THE MECHANISM OF PRODUCTION OF SPONTANEOUS CARDIAC IRREGULARITIES WITH HIGH CONCENTRATIONS OF CYCLOPROPANE * †

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CARDIAC arrhythmias may occur spontaneously during cyclopropane anesthesia. The mechanisms of their production and prevention have been the subject of investigation and speculation in various laboratories. Robbins (1) is inclined to attribute much of the arrhythmia to hypoxemia and thinks that the barbiturates as premedication drugs afford some protection (2). Guedel *et al.* (3) believe there is an arrhythmic range in which irregularities occur, above and below which regular cardiac rhythm is found. Adriani and Rovenstine (4) investigated the action of cyclopropane on the hearts of cold blooded animals and attribute to it a parasympathomimetic effect. In our laboratories it has been shown that irregularities occur when there is no hypoxemia (5). A standard method of producing epinephrine-cyclopropane ventricular tachycardia was devised (6) and then used to determine the effectiveness of various drugs in blocking such action (7). Barbiturates administered intravenously were found not only to be ineffective in preventing such arrhythmias but some members of this group (5, 9) actually led to more serious irregularities.

The present report is a study of the action of cyclopropane in various concentrations on the heart of intact, unpremedicated dogs and on the isolated hearts of turtles, rabbits, cats and dogs. Epinephrine has not been used in these experiments.

METHODS

The procedure for intact animals consisted of anesthetic induction by means of a mask, introduction of a cuffed endotracheal tube and its connection through a soda-lime absorber and a 5 liter rubber bag to a large 100 liter bag which contained the cyclopropane-oxygen mixture of known content which was to be studied. In case the cyclopropane was concentrated enough to abolish respiratory movements, the small bag was used to carry out controlled respiration by rhythmical manual pressure. It was refilled every two to three minutes, only six to eight seconds being needed for the change. Only one concentration of an anesthetic mixture

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was tested on any one animal on any day. The length of time during which the various cyclopropane concentrations were administered was progressively decreased with increasing concentration. It was, however, thirty minutes or longer for all experiments until 65 per cent concentrations were reached. This is believed to be long enough for blood and tissues to come into approximate equilibrium with the anesthetic mixture (8). For concentrations of 65 per cent or higher, fifteen minute periods of anesthetization were used.

In a number of instances a small French ureteral catheter was passed through the endotracheal tube so that alveolar samples could be obtained in the course of the experiment. Direct tracings of blood pressure were made from the femoral artery. The animals were placed on their left sides and connected for continuous lead II electrocardiographic observation. Electrocardiograms were taken before the animal was anesthetized, at periodic intervals during anesthesia and whenever any suggestion of a change in rhythm was observed.

In most of the experiments blood samples were drawn by the use of mercury Hempel pipets. Using the Orcutt-Waters procedure (10), they were analyzed for carbon dioxide, oxygen and cyclopropane. Hemoglobin determinations were done routinely with the Evelyn photoelectric colorimeter to substantiate the validity of the blood analyses.

For protection studies, Robbins' technic (2) of premedication with 10 mg. of sodium amytal per kilogram of body weight was duplicated, but higher concentrations of cyclopropane than he had used were employed.

A cannula was inserted into the isolated turtle hearts by way of the right atrium, leaving the sinus venosus intact. Ringer's solution, saturated by passing an oxygen-nitrogen mixture through it, was then used for perfusion until a myocardiogram showed a steady phase of contraction. The perfusing fluid was then changed to a Ringer's solution which had been equilibrated by bubbling a known oxygen-cyclopropane mixture through it for at least thirty minutes. The gas content of the solutions was checked by Van Slyke analysis. The cyclopropane content of the gas mixture bubbled through the Ringer's solution was varied from 14 to 83 per cent. When a definite change had occurred in the myocardiogram, perfusion was again made with a control solution in which the cyclopropane was replaced by nitrogen. In preliminary tests it was found that prolonged perfusion with the cyclopropane-equilibrated solutions routinely caused cardiac standstill or fibrillation.

Coronary perfusion was employed for the isolated mammalian hearts by cannulation of the ascending aorta. Locke's solution was used for the rabbit and cat hearts and defibrinated homogeneous blood for the dog hearts. Control and experimental solutions for perfusion were saturated by using oxygen-air or cyclopropane-oxygen mixtures, but only a 50 per cent cyclopropane content was tested in them. Hearts which did not give vigorous, rhythmical responses with the control perfusions and which did not show recovery were ruled out of any consideration in the results.

RESULTS

Intact Animals.—A summary of the results of the intact animal experiments is given in the table. The totals of all experiments are grouped in the table. It is evident that both the type and number of irregularities increase with the cyclopropane concentrations. Twelve animals were tested with 38 to 44 per cent cyclopropane. In two of these ventricular extrasystoles were observed and recorded. When the amount of cyclopropane in the mixture was between 45 and 54 per cent, there were four instances in the 15 animals tested of auriculoventricular nodal block, five of auriculoventricular nodal rhythm, seven of ventricular extrasystoles, two of ventricular tachycardia, and one of cardiac depression which led to standstill and death.

Sixteen animals were tested with 55 to 64 per cent of cyclopropane in the anesthetizing mixture. In eight of the experiments there was auriculoventricular nodal block; in three, auriculoventricular nodal extrasystole; in four, auriculoventricular nodal rhythm; in eleven, ventricular extrasystole; in six, slow ventricular rhythm and in two ventricular tachycardia. Two animals also had ventricular fibrillation, one of these just after the anesthetic agent was withdrawn and pure oxygen given. This change had been made after an eleven minute period of ventricular rhythm, during which a blood sample was drawn. Later analysis of the blood showed it to be completely saturated with oxygen.

Fourteen animals were used when there was 65 to 80 per cent of cyclopropane in the mixture with oxygen. Thirteen of these animals are seen from table 1 to have had auriculoventricular nodal block, one auriculo-

TABLE 1

CARDIAC IRREGULARITIES ARISING DURING CONTROLLED RESPIRATION WITH CYCLOPROPANE-OXYGEN MIXTURES OF KNOWN CONCENTRATION, AS DETERMINED BY CHEMICAL ANALYSIS *

Cyclopropane in anesthetic mixture, per cent	Average time of administration, minutes	Number of animals	Auriculoventricular nodal block	A-V Extrasystole	A-V Nodal rhythm	Ventricular extrasystole	Slow ventricular rhythm	Ventricular tachycardia	Ventricular fibrillation	Cardiac depression
38 to 44	60	12				2				
45 to 54	45	15	4		5	7		2		1
55 to 64	30	16	8	3	4	11	6	2	2	
65 to 80	15	14	13	1	10	9	6	7	4	4

* The amount of cyclopropane in the mixture is shown in the first column at the left and the average time of administration of the various percentages is indicated in the second column. There was increased severity of irregularities with increasing cyclopropane percentages. Only one anesthetic mixture was tested on any animal in a day.

ventricular nodal extrasystole, ten auriculoventricular nodal rhythm, nine ventricular extrasystole, six slow ventricular rhythm, seven ventricular tachycardia—four of which succumbed quickly to ventricular fibrillation. Four other animals of this group were lost from cardiac standstill, three following ventricular rhythm and one ventricular tachycardia.

Since blood analyses of samples drawn during or at the height of the irregularities showed that there was always at least 90 per cent and usually complete oxygen saturation of the hemoglobin, hypoxemia was not the responsible factor. The maximum blood cyclopropane concentration was 58.9 mg. per cent. Alveolar gas samples showed the cyclopropane content always equal to or greater than that of the analyzed reservoir mixture, with minimum oxygen concentrations of 15 to 18 per cent and a carbon

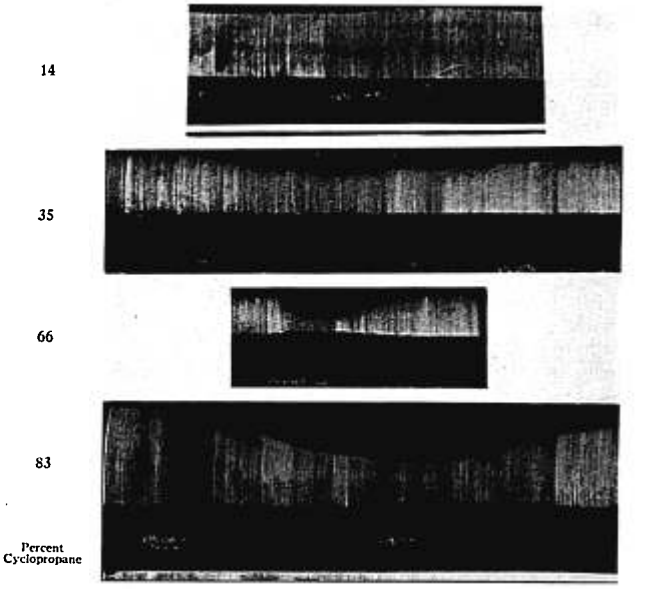

FIG. 1. Records of turtle heart perfusions with Ringer's solution. The control solution had a known oxygen-nitrogen mixture passed through it until saturated. In the test solution cyclopropane, in the percentages indicated, replaced the nitrogen. It can be seen in all the records that a very slight stimulation preceded the depression caused by the cyclopropane.

dioxide content of 1.0 to 3.5 per cent. This latter low figure was the result of the hyperventilation necessary to maintain a good color of the tongue with such a high cyclopropane content.

The effects of such concentrations of cyclopropane on direct blood pressure tracings are variable. In some animals there was essentially no change. Such animals had less serious cardiac irregularities. Those with pronounced irregularities usually had a progressive fall in pressure.

Twenty to thirty minutes after the intravenous administration of 10 mg. of sodium amytal per kilogram of body weight, ten animals were anesthetized from a reservoir mixture of oxygen-cyclopropane which contained approximately 60 per cent of the anesthetizing gas. One of these ten animals had less serious cardiac irregularities than when anesthetized with cyclopropane alone. On the other hand, two animals had ventricular fibrillation in the presence of amytal-cyclopropane. The other seven animals had the same type and duration of irregularities whether or not premedication with amytal was given. Previous studies had shown that dosages of amytal to 50 mg. per kilogram were ineffective in affording protection from irregularities (5, 9).

FIG. 2. A record of a rabbit heart perfusion with oxygenated Locke's solution (the control) and oxygen-cyclopropane saturated Locke's (the experimental solution), between "on" and "off." Cardiac depression similar to the last three records of figure 1 is clearly evident. Recovery follows as perfusion is again made with the control solution.

Isolated Hearts.—Since Thienes, Greeley and Guedel (3) have recently suggested that cyclopropane has a very low toxicity for heart muscle or that cardiac effects are dependent on hypothalamic centers (11), isolated heart perfusions were made. Representative graphs from 22 turtle hearts are shown in figure 1. It can be seen that cyclopropane had a very slight stimulating effect on the systolic amplitude, best shown in the record when 14 per cent cyclopropane was used with oxygen in saturating the Ringer's solution. Such stimulation generally occurs with cyclopropane percentages up to 50. Occasionally it is apparent with still higher percentages and may be noticed in the record of perfusion with 83 per cent.

After the initial stimulating effect, a depression of the amplitude of contraction occurred, as can be noted in the last three graphs of figure 1. With the higher percentages of cyclopropane there was occasionally a slowing of the heart and decreased relaxation, as is evident in the record of perfusion with 66 per cent cyclopropane. In a few experiments (no record shown) premature contractions were followed by a compensatory pause. To determine whether such changes were merely the result of a

parasympathomimetic action of cyclopropane (4), atropine 1 : 10,000 or physostigmine 1 : 20,000 was added to some of the perfusion solutions. The responses were unchanged and identical with those shown in figure 1.

In figure 2 is shown the result of perfusing a rabbit heart with oxygenated Locke's solution as a control, followed by a similar solution which

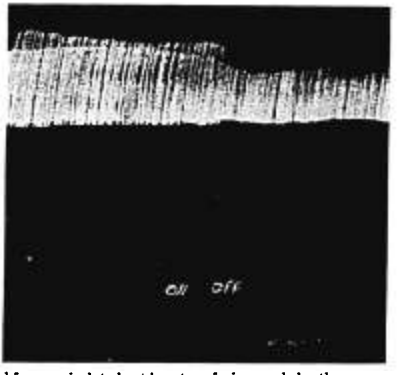

FIG. 3. A record from an isolated cat heart perfusion made by the same procedure as outlined in figure 2, and showing similar results to those obtained with the rabbit heart. The cyclopropane saturated solution was presented to the heart for only twenty-four seconds.

was saturated with 50 per cent cyclopropane. It can be seen that the same type of cardiac depression occurred as was found when similar cyclopropane concentrations were administered to the isolated turtle heart. In 20 experiments with hearts of this species occasional cases of ventricular extrasystole occurred and heart block was common. In a few instances ventricular fibrillation occurred. Similar depression took place when isolated cat hearts were perfused, as may be seen in figure 3, when the

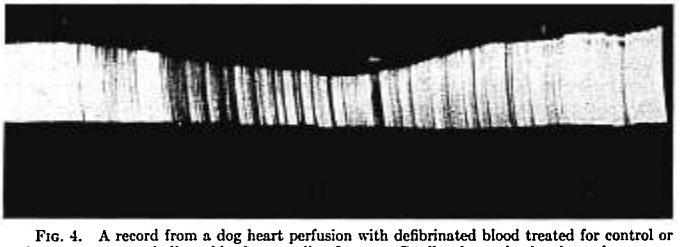

FIG. 4. A record from a dog heart perfusion with defibrinated blood treated for control or cyclopropane tests as indicated in the preceding figures. Cardiac depression by the cyclopropane, followed by recovery after its withdrawal, is evident, as was the case with the other species tested.

cyclopropane-treated solution was presented to the heart for only twenty-four seconds.

A record from one of the eight successful cases of perfusion of a dog heart with defibrinated blood is shown in figure 4. The results are essentially those enumerated for the turtle, cat and rabbit hearts.

DISCUSSION

From the results of these studies it is apparent that cardiac irregularities are aroused *spontaneously* in the dog when the depth of cyclopropane anesthesia approaches the stage of respiratory arrest. Centers of lower automaticity either are stimulated or they may become dominant due to depression of higher cardiac centers. The greater severity of irregularities in the groups with higher cyclopropane concentration, despite a shorter period of administration of the agent, is evident from the increasing number of cases of slow ventricular rhythm, ventricular tachycardia, and ultimately ventricular fibrillation or cardiac standstill. That these irregularities occurred without any degree of hypoxemia was proved by the oxyhemoglobin saturation of the blood samples drawn at the height of the irregularities. It is also apparent that cyclopropane may be directly toxic to the heart, since animals were lost by progressive depression of the automatic conducting system, death occurring by cardiac arrest rather than by ventricular fibrillation in several of the experiments.

In a few clinical cases 40 to 50 per cent cyclopropane has been employed during electrocardiographic studies. Patients with excellent color who had regular heart rates of 40 to 60 by palpation were found uniformly to have an auriculoventricular nodal rhythm when the electrocardiogram was studied.

In certain respects the results of the animal studies are in agreement with the clinical series of Guedel *et al.* (3) in which nine of ten patients had cardiac irregularities when anesthetized with cyclopropane. Each of the nine patients had ventricular extrasystoles during anesthesia. In three, such irregularities persisted at high concentrations and in two others a supposedly regular pulse and normal heart sounds gave electrocardiographic tracings of an auriculoventricular nodal rhythm. Thus, five of the nine patients in whom evidence appeared had irregularities at high concentrations of the agent. Our interpretation that the cardiac arrhythmias arising with cyclopropane may be of great importance to the possible outlook for the patient's safety are diametrically opposed to those of Guedel *et al.* who believe that they are relatively innocuous. A cardiac rhythm with the auriculoventricular node or a constant ventricular center as the pacemaker would be clinically indiscernible without electrocardiographic observations, a fact many clinicians overlook. That such rhythms might be early signs of processes which later might produce grave or even fatal disturbances would be denied by few cardiologists. Our repeated demonstrations that premature ventricular beats invariably precede ventricular fibrillation, and the recent researches of Wiggers (12) which show

that stimuli placed in the "vulnerable period" of a ventricular systole lead to ventricular fibrillation, all point to their importance. In cyclopropane anesthesia the increased myocardial irritability may make extrasystoles possible by lowering the threshold for stimuli which were previously ineffective. Both clinical and laboratory experiences, in our opinion, justify regarding extrasystoles in anesthesia as danger signals.

Since 3 : 1 bag mixtures of cyclopropane-oxygen were largely employed by Guedel, it is probable that often he was not using as great a concentration of the agent as he supposed. By chemical analysis of such a 3 : 1 bag mixture it can be shown that the cyclopropane content is nearer 65 per cent than the theoretical 75 per cent. Factors responsible for the loss of the agent may be: adsorption on the rubber bag surface, diffusion of its molecules through the pores of the bag, inaccuracies in flow meters, or nonspecific calibration of such meters for the physical constants of cyclopropane.

It is felt that the burden of proof that there is an "arrhythmic range" still rests with its proponents. It definitely was not passed in five of Guedel's nine cases and it is now stated that nodal rhythm persists or even may appear with high concentrations, although not previously present (11). Granted that an arrhythmic range does exist, there is a hazard to the patient in traversing it. Although we have made no detailed study of the point, we have observed several instances in which irregularities were more common in ascent than during descent in anesthesia, which agrees with Guedel's findings.

As in our previous studies of barbiturate premedication (5, 9), the present results again show that no consistent protection from these drugs can be depended upon since but one of ten animals was any better, and two were lost when amytal premedication was used. No doubt these drugs postpone the onset of hypoxemic irregularities, as Robbins showed (2), but such an initial qualifying condition is scarcely to be condoned.

The toxic effect of cyclopropane on the isolated hearts of turtles, rabbits, cats and dogs is shown by the reduction in contraction amplitude which progresses with increased concentration of the anesthetic agent. This may lead to a cardiac standstill or to fibrillation if the test solution is long continued.

Numerous studies and analyses of the arrhythmias which accompany cyclopropane anesthesia have been made in the ten years since its clinical usage began. Fully as detailed work should be done on the older anesthetic agents before valid comparisons can be made. All anesthetics have undesirable side actions. Cyclopropane cannot be discredited merely because it too is not perfect. It has long been known that ether and chloroform depress the heart. Clinical usage of cyclopropane at this institution is guided by the realization that arrhythmias may be present without the possibility of detection by palpation and the feeling that they are one of the very important warning or danger signals during the administration of the agent and should be coped with by a reduction in concentration or

by changing to another agent, rather than by increasing the apparent causative factor.

CONCLUSIONS

1. In the dog, cardiac irregularities arise spontaneously at about the level of respiratory arrest, even when adequate tidal exchange by controlled respiration is being maintained.

2. The incidence and severity of such irregularities increase as the percentage of cyclopropane is raised; hence no "arrhythmic range" is believed to exist.

3. Such irregularities are not of hypoxemic origin since the hemoglobin was shown by chemical analysis to be approximately saturated with oxygen.

4. Sodium amytal as a premedicant, in doses of 10 mg. per kilogram of body weight, gives no consistent protection from the irregularities. Dosages to 50 mg. per kilogram have previously been shown to be ineffective.

5. In the turtle, rabbit, cat and dog, perfusion of the isolated heart showed the myocardium to be directly depressed by high cyclopropane percentages. An initial period of stimulation frequently preceded such depression when low percentages were used on the turtle heart, but it was seen less frequently when mammalian hearts were perfused.

6. No parasympathomimetic effect of cyclopropane could be demonstrated on isolated perfused turtle hearts.

7. Present evidence indicates that arrhythmia is one of the important warning signals during anesthesia with any agent. It is the clinical experience at this institution that a reduction in the concentration of the agent or an actual change to another agent is a safer procedure than to increase its concentration.

We wish to thank Capt. Malcolm H. Hawk who aided with parts of this investigation. We are grateful also to Drs. Guedel and Thienes for frank discussions of the problems involved. Dr. Ralph Waters has aided in the formulation of the included clinical expressions.

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COMING EXAMINATIONS

The Part I (Written) Examinations for certification by the American Board of Anesthesiology, Inc., will be held at various places throughout the country on January 21, 1944. Final date for filing applications is October 23, 1943.

The Part II (Oral) Examinations of the Board probably will be held in June, 1944 at the place and just prior to the time of the meetings of the American Medical Association. Applications must be filed 90 days before date of examination. Sec., Paul M. Wood, M.D., 745 Fifth Avenue, New York, New York.