Comparative Effects of Anesthetic Agents on Incidence of Ventricular Fibrillation During Hypothermia. (22023)

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Cardiac ventricular fibrillation and asystole are two factors which have produced a limit for experimental and clinical hypothermic procedures. Fibrillation has generally occurred at higher temperatures than asystole. Elimination of factors which tend to cause fibrillation might therefore permit the use of lower temperatures for such procedures. Choice of anesthetic agent is conceivably involved in the production of fibrillation. Available data are on the whole inconclusive as to the role that various anesthetic agents play, although Covino *et al.*(1) state that ventricular fibrillation occurs less frequently in dogs receiving thiopental or ether than in those receiving pentobarbital.

It therefore seemed desirable to study the effects of commonly used agents, ether, cyclopropane and pentobarbital with regard to their effect on production of ventricular fibrillation or asystole during hypothermic anesthesia.

Methods. Healthy mongrel dogs of both sexes ranging in age from 6 to 12 months and weighing between 3.6 and 9.1 kg were used. No premedication was given. Eleven dogs were anesthetized with cyclopropane and 10 anesthetized with ether. They were intubated as soon as depth of anesthesia was sufficient to permit it. They were connected to a closed to-and-fro CO_2 absorption system with controlled hyperventilation at 50 ± 5 respirations per minute. The hair was removed from body, neck and proximal parts of legs. A rectal thermometer was inserted at least 10 cm. Needle electrodes for Lead II of electrocardiograph were attached. The animals were immersed on their sides in ice bath at 1 to 3°C with only head and part of neck elevated above bath. The level of anesthesia was maintained so lateral canthus reflex was lost and medial canthus reflex present. This provided anesthesia which would be adequate for surgical procedures. When rectal temperature reached 22°C artificial respiration with 100% oxygen was continued with a controlled phase respirator regulated at 50 ± 5 respirations per minute. A third series of dogs was given 30 mg per kilo of pentobarbital intravenously and intubated as soon as possible. Hair was removed, rectal thermometer inserted, needle electrodes attached and animals were at once connected to a control phase respirator using 100% oxygen at 50 ± 5 respirations per minute and immersed in ice bath. Time required for cooling was recorded. Electrocardiographic tracings, rectal temperatures and pulse were noted continuously and records made at 5-minute intervals or less. No surgical procedures were carried out.

Results. The pulse diminished approximately 12 beats per minute for each degree C of cooling of dogs down to approximately 16°. At lower temperatures, the rate of slowing could not be correlated with rate of cooling. Variable periods of asystole occurred when the pulse was 10 per minute or less and only by electrocardiographic observations could the heart be determined to still be active.

As indicated in Table I, 8 of 11 dogs receiving cyclopropane went into ventricular fibrillation (average temp. 19.6°), 2 of 10 dogs on ether fibrillated (average temp. 18.9°), while none of the dogs receiving pentobarbital showed ventricular fibrillation. As might have been expected, animals that fibril-

TABLE I. Terminal Cardiac Event in Dogs Receiving Different Anesthetic Agents.

	Cyclopropane	Ether	Pentobarbital sodium
No. of dogs	11	10	10
Asystolic deaths	3	8	10
Mean rectal temp., °C	9.3	12.0	11.3
Mean cooling time, min.	107	100	110
Ventricular fibrillation	8*	2†	0‡
Mean rectal temp., °C	19.6	18.2	
Mean cooling time, min.	63	54	

*-† $p < .001$ Significant
*-‡ $p < .05$ "
†-‡ $p > .05$ Not significant

lated died at higher temperatures than those which died of asystole. There were considerable differences in muscular activity of the 3 groups of animals. Animals receiving cyclopropane tended to be relatively active even though eye signs indicated that a stage of surgical anesthesia had been reached. Gross movements and even respiratory efforts appeared when the cyclopropane was gone at temperature below 28°. The animals that received ether showed some muscular action at temperatures below 28° but these movements were not marked. Animals receiving pentobarbital were quiet and showed no shivering or other muscular action after being cooled.

The 3 animals in the cyclopropane group dying of asystole expired at a mean temperature of 9.3°, the 8 asystolic ether deaths occurred at an average temperature of 12° while the asystolic pentobarbital deaths occurred at an average of 11.3°.

Discussion. It has been pointed out that an anesthetic agent or relaxing agent is necessary during the early phase of cooling to prevent shivering or other protective movements by the dog which inhibit body cooling. Haterius and Maison(2) suggested that the ideal anesthetic agent should control muscle activity and shivering until cold narcosis itself was sufficient for such control. They stated that cyclopropane was valuable an an anesthetic agent but were indefinite as to the number of animals used with cyclopropane or the average temperature to which they could be cooled successfully. One dog survived cooling to 11.7°. They also reported that dogs cooled during ether anesthesia could withstand cold better than those receiving sodium pentobarbital(3). Artificial respiration was given "as needed." In studies on effect of age on cooling, Maguire and Merendino(4) observed that adult dogs receiving 60 mg/kg of sodium pentobarbital died at average temperature of 20.4°. Eleven of these 15 died of ventricular fibrillation. Using young dogs, the average temperature of death was 12.6°, all from asystole. It appears that both youth and lack of occurrence of ventricular fibrillation influenced temperatures of death. Covino *et al.* (1) observed that 16 out of 19 dogs anesthetized with pentobarbital died of ventricular fibrillation. Those results would seem perhaps different from ours. No information, however, was given as to age of their animals. Judging from the weights (6.7 to 17.5 kg) it might be assumed that their dogs were older animals. Covino's group used push-pull artificial respiration with room air only below 26 to 24°C while our animals received hyperventilation with oxygen continuously. Our experiments, those of Maguire and Merendino(4), and of Covino *et al.*(1) all indicate that the temperature of animals dying of ventricular fibrillation is higher than that of those whose hearts have an asystolic termination of action.

Animals receiving pentobarbital undoubtedly have a considerable amount of the drug left in their bodies at the time of hypothermic deaths. Animals receiving ether probably have most of it eliminated when death occurs, but due to high solubility of ether in water and the progressively decreased circulation in hypothermic animals, some of the ether is undoubtedly left in the system. Cyclopropane is much more volatile than ether and is less soluble in water. It therefore may be assumed to be almost entirely gone from tissues by the time that cold narcosis has appeared. Anesthetization with cyclopropane followed by its practical elimination might be expected to diminish the tendency to ventricular arrhythmias, if the concept that deeper cyclopropane anesthesia increases the incidence of such irregularities(5) is accepted. Efficient concomitant elimination of carbon dioxide by assisted respiration is also said to prevent or abolish such arrhythmias(5). The use of cyclopropane, however, did not afford protection against ventricular fibrillation in the hypothermic dog, although those animals receiving cyclopropane which did not fibrillate reached the lowest temperatures of all those observed. The results obtained indicate that sodium pentobarbital may have had a protecting effect on the cardiac irritability while cyclopropane showed no such effect. The effects of ether were somewhat intermediate between those of the other two agents.

Summary. The terminal cardiac events of 31 hypothermic dogs, 6 to 12 months old, were observed. Eleven animals received cy-

clopropane and 10 each received ether and pentobarbital sodium as the pre-hypothermic anesthetic agents. All animals were hyperventilated with oxygen after intubation until the experiments were terminated. Rectal temperatures were continuously observed and electrocardiograms were taken at frequent intervals as the dogs were cooled until cardiac activity ceased. No surgical procedures were carried out. Eight of 11 animals receiving cyclopropane, 2 of 10 receiving ether, and none of 10 receiving pentobarbital died in ventricular fibrillation. The mean rectal temperature of animals on cyclopropane or ether dying of ventricular fibrillation was 19°C. The mean rectal temperatures of all the deaths after the use of cyclopropane was 16.7°, after ether, 13.4°, and after pentobarbital sodium, 11.3°.

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Effect of Malonate and Antimycin A on Renal Tubular Transport of p-Aminohippurate.*† (22024)

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The dependence of renal tubular transport systems on certain energy producing reactions might be established by the use of specific metabolic inhibitors. There exists, for example, a correlation between the capacity of certain chemical compounds to inhibit the oxidation of succinic acid *in vitro* and to decrease the renal tubular excretion of p-aminohippurate (PAH) and phenolsulfonphthalein (PSP) *in vivo*(1). In the present report additional data are presented to support the hypothesis of Shideman and Rene(1) that energy derived from succinate oxidation (and Krebs cycle oxidations) is involved in the renal tubular mechanism which effects the excretion of PAH.

Materials and methods. Female, albino rats (150-200 g) of the Holtzman strain were anesthetized by the intraperitoneal administration of 35 mg/kg of pentobarbital and the right (control) kidney was removed. Cortical slices from this kidney were prepared and approximately 100 mg of these slices were placed in 20 ml beakers containing a volume of 2.7 ml of the medium employed by Cross and Taggart(2). The concentration of PAH, however, was half that used by these authors. The

TABLE I. Effect of Malonate Administration on Ability of Renal Cortical Slices of Rat to Accumulate PAH. Each animal received 1.2 ml of M sodium malonate subcutaneously 2 hr before and 0.6 ml of the same solution one hr before removal of the left kidney (6 animals).

	S/M concentration		
Rat No.	Before malonate (right kidney)	After malonate (left kidney)	% inhibition
1	8.42	2.43	80.8
2	7.81	3.59	62.0
3	6.07	2.27	75.0
4	8.39	4.07	58.5
5	10.10	8.19	21.0
6	14.90	6.27	62.1
	Mean ± S.E.		59.9 ± 8.5
			P <.01

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