VENTRICULAR FIBRILLATION IN HYPOTHERMIC DOGS AS INFLUENCED BY THIOPENTAL, PENTOBARBITAL AND SUCCINYLCHOLINE

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A LIMITING factor in the clinical use of hypothermia has been the occurrence of ventricular fibrillation at reduced body temperature. Experiments in different laboratories have suggested that many factors may influence the occurrence of such ventricular fibrillation. These factors include the blood calcium-potassium ratio (1), carbon dioxide concentration in the blood (2), the rapidity of change of CO_2 concentration in the blood (3), blood pH (2, 4), the presence of intraventricular catheters (5), and the anesthetic drug used (6). In this paper we shall re-emphasize that the anesthetic agent influences the incidence of ventricular fibrillation during hypothermia in the normal dog. Thiopental, with and without the addition of succinylcholine, will be compared to pentobarbital from this standpoint.

METHODS

Adult healthy mongrel dogs with an average weight of 14.8 kg. were anesthetized with intravenous sodium thiopental. The left chest and femoral areas were clipped, the animal's trachea was intubated, and the endotracheal tube was connected to an automatic respirator. Room air was respired. The rate and volume of the respirator were adjusted to produce moderate hyperventilation, so that random pH determinations of arterial blood were found to be always in the alkaline range (7.45 to 7.8). A cannula inserted through the femoral artery into the aorta was connected to a Statham strain gauge. A continuous, standard limb lead electrocardiogram and blood pressure tracing were recorded by a Sanborn Polyviso throughout the experiment. A thermocouple was inserted 10 cm. into the rectum for continuous temperature recordings by means of a Brown potentiometer. The animal was immersed in an ice water bath at 4 C. Shivering, if it occurred, was controlled throughout the experiment by additional injections into the arterial cannula of sodium thiopental or succinylcholine. After the animal's temperature reached 27 C., shivering seldom occurred. The animals were cooled until ventricular fibrillation occurred or until the

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animal's rectal temperature reached 17 C. With the onset of ventricular fibrillation the respirator was removed and the ice water was drained from the bath. After thirty minutes, the animals were resuscitated by a method previously described (7). This consisted of left thoractomy, manual compression of the heart during continuous irrigation of saline solution at 45 C. through the thoracic cavity, and the application at each degree centigrade rise in rectal temperature of a single 160-volt, 0.1 second electric shock to the heart until defibrillation was accomplished.

Those animals which did not exhibit ventricular fibrillation upon cooling to 17 C. were rewarmed as the ice water bath was slowly warmed to a maximum of 45 C. The animal's temperature usually continued to decline another 1 to 2 degrees C., giving a minimum temperature in the majority of the non-fibrillating dogs in the range of 15 to 16 degrees C. This end point was selected since only 3 of a previous group of 42 dogs developed ventricular fibrillation below 15 C (7).

TABLE 1

SIGNS USED TO DETERMINE LEVEL OF THIOPENTAL ANESTHESIA

	Lid Reflex	Corneal Reflex	Pupil	Nictitating Membrane	Shivering	Average Amount Thiopental After Induction, mg./kg.
Light	Present	Present	75% constricted	Relaxed	Frequently present	23.7
Deep	Absent	Absent	100% constricted	Relaxed	Absent	46

The animals were rewarmed to 35 C. in the water bath and returned to their cages.

RESULTS

Group 1: Light Thiopental Anesthesia. In this group of 13 dogs the induction of anesthesia was accomplished by the administration of thiopental (30 mg. per kg.) in a 2.5 per cent solution. This dose was sufficient to permit the femoral cutdown, the intubation of the trachea and the initiation of cooling. Light anesthesia was maintained by the injection of thiopental in amounts necessary to abolish shivering. Lid and corneal reflexes were present, and the pupils were moderately constricted throughout the experiment in the majority of the animals (table 1). The size of each additional dose varied, but was usually in the range of 25 to 50 mg. of thiopental. The total dose of added thiopental after induction ranged from 0 to 61 mg. per kg., with an average of 23.7 mg. This dosage range is wide, but Dundee (8) observed that the duration of narcosis from thiopental in dogs receiving the same dose per kilogram of body weight was not predictable.

Seven of the 13 dogs in this group (54 per cent) developed ventric-

ular fibrillation. The temperature at which fibrillation occurred varied from 20.5 C to 15.25 C., with a mean low temperature of 16.7 C. The mean is calculated utilizing the temperatures of onset of fibrillation in the fibrillating animals and the lowest temperatures reached by the nonfibrillating animals. None of the dogs developed cardiac arrest.

Group 2: Deep Thiopental Anesthesia. There were 6 dogs in this group. Thiopental (30 mg. per kg.) was given for induction of anesthesia. Deeper anesthesia was obtained for the cooling phase by additional injections of the drug. The amount of additional thiopental required after induction in this group varied from 30 to 68 mg. per kg., averaging 46 mg. Loss of the corneal and lid reflexes, relaxation of

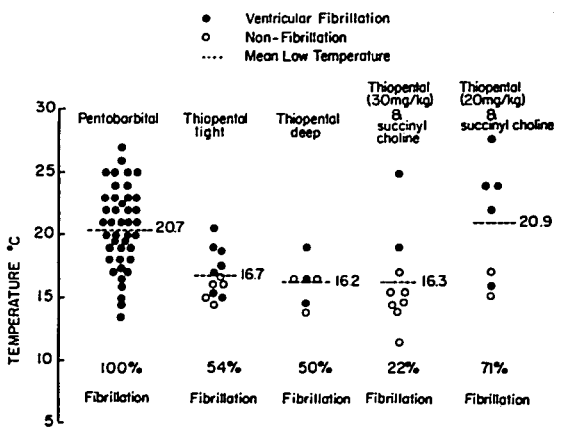

FIG. 1. Scattergram comparing data from all groups. Note the narrow range of onset of ventricular fibrillation in the thiopental groups.

the nictitating membrane, pin-point pupils, and absence of shivering were evidence of the deep level of anesthesia (table 1).

Three of the 6 animals in this group (50 per cent) developed ventricular fibrillation. The mean low temperature in the group was 16.2 C.

Group 3: Light Thiopental Induction with Succinylcholine to Control Shivering. Nine dogs received thiopental (30 mg. per kg.) as in Group 1, but shivering was controlled by the administration of succinylcholine in 1 mg. increments. This dose was usually sufficient to prevent shivering for ten to fifteen minutes.

Two of the 9 dogs (22 per cent) developed ventricular fibrillation. The temperature of onset of fibrillation was 25 C. and 19 C., respectively. The mean low temperature for the entire group was 16.3 C.

Group 4: Very Light Thiopental Induction with Succinylcholine to Control Shivering. Seven animals were given an induction dose of thiopental (20 mg. per kg.). This provided anesthesia for the time required to prepare the animals for the experiment. The dogs were awake when cooling began. Succinylcholine in doses of 1 mg. was then given to prevent shivering as cooling progressed.

Five of these 7 dogs (71 per cent) developed ventricular fibrillation. The mean low temperature for the group was 20.9 C.

Group 5: Pentobarbital Anesthesia. Forty-two dogs were anesthetized with intravenous pentobarbital (25 mg. per kg.). This dose was usually sufficient to control shivering throughout the experiment. No other drugs were added.

All the dogs in this group developed ventricular fibrillation, the onset ranging from 27 C. to 13.5 C., with an average of 20.7.

Figure 1 is a scattergram comparing data from all the groups. It can be seen that there was a reduction in the temperature of onset of ventricular fibrillation when thiopental was used as the sole anesthetic agent. Deeper thiopental anesthesia did not lower the average temperature of onset of fibrillation. Combining the light and deep thiopental groups, 10 of 19 dogs developed ventricular fibrillation (52 per cent). The mean low temperature of these combined groups was 16.5 C. The reduction in the incidence of ventricular fibrillation in the combined groups when compared to the pentobarbital group was statistically significant at the 1 per cent level ($P < 0.01$). When 30 mg. per kg. of thiopental was used to produce anesthesia for induction and initiation of cooling, and succinylcholine was given to control shivering, the average temperature of ventricular fibrillation was the same as in the thiopental groups. The incidence of ventricular fibrillation was lowest in this group, as only 2 of 9 dogs developed ventricular fibrillation. When thiopental anesthesia was used for induction only, and the animal was essentially unanesthetized during the experiment, with shivering controlled by succinylcholine, the average temperature of fibrillation was higher than in the other thiopental groups and about the same as in the pentobarbital group. The group without anesthesia also had the highest incidence (71 per cent) of ventricular fibrillation.

Discussion

The studies reported herein confirm the work of Covino *et al.* (6) who found that, in dogs undergoing immersion hypothermia, 84 per cent developed ventricular fibrillation during pentobarbital anesthesia whereas only 51 per cent showed this response during thiopental anesthesia. In addition, we have shown that the average temperature at which ventricular fibrillation occurred was lowered by the use of thiopental anesthesia when compared to pentobarbital anesthesia and to unanesthetized dogs. Increasing the dosage of thiopental did not

further reduce the incidence of or the temperature at which ventricular fibrillation occurred.

The mechanism by which thiopental reduces the incidence of ventricular fibrillation is not known. It will probably remain obscure until more is known of the cause of ventricular fibrillation itself. Nevertheless, some possibilities can be suggested from the known factors which influence the onset of ventricular fibrillation during hypothermia and the influence of anesthetic drugs on these factors or on the heart.

The effects of the derivatives of barbituric acid on the cardiovascular system have been studied by Gruber *et al.* (9). These investigators showed that the barbiturates, when injected into the perfusate of the excised normothermic rabbit heart, reduced the coronary flow. The addition of the oxygen analogues (pentobarbital) to the perfusate, caused a marked *increase* in coronary arterial blood flow. It was also shown that both drugs have a direct effect on the peripheral blood vessels, thiopental causing a more profound vasoconstriction than did pentobarbital. It is unlikely that either of these factors plays a role in the prevention of ventricular fibrillation. Sufficient evidence has accummulated that coronary blood flow is adequate with the anesthetic agents in question (10, 11). Measurements of blood pressure just prior to ventricular fibrillation in our animals showed no difference in the groups.

It is also possible that thiopental has a more selective depressant action on the Purkinje fibers of the heart muscle, thus altering the "vulnerable period" in which the dog ventricle is susceptible to fibrillation by means of an electrical stimulus. Hoffman *et al.* (17) have shown that epinephrine and norepinephrine may affect ventricular vulnerability to fibrillation. These drugs enhance ventricular vulnerability to fibrillation. It is unlikely that thiopental or pentobarbital influences cell membrane permeability affecting the ionic transfer involved in the polarization process of the cardiac cycle.

The peripheral autonomic effects of the barbiturates might serve to explain the apparent protection afforded by thiopental. Goodman and Gilman (12) state that, in animals, a number of the barbiturates in anesthetic doses depress the cardiac effects of electrical excitation of the vagus nerve, in some cases to the extent of complete blockade. They point out further that this parasympatholytic action does not occur after the administration of thiobarbiturates. Indeed, the cardiac responsiveness to vagal stimulation may even be enhanced. Gruber (13) has also shown that the barbiturates may directly depress postganglionic cardiac vagal fibers as well as the ganglia. This selective action of the thiobarbiturates on the autonomic nervous system might be the protective mechanism involved in our experiments. The work of Radigan (14) and of Riberi and Shumacker (15) lends further credence to this theory. Radigan showed that procaine block of the

S–A node reduced the incidence of ventricular fibrillation in dogs undergoing hypothermia and cardiac manipulation from 18/20 in a control series to 0/20 in dogs with the procaine block. Riberi and Shumacker have shown that upper dorsal and stellate ganglionectomy protected all dogs from ventricular fibrillation during a standardized cardiac manipulation which routinely produced ventricular fibrillation in control dogs. Arfonad,® a ganglionic blocking agent, was similarly effective. They also found that bilateral section of the cervical vago-sympathetic trunks, which interrupted vagal but not sympathetic fibers to the heart, resulted in almost as high a percentage of ventricular fibrillation as occurred in untreated animals. Montgomery *et al.* (16) have reported that stimulation of the right vagus lowered the incidence of ventricular fibrillation in hypothermic dogs.

Blood oxygen and carbon dioxide tensions in our dogs are to be reported elsewhere (18). The anesthetic agents used had no apparent effect on the blood or pulmonary tensions of these constituents.

SUMMARY

1. Experiments on dogs in immersion hypothermia were carried out with pentobarbital, thiopental and thiopental with succinylcholine as the anesthetic agents.

2. With light thiopental anesthesia, the mean low temperature at which ventricular fibrillation occurred was 16.7 C., whereas with deep thiopental anesthesia this average was 16.2 C. Combining both groups (19 dogs), 52 per cent showed ventricular fibrillation in the temperature ranges which we employed. The mean low temperature of the combined thiopental groups was 16.5 C.

3. Increasing the dosage of thiopental did not further lower the incidence of ventricular fibrillation nor the temperature at which it occurred.

4. With thiopental induction (30 mg. per kg.) and shivering controlled by succinylcholine, 2 of 9 dogs (22 per cent) developed ventricular fibrillation. The mean low temperature of these 9 dogs was 16.3 C. Using thiopental induction (20 mg. per kg.) and with shivering controlled by succinylcholine, 5 of 7 dogs (71 per cent) developed ventricular fibrillation. The mean low temperature of the group was 20.9 C.

5. The above four groups were compared to a group of 42 dogs receiving pentobarbital anesthesia in which 100 per cent developed ventricular fibrillation at an average temperature of 20.7 C.

CONCLUSIONS

Thiopental anesthesia in immersion hypothermia experiments on dogs significantly lowered the incidence of ventricular fibrillation and the mean temperature at which ventricular fibrillation occurred when compared to pentobarbital anesthesia.

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