were performed. In three, loading was accomplished by elevating the output at constant arterial pressure and again by elevating the arterial resistance while keeping the venous reservoir level constant; in the other two experiments, pressure loading alone was used. Cyclopropane determinations were made in two experiments; the results of all experiments were uniform and confirmed the observations obtained in the intact animal.

Figure 2 illustrates the response of the heart to volume loading when exposed to air and again when exposed to "20 per cent" and "40 per cent" cyclopropane in oxygen. (Cyclopropane analyses were not obtained in this experiment, but later it was found that the flowmeters of the anesthesia apparatus greatly overestimated the concentration of the anesthetic gas in the mixture.) During the control period, relatively slight changes of right and left auricular pressures occurred when left ventricular work was increased by 180 per cent by "volume" loading. During exposure to "20 per cent" cyclopropane a comparable increase of cardiac work produced significantly greater auricular pressure elevations on both sides of the heart, and under "40 per cent," auricular pressures were still further increased.

As is well known, the heart adapts to pressure loading less efficiently than to volume loading; elevation of arterial pressure in these experiments caused greater changes of auricular pressure than comparable work increments produced by volume loading. In one such experiment the work load was doubled by step-wise elevation of the pressure from 65 to 150 mm. of mercury during the control period, with a significant alteration of auricular pressures only at the highest arterial pressure level. Under 20 per cent cyclopropane (as estimated by the flowmeter), cardiac output diminished and auricular pressures increased sharply when arterial pressure was raised to 148 mm. of mercury, although the resulting left ventricular work was only 58 per cent greater than the control level. Under 40 per cent cyclopropane, severe dilatation and failure, with a great elevation of auricular pressures, occurred at a pressure of only 140 mm. of mercury.

In the final two experiments, including that illustrated in figure 3, cyclopropane analyses were carried out. As shown in the figure, se-
vere impairment of cardiac work capacity was produced by a cyclopropane concentration which in the intact animal would cause only moderately deep surgical anesthesia.

In all cases the changes caused by cyclopropane were reversible. Within a few minutes after the respiratory system was flushed out with oxygen, venous pressure returned to normal and the response to

**Figure 3.** Exp. 12-24-48. Heart-lung preparation, dog 16 Kg. Tracings as in figure 1, except that left auricular pressure tracing is above right auricular pressure. Segment A, respiration of air. Segment B, exposed to cyclopropane and oxygen, blood level 7.3 mg. per 100 cc. Segment C, cyclopropane concentration increased beginning at the signal; the gaps in the auricular pressure tracings resulted from the flush-out procedure. Segment D, cyclopropane concentration 16 mg. per 100 cc. Segment E, flush-out with 100 per cent oxygen begun at the signal.
loading improved (figure 3). Complete restoration to initial control conditions was not achieved, since spontaneous failure occurs progressively at a slow rate in the isolated heart.

**DISCUSSION**

Cyclopropane anesthesia in the dog may be carried to stage III plane 4 before cardiac output begins to fall (1). The experiments described demonstrate, however, that reduction of cardiac reserve begins when anesthesia has progressed only to the first plane of stage III. In the intact animal a comparable level of anesthesia with pentobarbital produces almost no impairment of cardiac contractility and the reduction caused by a respiratory arresting dose of pentobarbital is very much less than that resulting from deep cyclopropane anesthesia.

A search of the clinical literature on cyclopropane failed to reveal any serious objection to the use of this agent in patients with cardiac disease. Griffith (10), in a summary of 5000 anesthetics with cyclopropane, said in 1940: "Clinical experience leads me to the firm belief that cyclopropane is the safest anesthetic agent which we have available at present for patients with serious heart disease." Marshall and Daly (11) also recommended cyclopropane for patients with heart disease. Rare occurrence of acute pulmonary edema following administration of cyclopropane has been observed, but was not considered to be due to an action on the heart [Griffith (12); Bonham (13)]. Whitaere and Sankey (14) stated that cyclopropane is not advisable for deep anesthesia in patients with hypertension, but do not give their reasons. Gross (15) recently stated his belief that cyclopropane anesthesia is dangerous for the entire duration of operations for the repair of coarctation of the aorta. For intrathoracic surgery the chief objection to cyclopropane has been the occurrence of cardiac arrhythmias or cardiac arrest (16).

In none of these reports has cyclopropane been proved to cause or contribute to the development of acute cardiac failure. The action of cyclopropane on cardiac work capacity is clearly demonstrated, however, and should be considered as a possible hazard when the gas is used in patients with cardiac disease.

**SUMMARY**

The response of the heart to an increase in its work load was determined in intact dogs and in heart-lung preparations exposed to cyclopropane. Significant reduction of cardiac reserve was apparent at cyclopropane concentrations of less than 15 per cent, and severe reduction appeared at concentrations of 25 to 35 per cent, corresponding in these experiments to blood levels of 15 to 20 mg. per 100 cc.
REFERENCES


(Continued from page 705)

North Ballroom
2:00 P.M. to 4:30 P.M.
"Obstetrical Amnesia, Analgesia and Anesthesia"
Richard Torpin, M.D., Chairman, Professor of Obstetrics and Gynecology, University of Georgia
Franklin F. Snyder, M.D., Associate Professor of Obstetrics, Harvard University
John Adriani, M.D., Director of Anesthesia, Charity Hospital of Louisiana
Perry P. Volpitto, M.D., Professor of Anesthesiology, University of Georgia

EVENING
Parlors E and H
5:45 P.M.
Dinner, Board of Governors, American College of Anesthesiologists

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