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CESSATION OF CIRCULATION IN GENERAL HYPOTHERMIA II. ANESTHETIC MANAGEMENT * †

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IN 1805, J. Currie (1) mentioned the use of "cold in extreme degree" as being a powerful and effective sedative. In 1862, Walther (2) in experiments on non-narcotized, immobilized rabbits, found that at 20 C., the animals underwent a cold narcosis by means of which he could operate. In 1902, Simpson (3) found that after inducing anesthesia with ether in the monkey, no further anesthetic was needed after the animal was cooled to 25 C. Simpson and Herring (4), in 1905, demonstrated in deeply anesthetized, cooled cats, in which shivering was not present, that the reflexes disappeared from above downward. The only reflex which remained at low temperatures until death was the knee jerk. This reflex was the only factor by which death could be determined. In 1937, Hamilton (5) showed that in the unanesthetized rat, mouse or kitten, when exposed to cold to induce hypothermia, there was a descending paralysis of the central nervous system. On rewarming there was a return of the reflexes in the opposite order to that in which they disappeared. This, he thought, indicated the narcotizing effect of hypothermia. Troedsson (6), in 1939, reported that Barcroft cooled himself until he virtually lost consciousness. Barcroft believed that the higher centers of the brain were the first to lose their function. Troedsson (6) found that wetting the skin hastened cooling, and the temperature could be lowered to 20 C. when this was practiced. He claimed that hypothermia might be used to give the heart a rest. He also predicted that this method could safely be used in human beings,

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and that operations could be performed with the patient under cold narcosis.

In 1940, Fay (7), and Smith and Fay (8) reported their observations on human beings maintained at temperatures between 75 and 90 F. All of these patients had far advanced metastatic malignant disease. The patients were lightly anesthetized with evipal® and anesthesia was maintained with paraldehyde by nasal tube. The hypothermia was carried on for days at a time, the patients being in a more or less somnolent state, awakening if spoken to, being able to take food, and so forth. Relief of pain was so striking that even narcotic addicts no longer required opiates. These patients shivered occasionally. They (7, 8) observed that auricular fibrillation was common during hypothermia in human beings.

Talbott (9), in 1941, reviewed the status of hypothermia, and coined the term at that time. Bigelow and co-workers (10), in 1950, showed that the transport and utilization of oxygen in dogs at low temperatures were essentially good. They pointed out that the control of shivering is important. Artificial respiration was necessary to maintain normal arterial oxygen saturations. Penrod (11), in 1951, found that the coronary arteriovenous oxygen differences remained adequate to temperatures of 20 C. despite low partial pressure oxygen values in coronary sinus blood. He concluded that cardiac muscle has a striking ability to extract oxygen from blood with very low oxygen tensions. Rosenhain and Penrod (12) found that the solubility of oxygen is 33 per cent greater at 25 than at 38 and they believed that the major portion of lowered oxygen requirements of the hypothermic dog may be met with dissolved oxygen if the animal is breathing pure oxygen. Hegnauer and his group published three papers (13, 14, 15) in 1950 and 1951 on the cardiovascular effects of immersion hypothermia on dogs. They found that use of intraventricular catheters produced a greater incidence of ventricular fibrillation at low temperatures.

Bigelow *et al.* (16, 17), in 1950, published reports of experiments in which they utilized hypothermia during production of circulatory arrest by occlusion of cardiac inflow for fifteen minutes. Thus, operations on the heart under direct vision could be performed. Fifteen per cent of their dogs survived the procedure without brain damage. Boerema (18) reported similar results. He emphasized rapid cooling and warming in a central manner—by cooling and warming the blood. Bigelow ventilated his animals with 5 per cent carbon dioxide because at low temperatures oxyhemoglobin dissociates poorly. He believed that the low hydrogen ion concentration of hypercapnia helped that dissociation. He found that the oxygen requirement at 20 C. was only about one fifth that at normal body temperature. Cookson *et al.* (19, 20, 21) modified Bigelow's procedure by ventilating the animals with 100 per cent oxygen. They also used various pharmacological agents, such as benodaine®, and were able to reduce the incidence of fibrillation so that they obtained 80 per cent survival of their animals after twelve minutes of occlusion of cardiac inflow.

McQuiston (22) was the first to use cold clinically in cardiac patients undergoing surgical procedures by placing them on a cooled mattress. He found that by this procedure the postoperative hyperthermia was avoided that had been present in many of the patients who died. His cooling was of the order of 2 C. and, of course, was not hypothermic anesthesia. Recently, Lewis and Taufic (23) have reported on the use of hypothermia in dogs for creation and closure of interatrial septal defects. They had 20 deaths in 65 operations. They were able to use an electric defibrillator successfully in two instances, and on five occasions they were able to defibrillate the hypothermic animals with massage lasting five to thirty-five minutes. They also reported successful closure of an interatrial septal defect in a 5 year old child using this method of hypothermia.

EXPERIMENTAL DATA

More than 100 dogs were used in our laboratory before we were satisfied that optimal conditions for hypothermia and avoidance of circulatory arrest were obtained (24). It was observed that below 21 C., ventricular fibrillation was a frequent problem. The use of 100 per cent oxygen through an endotracheal tube with rapid ventilation, between 40 and 60 excursions per minute, in 12 dogs at temperatures between 24 and 26 C., with fifteen minutes of occlusion of cardiac inflow, resulted in a mortality rate attributable to ventricular fibrillation of only 8 per cent. Using the same procedure in 10 dogs subjected to hypoventilation, in whom carbon dioxide was allowed to accumulate, the incidence of ventricular fibrillation was 50 per cent.

It was thought that a rapid drop in hydrogen ion concentration occurred in the tissue of the still beating heart during complete occlusion of cardiac inflow. Reperfusion of the heart after resumption of circulation produced a rapid shift from a very low to a higher hydrogen ion concentration in the tissue of the heart itself. By analogy of the work of Brown and collaborators (25, 26, 27) it was thought that this was the source of the frequent ventricular fibrillation that occurred on the release of the occlusion of cardiac inflow, which most investigators have found.

The dogs cooled more rapidly if they were not permitted to shiver. This was controlled by giving more than the usual dose of nembutal.® Hyperventilation by itself was found to produce cooling of about 10 C. if allowed to continue for several hours. The animals were cooled by immersion in ice water. They were closely clipped and wetted before immersion. The early experiments were done in a cold room at 4 C. Cooling by this method was too slow. A Brown potentiometer was used to measure temperature with the thermocouple inserted deeply into the rectum. When the animals were removed from the ice water, their temperatures continued to drop approximately another 5.

The electric defibrillator has been of no value to us in the cold dog. Because of this situation, experiments were carried out to devise some other method. A consistent drop in serum potassium concentration during cooling was found. It was thought that this ion might have something to do with ventricular fibrillation. Hooker (28) had shown many years ago that intra-arterial administration of potassium chloride was effective in arresting ventricular fibrillation. He used calcium chloride to return the heart to a regular sinus rhythm. A method was found in this laboratory of occluding the aorta at its origin by a clamp, and proximal to this occlusion 5 cc. of potassium chloride (0.5 mEq. per cubic centimeter) was injected and this injection was repeated if necessary. The heart was massaged against the clamp so that the potassium was forced into the coronary arterial system and the action of the heart then came to a standstill. The clamp was removed and the heart massaged. If tone did not return soon, the same procedure was done using calcium chloride in the same equivalent amount. The calcium easily brought tone back to the heart and a regular ventricular rhythm began. This later changed to a sinus rhythm on rewarming. After continued success was obtained at temperatures between 24 and 26 C. with fifteen minutes of occlusion of cardiac inflow, the procedure was applied to human beings in the operating room.

RESULTS

To date, this method has been employed in 11 cases. All patients recovered satisfactorily from the anesthesia. The premedication was the same as for surgical procedures at normal temperatures. The dosages of morphine sulfate and atropine have depended on age, size and condition of the patient. The night before operation, a size 18 or larger polyethylene catheter was placed in the long saphenous vein. Smaller polyethylene tubes do not permit adequate flow. If the patient had been apprehensive, sleep was induced with pentothal®, followed by cyclopropane and ether; otherwise pentothal was not used. The patient was permitted to breath oxygen for several minutes before any anesthetic agent was given. Cyclopropane was used only to diminish reflexes to the point where ether could be added without stimulation. Continuous electrocardiographic tracings were started before cooling. Lower second plane ether anesthesia was induced and then the patient was immersed in ice water. On a few occasions, the patient showed signs of stimulation, that is shivering or greater depth of respiration on immersion in ice water. In those cases, cyclopropane was added to the anesthetic mixture to deepen anesthesia rapidly. At about 29 C. spontaneous respiratory efforts usually ceased. There-after, until the end of the procedure, hyperventilation was employed, using oxygen. Some of the patients made slight respiratory efforts at body temperatures as low as 25 C. In 2 cases it was noted while the patient was in ice water that after inflation of the lungs by pressure on the breathing bag, they were very slow in deflating; as much as two seconds elapsed before the lungs became deflated. No explanation is known for this phenomenon. Usually, the patients were not well relaxed by the time the incision was made. In 2 cases it was necessary to give curare intravenously to keep the patient quiet on the operating table.

It should be emphasized that the temperature of the patient continued to drop after removal from the ice bath. In table 1 this drop is indicated as it occurred in each case. The patients weighed from 34 to 140 pounds. Two were adults. Cooling required from twenty-three to seventy-seven minutes. The skin touched by the cold water became hyperemic. The face of the patient became white. The pupils were usually fairly large, probably because the anesthetic agent was no longer administered when hypothermia appeared, and the plane of anesthesia became quite light. In one patient, on occlusion of the venae cava, there was a violent movement of the diaphragm. Because of this experience, the patients have usually been given flaxedil® a few minutes before circulatory arrest was produced in order to keep the diaphragm quiet for manipulations by the surgeon.

After the occlusion, the patients frequently have moved fairly soon, indicating awakening. Usually warm water was circulated through the mattress when the patient was placed on the table, so that the temperature would stop falling and be between 23 and 25 at the time of circulatory arrest. Inasmuch as anesthesia was maintained without administration of much drug, the patient frequently started to move as soon as the temperature began to rise. This usually occurred before closure was completed. Fifty per cent nitrous oxide in oxygen was used to keep the patient quiet for closure and for warming. The sutured incision was covered with collodion. Sections of rubber gloves were placed around the chest tubes and their edges were also covered with collodion. The patients were then placed in water at 45 C. until their own temperature rose to about 33. This has required about an hour after the end of the surgical procedure. Nasal oxygen has been given in the Recovery Room because the peripheral circulation has seemed to be slow.

Ventricular fibrillation occurred in case 8 some time between removal from ice and the moment the electrocardiogram was connected on the operating table. This interval was about five minutes. It was exactly two minutes after the electrocardiogram showed ventricular fibrillation that cardiac massage was actually begun. That massage was adequate was evidenced by a good peripheral pulse. The patient was given 0.5 mEq. of potassium chloride in the aorta, the distal aorta

TABLE I

Case	Age, years	Weight, pounds	Premedication		Pentothal, mg.	Cooling Period, minutes	Temp. when Removed from Ice, °C.	Lowest Temp., °C.	Skin-to-Skin, minutes	Time of Occlusion, min. sec.	Time in Warm Water min.	Operation	Temp. when Removed from Water, °C.
			Morphine, mg.	Atropine, mg.									
1	11	74	10	0.4	125	37	34	28.0	96	None	55	Pulmonary Valvulotomy	33
2	8	63	8	0.3	175	44	29	25.2	85	7'30"	33	Pulmonary Valvulectomy	34
3	7	51	7	0.3	125	37	30	23.6	118	2'00"	31	Pulmonary Valvulectomy	33
4	8	66	8	0.3	125	39	30	25.7	99	3'05"	30	Pulmonary Valvulectomy	32
5	9	66	8	0.3	150	35	30.8	23.7	79	2'25"	45	Pulmonary Valvulectomy	33
6	26	104	10	0.4	150	77	29	22.3	77	7'30"	90	Close Interatrial Septal Defect	33
7	10	70	10	0.4	0	45	31	24.6	105	8'25"	30	Pulmonary Infundibulotomy	33
8*	6	41	5	0.3	75	40	29	22.6	105	5'30"	45	Close Interatrial Defect	32
9	52	140	15	0.4†	135‡	43	31.7	30.0§	320	None	70	Left Hepatectomy	32
10	11	60	3	0.3	150	35	31	26.0	230	None	0	Anastomosis Aorta to Pulmonary Artery	32
11	3	34	3	0.2	0	23	30	25.5	108	2'10"	75	Pulmonary Valvulotomy	37

* Fibrillation at 27.5 C. before operation began.
† Scopolamine.
‡ Seconal.
§ Maintained at 30.0 C. for 5½ hours.

being clamped; by cardiac massage this solution was then pushed through the coronary circulation. The heart stopped. Calcium chloride, 2 cc. of a 2 per cent solution, was given. Cardiac massage was begun and the heart soon beat spontaneously.

A 52 year old patient who had undergone surgical intervention three times in unsuccessful attempts to stop bleeding from a ruptured liver was cooled to 30 C., at which temperature her blood pressure reading could not be obtained. The surgeon, for the first time, was able to see the lesion. The infected cavitated left lobe of the liver was removed. The patient awoke satisfactorily and the blood pressure was normal when she was warmed. The "skin-to-skin" time was five hours, twenty minutes. It was the concensus of those present that hypotensive anesthesia produced by drugs would have put more strain on the patient.

Table 1 gives some data pertinent to the 11 cases.

COMMENT

There is no doubt that hypothermia is effective as an anesthetic agent. None of the 11 patients who underwent this procedure have had deleterious effects from it. ‡ The main danger as reported by all investigators is circulatory failure. This consists for the most part of ventricular fibrillation. The cause of this dangerous arrhythmia appears to be a prolongation of the latent period in the conduction system of the heart, so that any stimulation, however slight, results in incoordinated fibrillary twitching of the ventricles. This was well shown by Hegnauer *et al.* (15) during their work on hypothermia with and without ventricular catheters in place. In our hands electric defibrillation has been ineffective. Arrest of ventricular fibrillation by injection of potassium chloride into the coronary arteries has been most efficient in our laboratory. We believe that this is the method of choice. This is well exemplified by the one patient (case 8) in the series who was resuscitated from this dread arrhythmia without difficulty by injection of an extremely small dose of potassium chloride into the coronary circulation where it was needed. The efficacy of the method is further illustrated by the fact that the patient then underwent five minutes of circulatory arrest and closure of an interatrial septal defect under direct vision without difficulty.

The hypotension achieved with hypothermia is a "physiological" one, in that it is accompanied by a reduced oxygen demand of the organism. The success achieved with hypothermia in this respect is well illustrated in case 9 in which three previous attempts were unsuccessful in arresting profuse hemorrhage. It is seldom that such definite "control experiments" are obtained in clinical surgery. At the low temperature, the bleeding point was well seen, and a direct attack on it by resecting the left lobe of the liver was successful. This extremely ill

‡ Patient 9 (table 1) died two days later of pre-existing antibiotic-resistant pneumonia.

woman tolerated more than five hours of major surgery. In this case the anesthesia was of major technical assistance to the surgeon.

Muller (29) has used hypothermia without cessation of the circulation in 22 children, chiefly with cyanotic heart disease. He has had no deaths and considers that it has been of great benefit. Collins (30) has had a similar experience in 6 adults with aortic aneurysms. In 2 of these cases circulation to the brain was interrupted three different times for as long as four minutes at a time. Without hypothermia the blood flow to the heart could not be occluded for a period long enough to permit intracardiac maneuvers under direct vision.

Our experience indicated that air embolism can be prevented and that interatrial septal defects can be successfully closed under direct vision. We have successfully cooled 2 adults. These facts are in direct contradiction to the reports of others (20, 21). The rapidity of cooling and warming may be of importance. The thesis of hyperventilation and the prevention of respiratory acidosis which is so important in any patient, looms even larger where occlusion of cardiac inflow is contemplated (24).

SUMMARY

Basic changes occurring in the dog during hypothermia have been described. Hyperventilation is of extreme importance for successful hypothermic anesthesia. The use of potassium chloride has, in our hands, been the only method of defibrillation of the ventricles. It must enter the coronary circulation. The method for administration is described.

Hypothermic anesthesia seems to be indicated:

1. Only when the operating room team is prepared to recognize instantly and cope with cardiac standstill or ventricular fibrillation of the cold heart.
2. When occlusion of the entire circulation is required to perform intracardiac surgical procedures.
3. When hypotension is desired in poor risk patents.
4. For cyanotic patients whose oxygen demand should be reduced.
5. When regional occlusion of the circulation is desired for prolonged periods.

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