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CARDIAC ARRHYTHMIAS UNDER CYCLOPROPANE ANESTHESIA *

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CARDIAC irregularities during cyclopropane anesthesia are well known and have been the subject of experimental study by a number of investigators (for the complete literature up to the end of 1939 see the review by Robbins (1)). In a previous paper (2), clinical observations were described which indicated that the irregularities tend to disappear with very high cyclopropane concentrations and that they are of reflex origin. The experiments to be described below were planned in an attempt to gain more information concerning the cardiac actions of cyclopropane. These experiments were mentioned in the previous paper (2) and formed a part of the basis for the conclusions drawn. Electrocardiographic studies were made on 10 dogs, followed by more detailed observations on 10 surgical patients. ‡

Dog Series.—Seven dogs, weighing from 15 to 20 kilograms, were each given a total dose of 10 mg. of morphine sulfate and 0.5 mg. of atropine sulfate, subcutaneously, thirty to sixty minutes before anesthesia. One of these 7 dogs was tested with the same cyclopropane procedure a week previously without premedication. An eighth dog received only atropine premedication and a ninth and a tenth dog no premedication. There were, therefore, three experiments without

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atropine, four with atropine alone and seven with both atropine and morphine. Anesthesia was conducted by the CO_2 absorption technic and was induced with equal parts of cyclopropane and oxygen, with cyclopropane added to the point of respiratory paralysis, following which closed endotracheal anesthesia was carried on by passive respiration. The bag was then refilled with 3 liters of cyclopropane and 1 liter of oxygen at intervals of about three minutes (2 to 6 bags, average 4.5). The breathing bag concentrations of cyclopropane were finally increased to 85 per cent or more in each experiment, until cyanosis of the tongue appeared. Then 1 to 3 bags of pure cyclopropane (average 2) were administered for a total interval of one-half to eight minutes (average three minutes per bag). This was done to displace as much oxygen as possible from the tissues and to saturate the tissues with cyclopropane as nearly as possible. By this means it was hoped to obtain evidence of the direct toxicity of the gas upon the heart. The total time during which the dogs were exposed to 50 per cent or more of cyclopropane in the bag varied from twenty-two to fifty-one minutes; cyclopropane concentrations of 75 per cent or higher were maintained for from nine to forty-one minutes (average twenty minutes). The bag was then emptied of its mixture and filled with oxygen every one to three minutes until recovery of spontaneous respirations, after which the tracheal tube was withdrawn and the animal allowed to go on to complete recovery. This required an average of 3.5 bags over a total average period of seven and four-tenths minutes. Throughout each experiment, the animal was attached by lead II to the electrocardiograph and continued direct observation of the string shadow was made. At intervals, the movements of the shadow were recorded on sensitive paper.

Of the three dogs not given preliminary atropine or morphine, one exhibited idioventricular beats at 50 per cent cyclopropane during induction (fig. 1). The auricles were beating at a rate slightly less than were the ventricles (auricular rate 88 per minute, ventricular rate 100 per minute). On increasing the cyclopropane concentration to 75 per cent the idioventricular phenomena disappeared, the rate increased to 140 beats per minute and the T wave was quite coved. At 100 per cent cyclopropane in the breathing bag, the rate decreased to 120 beats per minute, the P–R interval lengthened from 0.14 second to 0.2 second. Just before ventilation with pure oxygen was started, idioventricular rhythm occurred with evidence of a very much delayed conduction. Thirty seconds after changing to pure oxygen, idioventricular rhythm was still present but the rate had decreased from 90 per minute to 80 per minute. Four minutes later the protocol showed marked irregularities but unfortunately no E. C. G. tracing was taken at this time. Three minutes later, the tracings showed normal complexes similar to those taken before anesthesia was started.

In a second dog the first E. C. G. was taken at the time apnea occurred. Idioventricular rhythm with a shifting origin in the pacemaker was present, in one complex back to the S. A. node. This same phenomenon was still present even with 100 per cent cyclopropane. Just before giving oxygen, the E. C. G. appeared to show two pacemakers, probably nodal and ventricular, since the A. V. interval was very

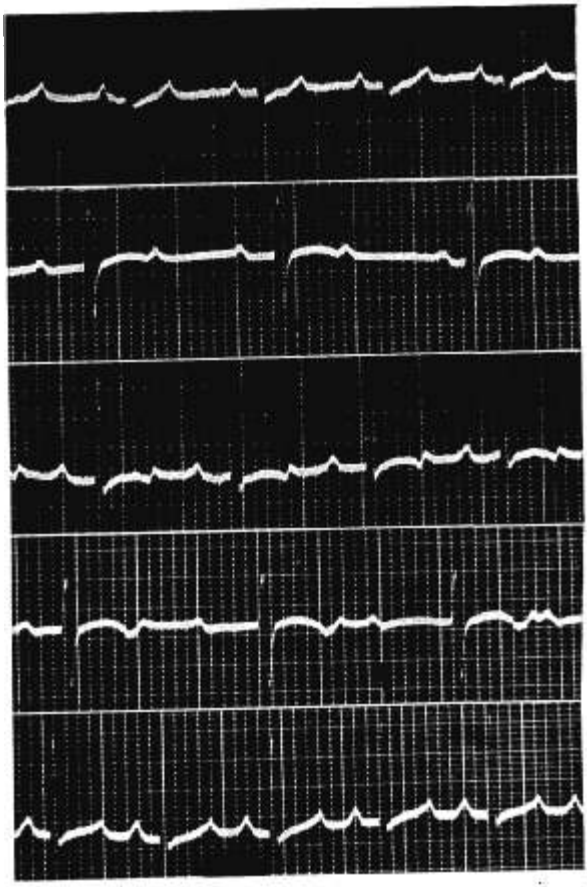

FIG. 1. Dog 4. No premedication. Tracing 1, before anesthesia; 2, after eight minutes of 50 per cent cyclopropane; 3, during administration of 75 per cent cyclopropane; 4, pure cyclopropane with asphyxia; 5, after seven and one-half minutes of pure oxygen.

variable. On changing to pure oxygen the A. V. node almost always acted as the pacemaker, but one complex indicated that the S. A. node was also active with delayed A. V. conduction. After two and one-half minutes of pure oxygen, normal complexes were present with an A. V. interval of 0.13 second and a rate of 60 per minute.

The third dog showed no arrhythmias until the bag contained 85 per cent or more cyclopropane and definite cyanosis of the tongue was noted when rapid nodal rhythm occurred. This type of arrhythmia was not recognized during the experiment (that is, not until the tracings were developed and examined), hence the dog was maintained at 100 per cent cyclopropane in an attempt to produce arrhythmias. After eight minutes, ventricular fibrillation suddenly occurred.

The one dog given atropine, but no morphine, showed no change in the rhythm until asphyxial concentrations of cyclopropane were reached, when first coving, then inversion of the T wave and nodal rhythm were recorded.

Of the 7 dogs given preliminary morphine and atropine, 5 exhibited flattening, coving or inversion of the T wave before cyclopropane was started. On administration of cyclopropane, only 3 dogs developed further irregularities. These were as follows: One dog developed gradual deepening of the inverted T on increasing the concentration of cyclopropane. After eight minutes of pure cyclopropane, regular nodal rhythm developed. One minute after changing back to pure oxygen, the ventricular rate became irregular, with continued nodal rhythm and delayed conduction. In one complex there was an apparent shift back to the S. A. node as pacemaker. Results with the other two dogs were essentially the same, except that on reaching a concentration of 100 per cent cyclopropane in the bag, nodal rhythm appeared within two or three minutes. Reversal of anesthesia by repeatedly filling the bag with oxygen was followed by arrhythmias in 3 other dogs, as seen either in the electrocardiographic tracings or by direct observation of the movements of the string shadow on the screen.

Figure 1 illustrates the changes in a dog without atropine. Figure 2 illustrates nodal rhythm in a dog with morphine and atropine premedication.

Human Series.—Ten major abdominal operations were done in unselected cases. A continuous blood pressure record was kept and electrocardiographic tracings were made at intervals as indicated by the heart sounds heard through a stethoscope fixed to the precordium. The subjects were between 24 and 56 years of age. All had morphine, 10 mg., and scopolamine, 0.4 mg., or morphine, 15 mg., and atropine, 0.65 mg., one hour before anesthesia. Four cases showed cardiac arrhythmias immediately before anesthesia. The technic employed was the same as in the dogs, except that the oxygen concentration in the bag was maintained for forty-seven to one-hundred thirteen minutes

during induction and the period of surgery at not less than 25 per cent (cyclopropane 50 to 75 per cent as determined by actual chemical analysis). No cyanosis was permitted at any time.

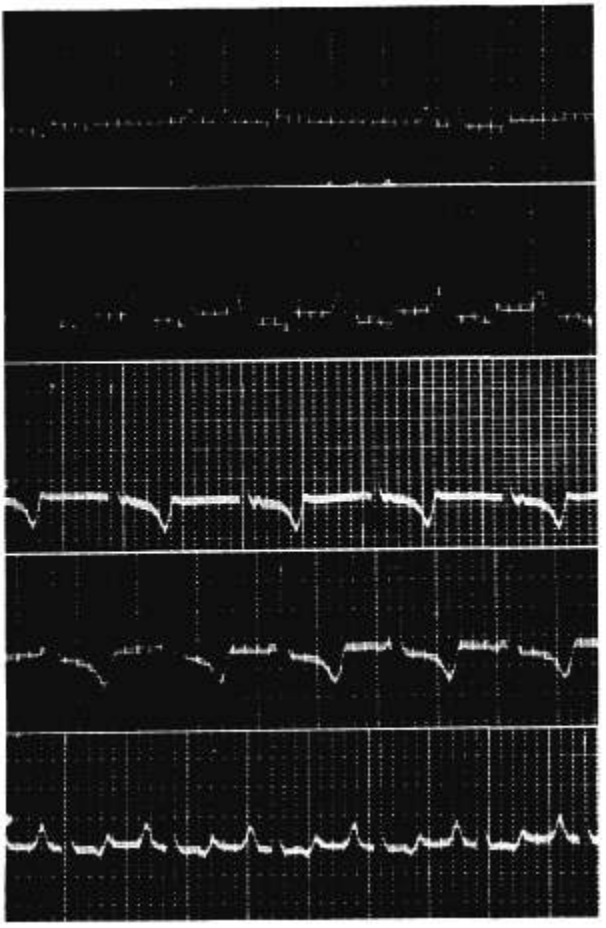

FIG. 2. Dog 7. Morphine and atropine premedication. Tracing 1, before anesthesia, coved T-wave; 2, three minutes at 75 per cent cyclopropane, beginning nodal rhythm, inverted T-wave; 3, nine minutes at 75 per cent cyclopropane, A–V nodal rhythm, inverted T-wave; 4, after five minutes of pure cyclopropane; 5, after five minutes of pure oxygen.

Our starting point for observation was slightly above respiratory paralysis. From this point anesthesia was deepened and maintained by passive respirations.

There were no noteworthy changes in blood pressure.

Of the 10 cases, 1 exhibited no irregularity of pulse or electrocardiographic record. Three developed ventricular extrasystoles during induction, which persisted at high concentrations, but which became much worse on ascent. Of these 3, 1 case became regular at 65 per cent cyclopropane (bag concentration), with intervals of irregularity.

In the remaining 6 cases, ventricular extrasystoles (E.C.G.) and marked irregularity of the pulse were noted on descent of anesthesia, but these irregularities disappeared at the high cyclopropane concentrations (55–70 per cent). On ascent from deep anesthesia, during the period of oxygen inhalation, the same irregularities reappeared, and usually they were more marked than during descent of anesthesia. With 2 of these 6 cases the regular pulse and heart sounds at high cyclopropane concentrations were associated with electrocardiographic evidence of A–V nodal rhythm.

In subsequent clinical observations (without electrocardiographic records), induction of anesthesia by intravenous evipal or pentothal prevented or minimized arrhythmias during the administration of cyclopropane for a period of thirty to sixty minutes (2).

COMMENT

During anesthesia with cyclopropane, electrocardiographic changes develop at concentrations of cyclopropane sufficient to depress or paralyze the respiratory centers. This is not an invariable occurrence, however, either in dogs or human subjects. Robbins and Baxter (3) showed that early arrhythmias may be abolished by artificial respiration indicating the importance of anoxia in their production. Perhaps failure to observe arrhythmias in several of our subjects was due to early institution of artificial respiration, before anoxemia developed. Our experience with dogs confirmed the results of Seevers, Meek, Rovenstine and Stiles (4) that atropine alters the type of the arrhythmias. The atropine dose used with human subjects was apparently without effect on the arrhythmias.

Robbins and Baxter (5) found that morphine increased the arrhythmias in dogs. However, the dose of morphine used in their experiments was as much as ten to twenty times that employed in our experiments. It was our observation that the dose of morphine we used had little effect on the cyclopropane arrhythmias, but did produce a coved diphasic T wave, even in the absence of cyclopropane. We attemped to keep our doses of atropine and morphine comparable in effect to those used in human anesthesia, but apparently used too much atropine in the dogs.

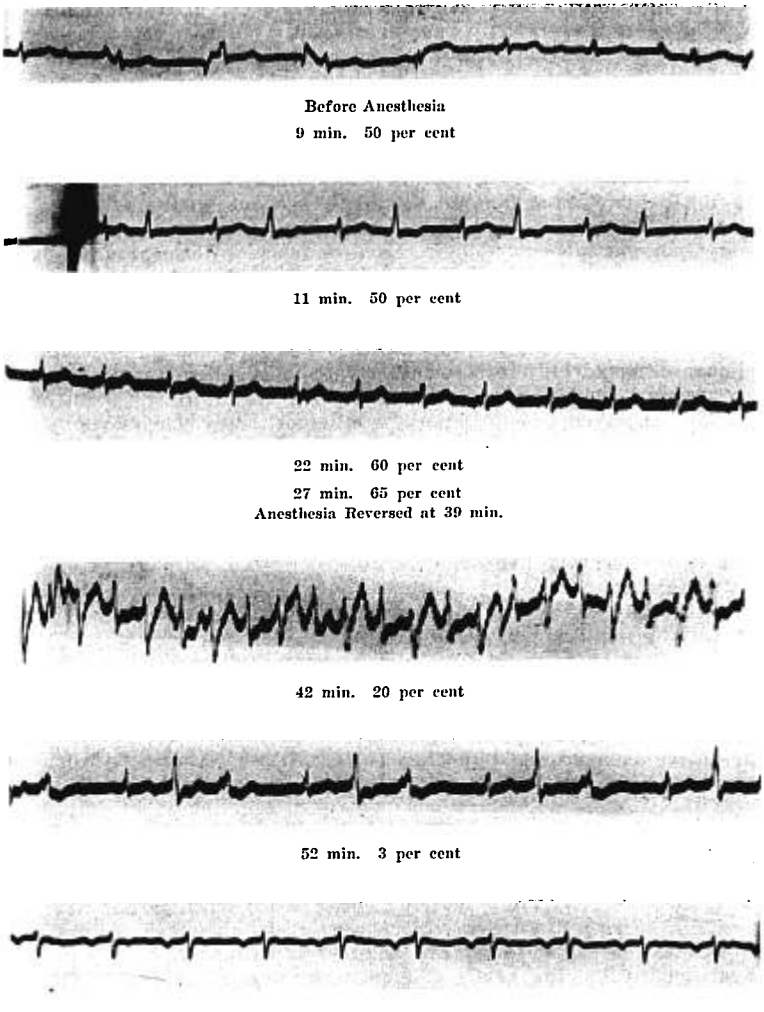

FIG. 3. Human subject. This patient showed arrhythmias before anesthesia. Bigeminal beats developed eleven minutes after the beginning of anesthesia, at 50 per cent cyclopropane; the pulse became regular at 60 per cent cyclopropane, with return of irregularities on reversal and regular pulse after resumption of spontaneous respirations.

It was apparent that in a fair proportion of our dog and human subjects very deep cyclopropane anesthesia (60–75 per cent concentration without asphyxia) was not associated with clinically discernible arrhythmias. In these cases, arrhythmias were observed only during descent or ascent, or both. Ascent arrhythmias, especially in the human cases, were greater, both as to pulse and heart sounds, and as to E.C.G. records; that is, there were more intervals of bigeminus rhythm and of absolute irregularity due to ventricular extrasystoles. The A–V nodal rhythm exhibited by 2 of the cases, was, of course, not distinguishable from regular beat by the stethoscope or by the finger on the pulse, nor was there any other clinical evidence of deficient circulation. Blood pressure, color, force of the pulse and capillary filling of the skin of the forehead after pressure were normal.

A–V nodal rhythm or idioventricular regular rhythm occurred in several of the experiments on the dog, but in all except 2, this type of change occurred only in association with marked asphyxia. In most instances, the bag contained pure cyclopropane.

The proportion of human cases in this short study which do not show disappearance of arrhythmia at cyclopropane concentrations of 60 to 70 per cent is less than in the clinical series of several hundred cases reported previously (2). The trend of the experiments, however, seems to support the former conclusions.

On the basis of the early experiments of Levy (6), and the more recent experiments of Beattie, Brow and Long (7), Dikshit (8) and of Allen, Stutzman and Meek (9), it is possible to explain the disappearance of arrhythmias with high concentrations of cyclopropane. Levy showed that chloroform arrhythmias were infrequent in deep chloroform anesthesia. Beattie, Brow and Long located centers in the hypothalamus which were essential to the production of chloroform arrhythmias. Electrical stimulation of these centers, even in the absence of chloroform, caused marked ventricular extrasystoles. Allen, Stutzman and Meek abolished epinephrine arrhythmias associated with cyclopropane anesthesia by functional or surgical removal of hypothalamic centers. Most investigators consider a concentration of more than 25 to 30 per cent cyclopropane to be high, and that the resulting anesthesia is deep. Ordinarily, anesthesia is said to be deep when respirations are depressed. However, it is apparent that with cyclopropane, as with morphine, the respiratory centers are depressed much earlier with respect to other centers than is the case with ether and chloroform. Now, it is reasonable to assume from the experiments of Levy and of Beattie et al that the failure of appearance of cardiac arrhythmias in deep chloroform anesthesia is due to the depression of the hypothalamus by the higher concentrations of chloroform. From the fact that in our human subjects ventricular extrasystoles were abolished, or nearly so, with concentrations of cyclopropane above 50 to 60 per cent, it would seem that with cyclopropane anesthesia the hypothalamic cen-

ters are not strongly depressed until well after respiratory failure. It should also be pointed out that cord depression is not complete, as manifested by depression of skeletal muscles, except at concentrations of cyclopropane well above those required to abolish spontaneous respirations. To state the hypothesis in other words, depression of the arrhythmic centers of the hypothalamus by high concentrations of anesthetic agents largely overcomes cardiac arrhythmias ordinarily associated with inhalation anesthesia. With chloroform, these centers are depressed before depression of the respiratory centers, but with cyclopropane, the respiratory centers are depressed before the hypothalamic centers.

The clinical protection afforded by intravenous barbiturates may possibly be explained by depression of the hypothalamus. It is also possible that the barbiturates decrease the output of epinephrine by the suprarenal glands (10). There is much experimental evidence pointing to epinephrine as an important factor in the production of arrhythmias and to a close relationship between the hypothalamus and output of epinephrine (11).

The experiments described in this report were planned originally for the purpose of determining whether cyclopropane is a myocardial poison in the same sense as is chloroform. Much attention has been given to a statement in the summary on page 16 of the paper by Seevers, Meek, Rovenstine and Stiles (4) to the effect that deaths occurred in dogs under 50 per cent or more cyclopropane with adequate oxygen in the breathing bag. The protocols on page 12 record two deaths. One of these dogs was cyanotic in spite of 47 per cent oxygen; the other was exposed to 17 per cent oxygen, and, under experimental conditions, could readily have been in an anoxic state. From the fact that a concentration of 75 per cent cyclopropane in the absence of anoxia was not incompatible with apparently normal circulation, according to our observations, it would seem that this gas has a very low toxicity for the heart muscle. Prevailing evidence suggests that the ventricular extrasystoles associated with cyclopropane anesthesia are of reflex nature, involving the hypothalamus. The mechanism of production and the significance of the A–V nodal rhythm occasionally observed during very deep anesthesia must be determined before a direct action of cyclopropane upon the heart muscle can be ruled out. Whatever may be the cause, it would seem that this electrocardiographic change is not a dangerous indication, since it is entirely and quickly reversible, and has never been seen to lead to a fatal arrhythmia, except in the presence of prolonged, severe asphyxia in dogs.

SUMMARY AND CONCLUSIONS

1. Cardiac arrhythmias occur in cyclopropane anesthesia. These arrhythmias appear at about the beginning of respiratory failure, and are typically of the nature of ventricular extrasystoles.

2. High concentrations of cyclopropane (50 to 75 per cent in alveolar air), or larger doses of atropine, abolish or minimize these arrhythmias in a large proportion of subjects.

3. Cyclopropane does not seem to be toxic to the heart, since extreme concentrations failed to produce changes in cardiac activity which we can interpret as muscle depression, except in the presence of anoxemia (experiments on the dog).

4. A–V nodal rhythm occurred in a small number of human and dog subjects at 70 per cent cyclopropane. Increasing the concentration to 100 per cent resulted in A–V nodal rhythm in most dogs.

5. An explanation of the effect of high concentrations of cyclopropane on cardiac arrhythmias is suggested.

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