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ESOPHAGEAL COOLING AS A TECHNIC OF SELECTIVE BRAIN HYPOTHERMIA

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FOREWORD

This report was prepared by the following personnel of the Experimental Surgery Department:
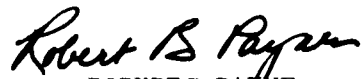
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ABSTRACT

An experiment using 17 mongrel dogs was performed comparing the production of selective brain hypothermia by esophageal cooling alone and with external neck cooling. A second experiment on 4 of these dogs, using the latter technic, compared the effects of increased carbon dioxide inhalation and bilateral vertebral artery ligation on the production of selective hypothermia. Although selective brain hypothermia was achieved in all animals to varying degrees, it was not of a sufficient magnitude to be recommended for clinical use. The clinical and pathologic changes are described.

This technical documentary report has been reviewed and is approved.

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ESOPHAGEAL COOLING AS A TECHNIC OF SELECTIVE BRAIN HYPOTHERMIA

1. INTRODUCTION

In the past few years, much attention has been focused on the production of selective brain hypothermia. This interest has been attributed to the benefits of reduced blood flow to the brain, reduced brain volume, and increased tolerance to hypoxia of the brain, which can be achieved by brain hypothermia without the hazard of cardiac fibrillation which occurs in total-body hypothermia. The principal application of selective brain hypothermia has been in neurosurgical procedures, especially in cerebrovascular surgery. It has also been used successfully in cardiovascular surgery, brain trauma, cerebrovascular occlusion, cerebral edema, and encephalitis. Since the work of Parkins et al. (11), Lougheed and Kahn (8), and Kimoto et al. (6) with the carotid artery by-pass technic, most of the investigations and clinical applications have utilized a shunt system, shunting blood from a proximal carotid artery or arteries, through a cooling system, and back into the distal carotids to the brain. Although this method has received much attention, it has been noted by Bucknam and Galindo (3) that there is excessive temperature drift below 25° C. It also has been poorly accepted because of the hazards of carotid artery surgery. Other technics which have been tried include: (1) cooling of the CSF (12), (2) coils in the subdural and subarachnoid spaces (10), and (3) external scalp cooling (7). There is little doubt that these technics present hazards, complexities, and inefficiencies for practical clinical application. Since none of these methods have uniformly been accepted, it seems apparent that if an efficient, simple, and safe technic of achieving selective brain hypothermia were available, it would have much more application and utilization than the methods that are now used.

FIGURE 1

Cooling coil and collar with dye in circulating portion of collar.

The following investigation was undertaken to determine the efficiency, simplicity, and the margin of safety of esophageal cooling as a technic of selective brain cooling. Benjamin et al. (2) used a balloon in the esophagus of dogs (circulating cold water through the balloon) and noted that the temperature of the blood in the carotid arteries dropped more rapidly than the core temperature. This was attributed to the proximity of the carotids to the upper half of the esophagus and the consequent selective cooling of the blood in the carotids. It follows that the brain should be selectively cooled by placing a cooling unit in the upper half of the esophagus.

We designed and constructed a cooling coil and nylon core, wrapped with Silastic tubing, which circulates a cold solution through it and can easily be placed in the upper half of the esophagus (fig. 1). It was noted in pilot studies that when external cooling of the neck was combined with the esophageal cooling, a

TABLE I

Experimental groups

	Dog No.	Esophagus coil	Neck collar	Gas mixtures inspired		Vertebral arteries	
				40% O_2 – 60% air	96% O_2 – 5% CO_2	Intact	Ligated
Group I	1 to 5	x		x		x	
Group II	6 to 17	x	x	x		x	
Group II$_a$	14 and 15	x	x		x	x	
Group II$_b$	16 and 17	x	x	x			x
Group II$_c$	16 and 17	x	x		x		x
Control	18	x	x	x		x	

greater degree of selective brain hypothermia occurred. We also constructed a plastic bag which circulates the same coolant through it and is applied to the ventral half of the neck.

2. METHODS

Seventeen mongrel dogs, ranging in weight from 10 to 23 kg., were divided into two groups. The first group, composed of 5 dogs, used only the esophageal coil. The second group of 12 dogs used the coil, plus the plastic bag for external neck cooling. In a control experiment on 1 dog, water was circulated through the coil and bag at body temperature.

Four dogs of the second group were cooled a second time. Two of these composed group II$_a$, which inspired 5% CO_2 and 95% O_2 during the second cooling. Group II$_b$ had their vertebral arteries ligated and transected through a ventral midline neck incision after their first cooling. Two days postoperative, an aortogram was performed to confirm the ligation. This group was then cooled for a second time under the same conditions as in group II. The 2 animals in group II$_b$ were subjected to the cooling procedure a third time, and a mixture of 5% CO_2 and 95% O_2 inspired air was used. This last procedure is listed as group II$_c$ (table I).

All dogs were anesthetized and maintained with thiopental sodium, intubated with a cuffed endotracheal tube, and given 0.4 mg. atropine. Under sterile conditions, a YSI-thermistor was inserted approximately 13 mm. in the frontal lobe of the brain through a ³⁄₈-inch bur hole in the skull. Blood pressure was measured from a femoral artery catheter connected to a transducer and recorded on a Sanborn amplifier and recorder. The esophageal-cooling coil was placed in the upper esophagus so that the upper end was adjacent to the epiglottis and the lower end below the sternal notch. YSI-thermistors were placed in the stomach and upper esophagus in all dogs, and in the rectum and abdominal cavity, alternately. The stomach thermistor was passed through a hole in the center of the coil into the stomach, and the esophageal thermistor was placed between the esophageal mucosa and the cooling surface of the coil. The dog was then paralyzed with succinylcholine given via intravenous drip, which was maintained during the entire cooling phase. Respiration was maintained with a Bird respirator in a closed system (combination of Mark IV and Mark VII) at the rate which the dog respired before the succinylcholine was given. An inspiratory pressure of 10 to 15 cm./H_2O and expiratory pressure of 0 to —5 cm./H_2O were used. After baseline temperatures, blood pressure, and ECG were taken,

TABLE II

Temperatures, weight, autopsy day, and duration of procedure in
groups I and II. The core-brain differentials are those obtained
at the end of each experiment

Group No.	Dog No.	Weight (lb.)	Day of autopsy	Initial brain temp.	Final brain temp.	Initial core temp.	Final core temp.	Final esophagus temp.	Core-brain differential	Time (hours)
I	1	28	0*	37.8	29.4	38.1	31.7	8.9	2.3	3
	2	23	14	35.8	26.1	35.9	28.3	8.1	2.2	2.5
	3	27	3*	38.3	28.3	37.8	29.4	3.1	1.1	3
	4	30	18	37.8	30.6	37.8	31.4	6.4	0.8	3
	5	39	13	39.2	32.0	38.9	33.9	7.8	1.9	3
Mean		29.4		37.7	29.2	37.6	30.9	6.9	1.7	
II	6	50	6	36.4	24.2	36.4	28.1	7.8	3.9	3
	7	30	14	38.1	26.4	37.8	30.6	13.3	4.2	3
	8	26	24	37.2	26.1	36.7	29.4	11.1	3.3	3
	9	49	19	37.8	29.4	37.2	30.6	8.3	1.2	3
	10	42	13	37.0	29.4	36.7	30.0	10.9	0.6	3
	11	35	14	35.0	25.9	35.3	27.8	9.2	1.9	3
	12	38	9	35.0	26.7	35.3	27.8	11.7	1.1	2.75
	13	40	35	35.6	26.1	35.3	28.1	8.6	2.0	3
	14	36	12	36.7	24.7	36.1	27.2	8.1	2.5	2.5
	15	27	21*	35.0	26.4	35.0	27.5	10.9	1.1	2.25
	16	50	60	34.4	26.4	35.0	27.5	6.7	1.1	3
	17	43	14	35.6	25.6	35.6	27.5	10.0	1.9	2
Mean		38.8		36.1	26.4	36.0	28.5	9.7	2.1	

*Death

a mixture of 50% ethylene glycol and 50% ethyl alcohol was circulated through the coil (and collar) for a period of 3 hours, or until the core temperature reached 28° C. During the cooling phase, temperatures, blood pressure, pulse, and respiration were recorded every 5 minutes for 30 minutes, and then every 15 minutes. The animals were then rewarmed by circulating warm water through the coil and were revived and sacrificed at varying periods up to 60 days. Physical and neurologic examinations were performed and recorded preoperatively, and the same examinations were performed on the first, second, fourth, sixth, eighth, tenth, and fourteenth days postoperatively. They received no medication postoperatively unless a disease process was clinically evident. An autopsy was done on each animal, and sections that were taken from the

esophagus, liver, kidney, spleen, lung, heart, and brain were examined microscopically. At the time of autopsy, the common carotid and vertebral arteries were dissected from origin to termination, and a 3 to 5 mm. section was excised from the middle. These sections were longitudinally incised and the internal circumference was measured and recorded.

3. RESULTS

Temperatures

The temperatures for groups I and II are shown in table II. The initial brain temperatures in the two groups were significantly different (P < .025) as was the initial body core temperature (P < .01). Similarly, the
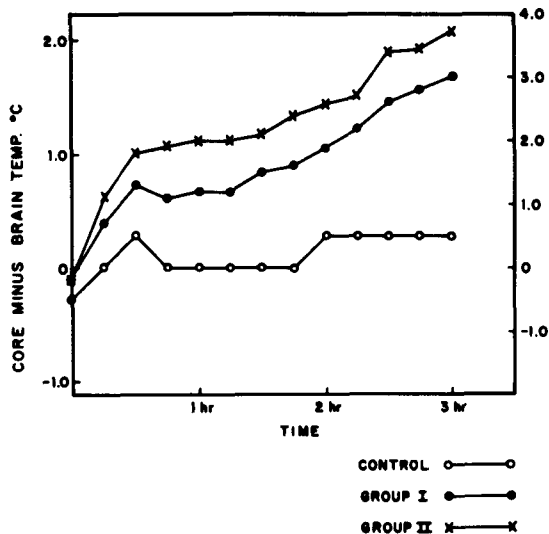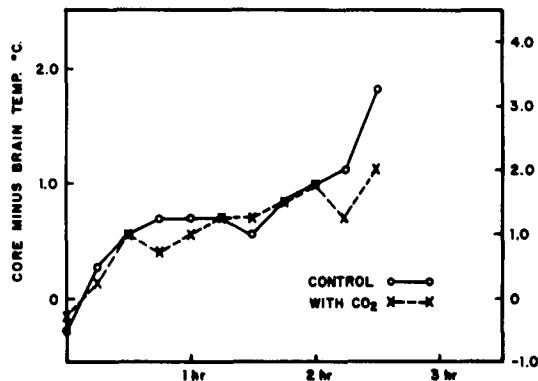
CONTROL o———o

GROUP I ●———●

GROUP II X———X

FIGURE 2

Group I vs. group II.

FIGURE 3

Dogs in group II_a (Nos. 14 and 15) that received 5% CO_2 inspired air.

FIGURE 4

· *Dogs 16 and 17. Control values from first procedure in group II. Vertebral arteries ligated as in group II_b and with 5% CO_2 and vertebral ligated as in group II_c.*

final brain temperature and body core temperature were significantly different for the two groups (P < .01). The difference between final brain and core temperature, however, was not significant. The difference for group I was 1.7° C., and for group II, 2.1° C. The control dog showed a difference between brain and core of 0.3° C. after 3 hours (fig. 2). Only
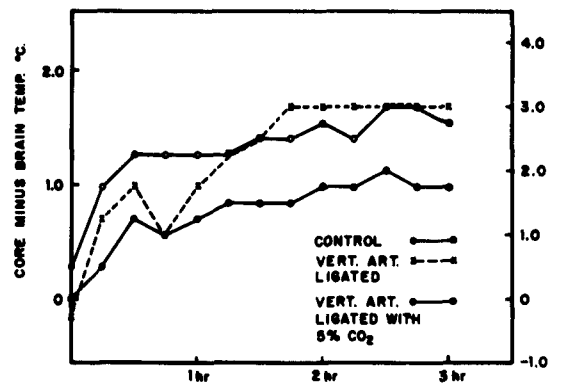
5 of the dogs achieved a body temperature of 28° C. in less than 3 hours. Three dogs in group II achieved a mean difference between the final brain and core temperature of 3.8° C., but the remainder of the group had only 1.5° C. This marked variation in response was not related to weight, esophageal temperature, or the ratio of carotid artery–vertebral artery circumference. The mean weight between the two groups was significantly different, but there was no correlation between weight and amount of brain-core temperature differential.

The dogs in group II_a, that had 5% CO_2 inspired air during the second procedure, showed no significant increase in the brain-core differential (fig. 3). The dogs in groups II_b and II_c had their vertebral arteries ligated and transected for the second procedure and, on the third procedure, they received 5% CO_2. They showed no significant change in the final brain-core differential or the final brain temperatures (fig. 4). The venous blood, pH, and the percentage of CO_2 in the expired air for the animals in groups II_a and II_c are shown in table III. The control values in table III (i.e., without CO_2) and figures 3 and 4 represent the changes which occurred when 40% oxygen and 60% room air were inspired during the initial procedure in group II.

TABLE III

Percentage CO_2 and pH in alveolar air for groups II_a and II_c

|	Mean pH		Mean percent CO_2	
	Initial	Final	Initial	Final
Without CO_2	7.37	7.30	3.42	4.40
With CO_2	7.27	6.98	6.28	9.01

The mean pH values of venous blood were equivalent to the mean hydrogen ion concentrations. Control values labeled "Without CO_2," were obtained from the experiment done with 40% O_2 and 60% air (group II).

Clinical evaluation

The ECG, pulse, and blood pressure changes during the procedures were comparable with those already well known at the appropriate core temperatures. The neurologic examinations showed transient signs of a nonlocalizing nature that were absent in all the animals 48 hours after each experiment. The postoperative course was notable only for persistent difficulty in reviving a good cough reflex. This observation was in addition to the difficulties encountered in the animals that died.

Pathology

Three dogs died and the remainder were sacrificed, as noted earlier. The first dog died 7 hours postoperatively. During the experiment, a malfunction of the respirator occurred, causing a period of anoxia during the warm-up phase. Autopsy revealed *Dirofilaria immitis* in the right ventricle. The presence of the worms and the anoxia were presumed to be sufficient to cause his death. The second dog that died had difficulty in regaining a good cough reflex after the procedure and died on the third postoperative day of bronchopneumonia. This was confirmed at autopsy and by microscopic examination. The third death occurred on the second day after the second procedure. The dog aspirated his gastric contents on the first postoperative day and developed a pneumonitis in the following 24 hours. At autopsy, he had a necrotizing bronchopneumonia and severe peptic esoph-
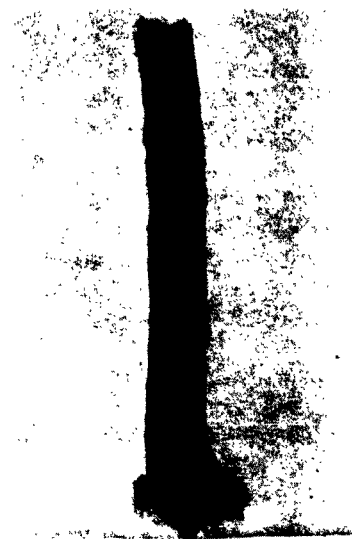
FIGURE 5

Esophagus of dog 16 in group II_c with ulcerations and submucosal hemorrhages in the area of the cooling coil (upper third of esophagus). This dog was subjected to the cooling procedure three times in 14 days.

agitis of the lower esophagus. Both the dogs in group II_c that were subjected to the cooling procedure 3 times were autopsied within 24 hours after the last procedure. At autopsy, there was ulceration and submucosal hemorrhages of the esophagus in the area of the cooling coil (fig. 5). Microscopically, there was mucosal ulceration with necrosis of the underlying tissue and surrounding inflammatory infiltration of polymorphonuclear cells, plasma cells, and mononuclear cells. This process extended into the muscularis, and many adjacent blood vessels were thrombosed. The control dog showed mild pulmonary edema and early, mild bronchopneumonia.

Gross and microscopic examinations of the remaining animals were within normal limits.

4. DISCUSSION

The statistical difference between groups I and II of the initial brain and core temperatures was most likely due to chance or to the level of anesthesia. This difference showed up in the

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final brain and core temperatures so that the final core, minus brain temperature, was not statistically different. Therefore, there was no statistical difference between using the coil alone or in combination with the neck collar.

The composite data from all of the experiments showed that we were able to achieve an average differential between brain and body of 1.9° C. with a range of 0.8 to 4.2° C. The practical significance of this difference is rightfully questioned, as it would seem that the difference between core and brain temperatures should be 5° or more for this to be a useful technic. However, Fisher et al. (4) have recently shown that the brain temperature is often as much as 10° C. higher than the core temperature when cooling by total body perfusion technic. We were able to cool the brain lower than the body in all animals, despite the wide variability of response. All the animals had some selective cooling 30 minutes after the cooling was started and, in most cases, this was progressive throughout the procedure.

The wide range of brain-core differential in group II is not readily explainable and was not statistically correlated to any of the parameters measured. The most likely cause lies in the variability of anatomy of the blood vessels to the brain in the dog (5). Whisnant et al. (13) did bilateral ligations of the common carotid, internal carotid, external carotid, vertebral, occipital, and ascending pharyngeal on 9 dogs. Three of these died within 20 hours, and the remaining 6 showed transient neurologic deficit, which was absent in 21 days. This work demonstrates the tremendous collateral system of blood circulation to the brain in the dog. In our experiments, the cooling of the carotids may have caused such spasm that the blood was shunted through the vertebrals or the anterior spinal systems and, thus, the blood reaching the brain would be relatively warm. We explored this possibility by ligating the vertebrals in groups II_b and II_c. The CO_2 was used in groups II_a and II_c to cause a maximum flow of blood to the brain and, thus, increase the flow in the carotids and cause more brain cooling. Bacharach et al. (1) showed that increased CO_2 inhalation in perfusion-cooling

made the brain temperature 3° to 4° C. lower than the core. The bilateral vertebral ligation and 5% CO_2 inspired air, alone or together, failed to significantly increase the differential in our dogs. Because of the work of Whisnant et al., the possibility of shunting blood through the collateral systems other than the vertebrals still exists and may explain the lack of response to CO_2 inhalation in our dogs. A more complete evaluation of the efficacy of this cooling technic is now being carried out in monkeys, whose blood supply to the brain is more comparable to that of the human.

The difficulty in regaining a good cough reflex in the recovery period no doubt played a role in the development of pneumonitis in the second and third dogs that died. This diminished reflex could, in part, be due to the local effects of the cold coil so near the epiglottis. However, the coil was easily inserted and withdrawn without any obvious sign of trauma to the local structures. It is also likely that the succinylcholine-induced respiratory paralysis played a role in the diminished respiratory function. This is illustrated in the control dog that was paralyzed as the others and had the coil in place with warm solution circulating through it. This dog had the same difficulty in regaining a good cough reflex in the recovery period as the others. Moreover, at autopsy, one week postoperatively, the dog showed mild pulmonary edema and early, mild bronchopneumonia.

The succinylcholine was used to eliminate shivering, an uncontrollable variable, and to allow us to regulate respiration. Mellinger (2) has demonstrated that succinylcholine and tubocurarine prolong the rate of core-temperature fall in surface-induced hypothermia in rats, guinea pigs, and rabbits. The effect of succinylcholine on cooling rate of the brain has not been explored to our knowledge, but according to Mellinger's report it should have slowed the rate of body cooling and, thus, enhanced the development of a larger brain-core differential.

The pathologic changes in the esophagus of the 2 dogs that were subjected to three

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procedures over a 14-day period were the only effects of the coil seen in this study. So far as we know, no similar effects of hypothermia in the esophagus have been noted. As these changes were the only ones seen in our experiments, we believe that they can be attributed to the trauma of repeated cooling.

In conclusion, we believe that these experiments have shown that esophageal cooling does cause selective brain hypothermia, but of a variable magnitude. The technic is simple and does offer a convenient way of rewarming the brain. The margin of safety is wide, as long as repeated procedures are not attempted in a short period of time. No difference occurred in the dogs when the coil was used alone or with the collar. Neither CO_2 inhalation, vertebral artery ligation, nor a combination of the two, enhanced selective brain cooling.

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