

THE EFFECTS OF ETHER, CYCLOPROPANE AND CHLOROFORM ON THE ISOLATED AURICLE OF THE CAT* †

LOUIS J. ACIERNO, M.D., ‡ AND JOSEPH R. DiPALMA, M.D. §

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INTRODUCTION

ALTHOUGH many investigations of the action of common anesthetic gases on cardiac muscle have been made, the results have been qualitative in nature (1-6). The cardiac actions of the various anesthetics and their propensity for inducing arrhythmias, can be explained only on the basis of alteration of the fundamental properties of cardiac muscle, that is, contractility, excitability, refractory period and spontaneous rhythmicity.

The advent of electronic stimulators of new design and the use of the oscilloscope to measure amplitude and duration of minute currents have rendered possible more accurate study of the effect of anesthetic agents on resting excitability, contractility, refractory period and spontaneous rhythm (7). In a previous communication, the normal range of variation of the fundamental properties of heart muscle has been defined by one of us (8).

This investigation is concerned with the effect of ether, cyclopropane and chloroform on the resting excitability, refractory period, contractility and spontaneous rhythm of the isolated auricle of the cat.

METHODS

The isolated cat auricle was suspended in Locke's solution maintained at a constant temperature of 30 C. and with the pH held at 7.5 by bubbling through the solution, at a rapid rate, a mixture of 95 per cent oxygen and 5 per cent carbon dioxide. The muscle was driven at a constant rate by a special dual pulse square wave stimulator with the second stimulus introduced at varying intervals for the determination of the refractory period. Strength-duration curves were obtained by utilizing the oscilloscope as a milliammeter with the durations of stimuli at 17, 10, 5, 2.5, 1, and 0.1 msec., respectively. An optical kymograph recorded the amplitude of contractions as indicated by the degree of

* Aided by a grant from the National Heart Institute, U. S. Public Health Service.

† Department of Physiology, State University of New York, State University Medical Center at New York, Brooklyn, New York.

‡ Post-doctorate Research Fellow, National Heart Institute, U. S. Public Health Service.

§ Present Address: Hahnemann Medical College and Hospital of Philadelphia, Philadelphia, Pa.

excursion of an isometric lever attached to the muscle. The electrodes were made of silver and coated with silver chloride.

Control determinations of resting excitability, contractility and refractory period were made for each muscle after attaining maximal muscular activity by stimulating at a rate of 75 per minute for at least fifteen minutes.

Because of the physical characteristics of the anesthetics used, and in order to avoid the evanescent effects obtained during the preliminary trials, the drugs were introduced into Locke's solution at a predetermined constant rate of flow by means of a separate inflow system consisting of a closed chamber vaporizer. The vaporizer was maintained at room temperature, which was usually around 25 C. The rates of flow varied from 2 to 100 ml. per minute with the muscle exposed to a particular rate of flow for a period of five minutes and observations begun at the end of the fourth minute. These observations were usually completed about one minute after the flow was terminated. A fresh muscle preparation was employed for each anesthetic used. In several experiments, similar observations were carried out with the isolated papillary muscle.

RESULTS

Refractory Period and Contractility.—All three anesthetics uniformly produced a shortening of the refractory period. There was a direct relationship between rate of flow and degree of shortening of the refractory period, the percentage decrease becoming increasingly marked with the higher rates of flow. There was little, if any, quantitative difference among the three anesthetic agents used (table 1). No change in refractory period was observed until the velocity of flow was in the neighborhood of 5 ml. per minute. The threshold for cyclopropane was 10 ml. per minute.

Contractility also progressively diminished with each increment of rate of flow. It was noted that for a given rate of flow, contractility was more markedly diminished than the corresponding refractory period. This was particularly true at the higher rates of flow so that,

TABLE 1

Dose	Ether		Chloroform		Cyclopropane	
	A*	B†	A	B	A	B
Rate of flow in ml.						
5	1	6	3	3	0	5
10	15	20	9	12	8	10
20	20	24	20	30	16	28
40	28	60	23	60	27	44
60			25	80		

* Percentage decrease in refractory period.

† Percentage decrease in contractility.

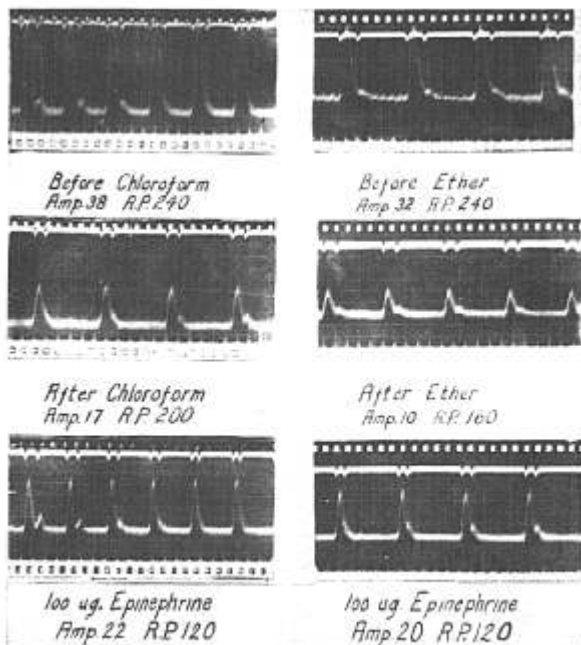


FIG. 1.

with the exception of cyclopropane, the contractility was so markedly diminished when the rate of flow was greater than 40 ml. per minute that the refractory period could not be determined.

The addition of epinephrine to a muscle previously exposed to ether or chloroform almost invariably produced a positive inotropic effect while simultaneously further shortening the refractory period. This was demonstrated in an earlier series of experiments in which 100 μ g. of epinephrine was added to the Locke's solution after the auricle or papillary muscle had been exposed to various concentrations of ether or chloroform. The technic of introducing the anesthetics had not been refined at that time, so that the rates of flow were only crudely estimated. These varied from 8 to 140 ml. per minute. Figure 1 is a kymographic recording of two experiments illustrating this relationship between epinephrine and ether or chloroform. The effects were the same whether ether or chloroform was used.

Resting Excitability.—Strength-duration curves were obtained in all experiments. It was found, however, that the data could be better presented by plotting the average percentage deviation of resting excitability from control levels at the various rates of flow and duration of stimuli (fig. 2). The durations of stimuli selected were those found by previous experiments to be suitable for the determination of strength-duration curves (8).

It can be seen from these curves that ether, at equivalent rates of flow, has a much more pronounced depressant effect on excitability than

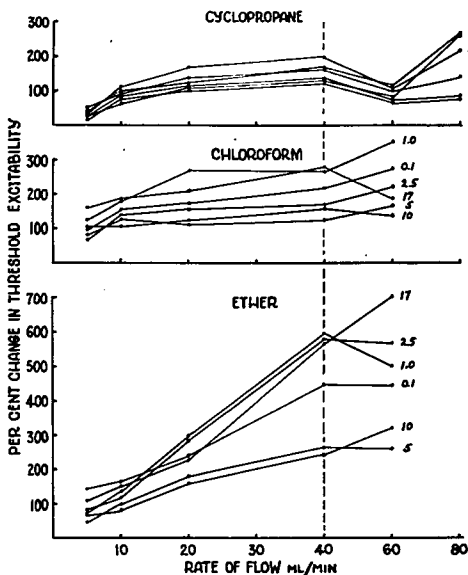


FIG. 2.

chloroform or cyclopropane. This is particularly true for the stimuli of longer duration. For ether, a plateau was reached at 40 ml. per minute with little or no change in excitability when rates of flow were beyond this level. The over-all depressant effect of cyclopropane and chloroform was more gradual. Beyond rates of 40 ml. per minute cyclopropane showed an increase in excitability up to 60 ml. per minute, after which a depressant effect was once again demonstrated. Curves for rates of flow greater than 60 ml. per minute with ether and

cyclopropane were not obtained because, at this rate, the ability of the muscles to contract had disappeared.

The effect of 100 μ g. of epinephrine on excitability after ether or chloroform was also determined. Epinephrine at this dosage level tended to restore to normal the previously depressant effect on auricular excitability of ether or chloroform.

Spontaneous Rhythm.—In general, all three anesthetics tended to stop spontaneous rhythm when present, although there was no correlation between this effect and dosage level. Epinephrine tended to restore spontaneous rhythm. Cyclopropane produced fibrillation of the isolated auricle on two occasions, but only in the highest concentration.

COMMENT

The results of this investigation are at variance with those of Garb and Chenoweth (2) who found that chloroform was more depressant than ether in equivalent doses. The addition to the bath of a certain amount of anesthetic agent in the liquid state and then determining the effect produced gave erratic and evanescent effects. By allowing the anesthetic agent to bubble through the bath at a regulated rate,

TABLE 2

Anesthetic Agent	Solubility in Water*	Oil-Water Coefficient†	Comment
Ether	3900	3.2	Much lower lipid solubility
Chloroform	690	100	High lipid and low water solubility
Cyclopropane	30	34.4	Solubility in blood almost twice that in water at same temperature

* Solubility in water expressed as cubic centimeters per 100 cc. of water at 20 C. and one atmosphere partial pressure.

† Oil-water coefficient at 37 C.

variable responses at equivalent rates of flow were circumvented. Evanescent effects which might occur because of vaporization of the anesthetic were avoided. This method more closely resembles the administration of an anesthetic gas to the intact animal.

Ether, at equivalent rates of flow, depressed excitability more than chloroform or cyclopropane. This is not surprising in view of the physical properties of these agents. At corresponding temperature levels, the solubility of ether in water is much higher than the other two agents (table 2). Thus, the concentration of ether available to act on the isolated auricle at the same rate of flow and temperature is higher than the concentration of either cyclopropane or chloroform. This explains the greater effect of ether under the physical set-up of this investigation. It must be pointed out, however, that in the case of cyclopropane, pure gas was bubbled through the bath in contrast to

ether or chloroform which were vaporized and contained unknown amounts of inert gases.

It is now generally understood that agents which enhance the occurrence of tachycardia and fibrillation in heart muscle do so by depressing excitability and shortening the refractory period (13, 14). All three agents studied had precisely this effect. It would be expected, therefore, that clinically, tachycardia and fibrillation would be common as side reactions with the administration of these gases. Although death from ventricular tachycardia and fibrillation has been reported with chloroform and cyclopropane, no such incidents have been reported with ether. Our experiments indicate that the action of ether on heart muscle was exactly the same as that of chloroform and of cyclopropane. Furthermore, no especial sensitizing effect of chloroform as compared to ether could be elicited when epinephrine was added to the bath (fig. 1). This suggests that a more rational explanation for the absence of ventricular fibrillation during ether anesthesia must be sought. This may lie in a difference in action on the central nervous system, particularly on the vagus center or in a peculiar physical property of ether as compared to chloroform which prevents fixation in cardiac muscle. For example, chloroform has a very high lipoid solubility and cyclopropane is more soluble in blood as compared to ether (table 2). It is these properties which, in the intact animal, may cause the selective difference in the incidence of fibrillation during and following anesthesia with these common agents.

SUMMARY AND CONCLUSIONS

The effects of ether, cyclopropane and chloroform on resting excitability, refractory period, contractility and spontaneous rhythmicity of the isolated auricle of the cat have been studied. This was done with the aid of a dual pulse square wave electronic stimulator. Strength-duration curves were obtained from which percentage deviations of excitability from control levels were determined. The refractory period was obtained by driving with one stimulus and testing with a second stimulus to find the minimal interval in which a premature contraction could be produced.

All three anesthetic agents uniformly produced shortening of the refractory period with little, if any, quantitative difference among them. Contractility was also diminished. Ether at equivalent rates of flow had a much more pronounced depressant effect on resting excitability than chloroform or cyclopropane. The addition of epinephrine to a muscle previously exposed to ether or chloroform almost invariably produced a positive inotropic effect while simultaneously shortening the refractory period further. In general, all three anesthetics tended to stop spontaneous rhythm when present. There was a tendency to reverse this effect when epinephrine was added.

The results were interpreted with respect to the physical properties of the agents used. An attempt was made to correlate the effects of these agents on the isolated auricle with the clinical occurrence of cardiac arrhythmias.

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