CESSATION OF CIRCULATION IN GENERAL HYPOTHERMIA
I. PHYSIOLOGIC CHANGES AND THEIR CONTROL*

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GOOD EXPOSURE OF THE surgical field is of primary importance in the ultimate success of any procedure. Thus, for many years the cardiac surgeon has been limited by his inability to operate safely within the empty heart under direct vision. There have been several methods devised in the effort to obtain intracardiac exposure with a dry field. There are pumps[9, 27, 39, 40, 50, 51] which shunt blood past one or both sides of the heart, utilizing the dog's own lungs as the oxygenator. Pumps with homologous lungs as the oxygenator have been used successfully in the laboratory[14, 33, 34, 36, 52] This technic avoids some of the complicated cannulations of pumps alone, but carries the problem of a supply of fresh lungs if used clinically. Pump oxygenators[6, 11, 12, 16, 17, 25, 31, 43] have been used with increasing success experimentally since Gibbon first reported the technic. However, there are many problems inherent in this type of work, not all of which have as yet been satisfactorily solved. Moreover, coronary blood flow returning to the heart yields a field far from dry. The equipment is complex and expensive. None of these technics are yet widely applicable with safety to the human patient.

Recently, Bigelow *et al.*[3, 4] reported a simpler method of obtaining a dry heart for intracardiac surgery. This was achieved by general hypothermia. Their mortality rate from ventricular fibrillation and shock was very high, but of prime interest was the fact that 15 per cent of their dogs survived 15 minutes of circulatory arrest. Brief periods of complete arrest of circulation had been previously used both experimentally and clinically in the warm subject. Haecker[19] in 1907, Carrel and Tuffier[8] and Tuffier[47] in 1914, showed the feasibility of inflow cardiac occlusion in the experimental animal. Templeton and Gibbon[46] and Swan *et al.*[44] had utilized the method extensively in the laboratory. Swan *et al.*[45] and Varco[49] had reported the use of the technic in the warm human patient. But the period of time available, one and one-half to two minutes, was too short to allow elaborate intracardiac procedures. By the use of the physical agent cold, Bigelow[3, 4] so reduced metabolism and oxygen consumption that the heart and brain of these surviving dogs had tolerated a really significant period bereft of circulation. Hoff and Stansfield[23] found that local cooling of a portion of the ventricle of dogs rendered the heart susceptible to fibrillation by a single shock anywhere in the non-cooled ventricle. Pursuing the use of general hypothermia, Cookson *et al.*,[10] after several initial experiments, succeeded in having nine out of 11 dogs survive 12 minutes of cardiac inflow occlusion with hypothermia. Because of the large and variable

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number of pharmaceutical agents employed in their experiments, the fundamentals of the control of fibrillation did not emerge. Lewis and Taufic[29] created interatrial septal defects in 39 dogs with a mortality of 31 per cent. The same mortality was found in the closure of the defects in the surviving dogs. They also presented a successful clinical case.

In their studies on hypothermia, Bigelow *et al.*[5] showed that O_2 consumption fell steadily with decreasing body temperature and that down to 20° C. the circulation remained adequate. That no tissue hypoxia occurred was evidenced by the absence of increased O_2 demand during the rewarming period. They also pointed out the importance of control of shivering during the cooling period, and the necessity of artificial respiration in maintaining normal arterial O_2 saturations. Hegnauer *et al.*[20] at first subscribed to the theory that hypoxia, possibly caused by prolongation of the "activity" phase of the cardiac cycle, arterial hypotension and increased blood viscosity, was the cause of the eventual ventricular fibrillation in progressive hypothermia. Later,[21] however, they concluded that the evidence for hypoxia as the cause of ventricular fibrillation was erroneous, as the dogs with fibrillation had ventricular catheters in place. Without catheters, their incidence of ventricular fibrillation was greatly lowered. This clearly suggested a greater sensitivity of the canine hypothermic heart to stimuli which are well tolerated in the normothermic. They tried intravenous procaine and adrenalin blocking agents without success in preventing the fibrillation. They also found no auricular fibrillation in 100 dogs, but report it as a common phenomenon in human hypothermia.[22] This corresponds to our experience. Rosenhain and Penrod[37] showed that due to the increased solubility of O_2 at low temperatures (33 per cent greater at 25° C. than at 38° C.), the reduced O_2 requirements of the hypothermic dog could be met with dissolved O_2 if the dog were breathing pure O_2. Penrod[35] showed that coronary arteriovenous O_2 differences remain adequate down to 20° C., despite low pO_2 values in coronary sinus blood. He concluded that cardiac muscle has a striking ability to extract O_2 from blood at very low pressures. There exists agreement of opinion, then, that tissue hypoxia is not the cause of ventricular fibrillation in general hypothermia in the dog.

Yet ventricular fibrillation occurred frequently in hypothermia, with or without occlusion of circulation, and comprised the major cause of death. For some unknown reason, fibrillation occurring in the cold state had proved to be largely refractory to the usual methods of resuscitation. Neither Bigelow nor we, in the early part of our work, could revert to normal rhythm the fibrillating heart by the use of electric shock, procaine, coramine, massage or other conventional agents or methods. Lewis and Taufic,[29] and Cookson *et al.*[10] had only moderate success. It was obvious that effective means of preventing ventricular fibrillation or of converting it to normal rhythm must be found if the use of hypothermia were to be made safe.

Hypoxia had been shown not to be the primary influence. Therefore, it appeared worthwhile to survey the effect of cold on a variety of physiologic body constants in an effort to uncover specific changes which might be related to alteration in the irritability of cardiac muscle. However, not only cold must be considered. If the technic is to be usable for cardiac surgery, interruption of circulation must occur. Cardiac inflow occlusion, therefore, was included as an integral part of this study. The investigation proved fruitful. This paper will present a rather large volume of data relating to the effect of cold and cessation of circulation on the general physiology of the body. Over 1500 determinations were made in over 100

dogs. Two specific changes, those occurring in the potassium concentration of the extracellular fluid and in blood pH as influenced by its CO_2 content, appeared to be related to ventricular fibrillation and are discussed from this point of view.

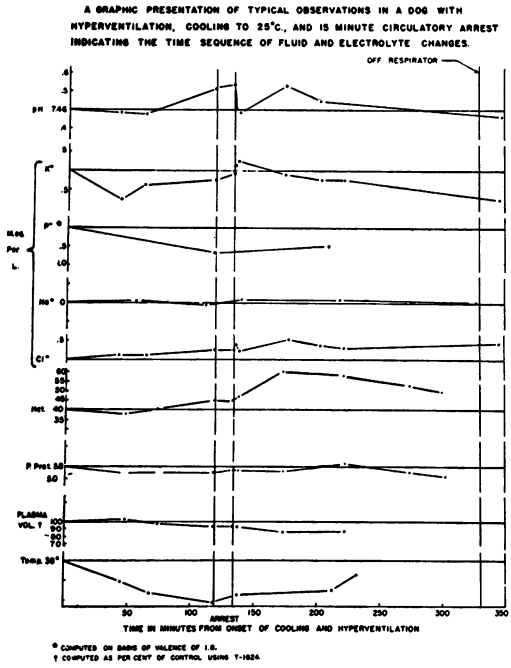

FIG. 1

METHODS

Adult[26] mongrel dogs of both sexes were used, weighing between 9 and 25 kilograms. Sodium Nembutal intravenously, 26.4 mg./kilo, was the anesthetic. None of them received pre- or postoperative digitalis, quinidine, or other cardiovascular drugs. The dogs were then clipped and immersed in ice water at a temperature of 1° C. Pure oxygen was administered through an intratracheal tube by an automatic respirator. The tube being smaller than the trachea, expiration occurred around it; no rebreathing system, therefore, was necessary. Respiratory rate and depth could thus be regulated. Most of the dogs were hyperventilated at 40 to 60 respirations per minute; 10 dogs were hypoventilated at one to three times per minute. A Cournand needle was in place in the external jugular vein for blood samples. In some experiments, a long polyethylene catheter was placed in the inferior vena cava by threading it up the femoral vein. The latter was used to draw blood samples for CO_2 determinations.[48] A thermocouple, inserted 10 cm. into the rectum, recorded body temperatures on a Brown Potentiometer. When the body temperature fell to 29° C. the dogs were removed from the ice-water mixture. They continued to cool another 3 to 5 degrees, and maintained this temperature for as long as six to eight hours. Shivering was never a problem if the dog was immersed in the ice-water soon after receiving his Nembutal. Most dogs cooled in less than an hour, and many of the smaller animals cooled in half an hour. This rapid cooling was considered an advantage over the longer times reported by others, who cooled the animals in air[3, 4, 5, 10] or between blankets containing cold solution.[29] Certainly the dog was hypothermic for a shorter period, and the time saved for laboratory personnel was considerable.

The operative procedure was done under aseptic precautions. The right fourth interspace was entered. The azygos vein was ligated and umbilical tapes were placed about both cavae. The pericardium was widely opened and the circulation stopped for 15 minutes by tightening up the tapes on the cardiac inflow tract. During this period, the heart continued to beat slowly. In most animals cardiotomy was performed by opening widely the right atrium and exploring the right side of the heart visually and digitally. The heart was found to be empty except for coronary sinus flow, which becomes insignificant after a few minutes. Even this amount of flow can be prevented by a clamp across the base of the aorta, occluding the coronary arteries. The heart was then filled with saline and the atrial

incision closed with a curved Potts clamp. After release of the cavae, suture was performed with figure-of-eight stitches of 3–0 silk. The superior vena cava was released first, allowing the heart to fill, but not be-

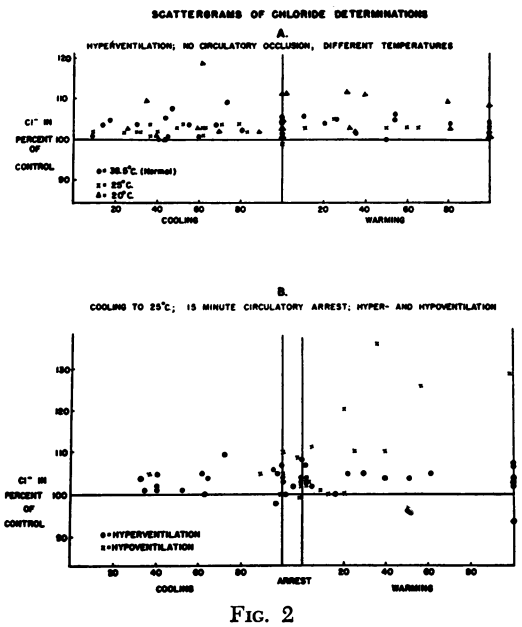

FIG. 2

come distended. Occasionally it required a few manual cardiac compressions to start it going well. When the beat appeared strong, usually about one minute later, the inferior vena cava was also released. The heart took this additional load well. All during the period of occlusion the respirator was stopped. With return of circulation, hyperventilation was resumed. After closure of the chest wall, temporary catheter suction drainage of the chest was routinely employed. The dog was rewarmed in a bath of water at 45° C. The rate of warming was even faster than the rate of cooling. After about 30 minutes, on arriving at a temperature of 33° C., the dogs usually resumed spontaneous breathing. Appropriate blood samples were drawn at various stages of the procedure for the multiple determinations.

In five dogs, a bilateral anterior thoracotomy was done in the fourth interspace. These dogs were hyperventilated. After establishing inflow occlusion, a 5 cm. incision was made in the right ventricle between the coronary artery supply along the ventricular outflow tract. Stay sutures had been inserted

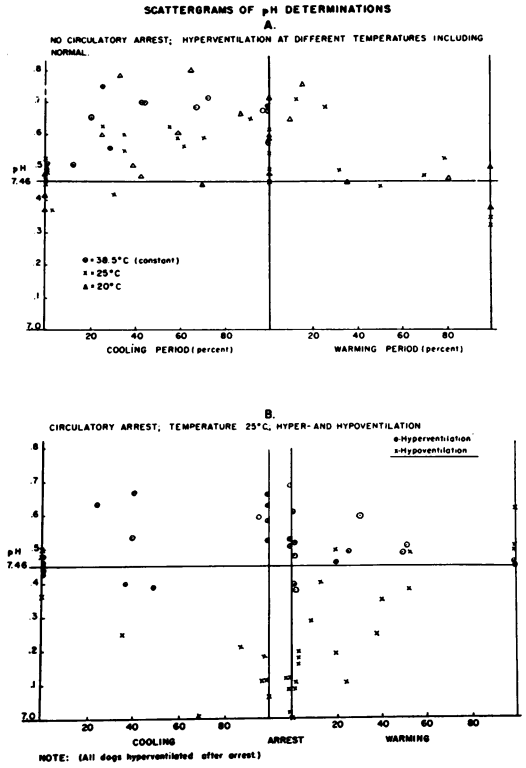

FIG. 3

previously. Ventricular fibrillation followed in all the hearts either after insertion of the stay sutures, or when the incision was made. The ventricles were sutured with interrupted figure-of-eights. Electric shock[2] and massage were ineffective in our hands in the defibrillation of these dogs. This group was then used as a control to study the effects of potassium on fibrillation. Seven dogs were then cooled and hyperventilated and subjected to the ventricular incision as above, and it routinely made them fibrillate. The incision was sutured after filling the heart with saline and then KCl (one-half milliequivalent per cc.) was injected, 2 cc. at a time, into the root of the aorta proximal

to a Potts clamp across that vessel through the transverse pericardial sinus. The solution thus could go only into the coronary arteries when the heart was massaged. Following the arrest of the fibrillation, 2 per cent $CaCl_2$ was cautiously injected in the same manner in minute amounts (0.1 cc. at a time) to bring about regular cardiac action. This was done after the manner of Hooker,[24] who showed in the normothermic animal that KCl and $CaCl_2$ were effective in controlling fibrillation only when given by the intra-arterial route.

Since these experiments involved five different physiological situations, namely, hyperventilation, hypoventilation, cooling to 25° C., cooling to 20° C., and occlusion of the circulation, a series of experiments were set up as follows: Attempt was made to carry four dogs through the following series of procedures spaced at weekly intervals.

1. Hyperventilation.
2. Hyperventilation and cooling to 25°.
3. Hyperventilation and cooling to 20°.
4. Hyperventilation, cooling to 25°, and occlusion of the circulation for 15 minutes. Three dogs survived the entire series. Additional animals were used to bring each group to four or more.

Four additional animals were used to comprise the fifth group, hypoventilation, cooling to 25° C., and occlusion of the circulation for 15 minutes. Venous blood samples were taken for all determinations. The dog was weighed at the end of each period so that fluid balance changes could be calculated from the weight changes and the urinary output which was obtained by catheter.

TABLE I.

The per cent change in plasma volume varies if calculated from (a) hematocrit, (b) the plasma dye, or (c) protein concentrations.

	Cooling						Warming + Recovery					
	Hct		PP		Dye		Hct		PP		Dye	
	No.	% Chg.	No.	% Chg.	No.	% Chg.	No.	% Chg.	No.	% Chg.	No.	% Chg.
Hyperventilation.....	4	−14.8	4	−4.2	2	0	4	−11.5	4	−3.7	4	−3
Hyperventilation 25°.....	5	−12.4	5	−1.2	3	−7.	5	−16	5	−2.8	3	−9
Hyperventilation 20°.....	4	−16	4	−4.5	4	−13.2	3	−19	3	−1.0	3	−13.3
Hypoventilation 25°.....	4	−4.8	4	+1.5	-	—	3	+2.0	3	−6.3	-	—
Hyperventilation 25° Occl.	5	−7	5	−1	2	−5	4	−21	4	+4	1	−5

BIOCHEMICAL DETERMINATIONS

Measurements were made of serum concentrations of proteins by the falling drop method of Barbour and Hamilton;[1] chlorides by the method of Schales;[38] sodium and potassium on the Janke flamephotometer; and phosphorus by the method of Fiske and Subbarow.[15] Blood pH was determined on the Beckman pH meter. The plasma (T-1824) and available fluid volumes (thiocyanate space) were determined as described by Gregerson and Stewart.[18] The technic was modified so that the experiment fell into the period after the dye slope had attained a constant disappearance rate (approximately two hours). Thus, the changes in plasma volume could be calculated from the changes in the dye slope. Urine analysis included chloride, sodium and potassium. The Wintrobe tube was used for hematocrit determinations.

PRESENTATION OF DATA

A typical experiment showing the changes observed with hyperventilation, cooling to 25°, and occlusion is shown in Fig. 1. The body temperature is shown at the bottom of the chart and can be correlated with the

other variations shown. The most significant changes seen in this chart are in the pH and in the serum potassium. These will be discussed in subsequent sections. There was also a slight but consistent rise in the serum chloride value up to approximately 5 per cent of the control value while the serum sodium showed no significant change. Serum phosphates showed a slight drop. During the cooling period, there was a

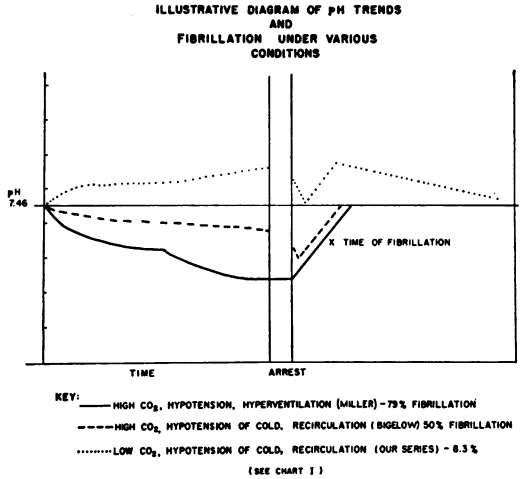

FIG. 4

minor drop in the hematocrit and a slight fall of the plasma protein concentration. With these trends fixed in the reader's mind, each will be discussed in relation to the effects of hyperventilation, hyperventilation and cooling, hypoventilation and cooling, and the addition of occlusion to the cooled animals.

SERUM SODIUM, CHLORIDE, AND PHOSPHORUS

Some 60-odd sodium determinations were made. In none of the experimental groups were any significant changes observed from the control level. Serum sodium does not change with cooling.

In all five groups of dogs there was a slight increase in chloride of about 5 per cent above the control level. Fig. 2 A is a scattergram comparing the effects of hyperventilation with the combination of hyperventilation plus cooling to 25° or 20° C. The overlapping of dots indicates that cooling did not significantly alter the effects of simple hyperventilation on the plasma chloride. Neither was there any significant change during the warming phase of the experiment.

Fig. 2 B compares the plasma chloride levels when one group of dogs was hyperventilated, and the other hypoventilated while cooling to 25° C. To the point of release of occlusion there does not appear to be any difference between the two groups. However, after release of occlusion and hyperventilation is imposed on both groups, there is a striking difference. The group which had been hypoventilated to this point showed a sharp increase in plasma chloride; whereas the group which had been hyperventilated throughout the experiment revealed no such change. Since no red cell chloride determinations were done, it is impossible to determine whether there was a shift of chloride from red cells to plasma or a decrease in volume of the chloride "compartment" due to the loss of water. The former seems more likely, since there was no decrease in the sodium "compartment" as one might expect, if the chloride "compartment" were to change.

The serum phosphorus control values averaged 2.91 mEq/L. (computed as phosphorus having a valence of 1.8). In nine out of ten dogs there was a drop in serum phosphorus. The average drop was 0.38 mEq/L. during cooling and hyperventilation, with an additional average drop of 0.16 mEq./L. during the warming period. There did not appear to be any appreciable difference between cooling to 20° C. or to 25° C., or the addition of occlusion to the experimental procedure. A typical pattern is seen in Fig. 1.

As will be described later, there was a concomitant fall in serum potassium levels. This suggests the possibility of movement of both phosphorus and potassium into the

body cells in association with a disturbance in carbohydrate metabolism.

FLUID SHIFTS

Previous work has made reference to the rise in the hematocrit value observed in the hypothermic animal.[20, 35] Hegnauer[20] reported an average increase in the hematocrit value of 32 per cent at 25° and 40 per cent at 20° C. In the present experiments there was an increase in the hematocrit value in 19 of 22 animals. This was seen in all groups including hyperventilation alone. When the change in plasma volume is calculated on the basis of hematocrit changes, there is a decrease in the average plasma volume for all groups as shown in Table I. The maximum decrease (16 per cent), was seen with hyperventilation and cooling to 20°. However, this was essentially no different from the 15 per cent decrease noted with hyperventilation alone. The minimum decrease of 5 per cent was noted with hypoventilation and cooling to 25°.

Examination of the plasma volume changes calculated from the proteins and dye concentration suggest that the changes estimated from changes in hematocrit do not represent a true decrease in plasma volume. The plasma volume decrease calculated from the proteins never exceeded 5 per cent, and frequently showed no change. The plasma volume changes calculated from the dye (T-1824) exceeded those calculated from the protein changes, but were always less than those calculated from the hematocrit. It can be concluded in general from Table I that the decrease in plasma volume in these experiments was small; rarely exceeding 10 per cent of the control, and in many instances showing no change at all. Cooling produced no variation from the changes observed with hyperventilation alone. The discrepancy shown by the hematocrit values might well represent a splenic discharge of red cells. Studies on splenectomized dogs will be reported at a later date.

During all procedures there is a consistent weight loss averaging from 4 to 6 per cent of the body weight during a 24-hour period for each group. Since this loss also occurred in the hyperventilation group,

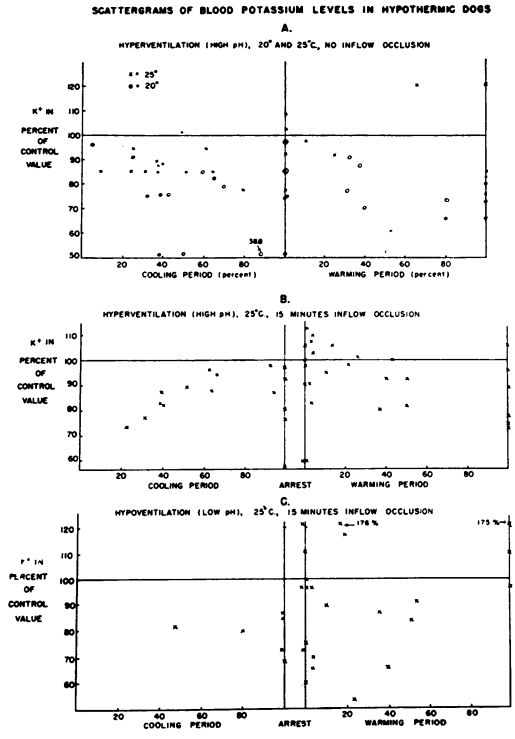

FIG. 5

one might well ascribe it primarily to water loss from the lungs. The urine flow during hyperventilation and cooling was low, but there was no significant change in pattern of electrolyte excretion. During the warming period, urine flow and electrolyte excretion showed a definite increase in all except the animals cooled to 20° C. The total urinary sodium or chloride loss was not sufficient to account for any appreciable change in volume of these two compartments. Measurements of the thiocyanate volumes and calculations of the "sodium compartment" by the method of Lavietes *et al.*[28] indicate that there was no significant change

in extracellular volume during any of these procedures. Thus, from the data presented, one can say there is a total loss of body fluid not to exceed 6 per cent of the body weight. This loss is probably distributed throughout the total body fluids without a disproportionate reduction in volume of any single compartment. The relation to thirst will be discussed in a subsequent paper.

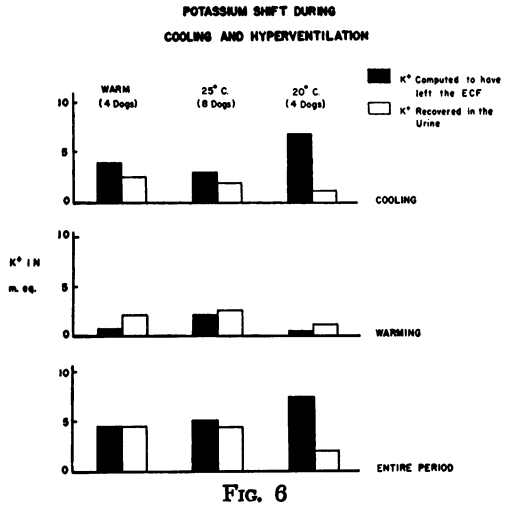

FIG. 6

THE RELATION OF CARBON DIOXIDE TO FIBRILLATION

Retention of carbon dioxide is known to have a profound effect upon cardiac action, presumably due to the associated changes in blood pH. The effect of hypercapnia on cardiac arrest induced by vagus stimulation has been documented by Sloan,[41] Young *et al.*,[53] and by Stewart *et al.*[42] Brown and Miller,[7] and Miller *et al.*,[32] showed the remarkable importance of sudden extreme changes in CO_2 levels. Dogs made hypercapnic by breathing a 30 per cent CO_2 mixture for two hours, followed by 40 per cent CO_2 for two more hours, almost invariably went in ventricular fibrillation if suddenly placed on room air and hyperventilated. On the other hand, if such dogs were slowly brought back to a normal pH by being graduated through stages of serially reduced CO_2 in the breathing mixtures, no fibrillation occurred. It was also observed that if the hypercapnic dogs were prevented from becoming hypotensive prior to hyperventilating them in air, they were protected, to a considerable extent, from fibrillation. Bigelow *et al.*,[3, 4, 5] on theoretical grounds (to promote oxyhemoglobin dissociation at low body temperature), had thought it wise to add 5 per cent CO_2 to his breathing mixtures. Moreover, during periods of circulatory arrest, CO_2 accumulates in all the tissues. On return of circulation, the CO_2 both in the blood and in the heart muscle of his dogs thus must have been high and also must have fallen rapidly as circulation and respiration were resumed. Bigelow's cold dogs, it seemed to us, were thus remarkably parallel to the warm dogs of Brown and Miller[7] in that they attained high levels of CO_2 during occlusion which underwent a sudden reduction in the presence of hypotension. Both groups had a very high incidence of fibrillation. It occurred to us that, if the dog were not only prevented from becoming hypercapnic during the cooling, but indeed were rendered hypocapnic by over-ventilation, the CO_2 might not build up to abnormal heights during the period of occlusion, and the lethal effect of a rapid fall from hypercapnia would thus be prevented.

To test this hypothesis, a series of animals were studied with cooling to 25° C., occlusion of circulation for 15 minutes, and deliberate hypoventilation using 100 per cent oxygen but allowing only three respirations a minute. Oxygen studies revealed normal arterial oxygen saturations and A-V oxygen differences in these animals. In this group of ten animals, five fibrillated, a rate of 50 per cent. In contrast to this, 12 dogs cooled to 25° C. with inflow occlusion for 15 minutes, but subjected to vigorous hyperventilation at 40 to 60 respirations a minute, only one fibrillated, a rate of 8.3 per cent.

That this type of ventilation control did, in fact, alter the blood CO_2 and pH in the

expected fashion is documented by the following table and by Figure 3.

In Table II, note that: (1) Venous oxygen content rose with cooling, fell immediately after release of occlusion as the tissues avidly picked up oxygen, but returned to pre-occlusion levels after five minutes; (2) the CO_2 content fell during pre-occlusion cooling because of the hyperventilation, then rose abruptly during occlusion, but only to the normal control level. This dog was never hypercapnic.

In Figure 3 (A) one observes that the pH determinations uniformly fall above the norm of 7.46 throughout hyperventilation irrespective of temperature; the pH shift mirrors the loss of CO_2. After warming, the pH seeks normal levels. In (B), where the degree of cooling was constant at about 25° and all dogs underwent circulatory arrest, the marked differences in pH levels effected by hyper- and hypoventilation are readily apparent.

It appears, then, that changes in CO_2 concentration of the blood have a relationship to the incidence of ventricular fibrillation in the hypothermic dog. We believe, as do Rosenhain and Penrod,[37] that it is not the CO_2 *per se*, but rather its effect on the pH which causes the arrhythmia. The CO_2 content of circulating venous blood (and thus the pH) is merely a mirror of changes which are going on in the tissues. Since tissue pH cannot be measured directly, we must accept measurements in the blood as a reflection of what is going on in the tissues.

However, during cessation of circulation, venous blood no longer mirrors the tissues. The following table illustrates this point.

It is apparent from Table III that although the animal was alive and the tissues were respiring, the CO_2 content of venous blood has not changed in value from two minutes before circulatory arrest to the point 14 minutes after it had been established. A glance at the CO_2 content 90 seconds after release of occlusion shows an abrupt rise in this figure. Thus the CO_2 has now appeared in venous blood following resumption of circulation. It is now quite obvious that during the 15 minutes of circulatory arrest, the tissues were respiring and CO_2 was eliminated along with other acid metabolites and staying in the vicinity of the cell. The pH of the tissue then would fall to low levels. This sequence of events would be especially true in heart muscle which continues to work all through the periods of circulatory arrest. When circulation resumes, arterial blood with a low CO_2 content perfuses the heart which is loaded with CO_2, and this acid metabolite, along with others, is rapidly washed out of the heart. The tissue pH rises from low to near normal levels in a space of a few heart beats. It is now that the pH change (in an opposite direction) appears in venous blood some time after it has happened in the tissues.

This change, which occurs on recirculation, is too rapid to be prevented by any other means than that of preliminary hyperventilation. This depletes the tissues of CO_2 before occlusion begins so that the build up in CO_2 during the period of no circulation will bring it to normal, or only slightly above normal. Thus the change on resuming circulation will occur at CO_2 levels near normal, rather than at levels well above normal, and, therefore, will be better tolerated by the heart. Thus, of ten dogs who entered inflow occlusion with a pH of 7.1 or lower, four fibrillated immediately after resumption of circulation. One other dog fibrillated before inflow occlusion was established. This one dog may indicate that low pH *per se* in hypothermia may be of serious import, even without rapid change as depicted above.

This concept is illustrated diagrammatically in Figure 4.

It was clear, on conclusion of this phase of the study, however, that although con-

trol of ventilation appeared to have a beneficial effect on the incidence of fibrillation, it was not the entire answer.

THE RELATION OF POTASSIUM TO FIBRILLATION

That serum potassium levels have a profound effect upon the function of cardiac muscles is well known. The ability of K to stop electrically induced ventricular fibrillation in the dog when injected intra-arterially was demonstrated by Hooker,[24] in 1929. The reciprocal relation of Ca and K in their effect on heart muscle has also been repeatedly demonstrated.

Moreover, changes in serum levels of K have been consistently found in hypothermia by everyone who has studied this ion in relation to cold. Elliot and Crimson[13] in 1947 noted that in shivering rats at 25° C., both K and Ca levels rose. They believed these ions came from the liver along with mobilized glycogen. They found that doubling the K content of plasma did not affect the normothermic rat; the same treatment put the hypothermic rat into cardiac arrest. The cold rat heart appeared more susceptible to the ion, they felt, than the normal heart. Bigelow *et al.*[4] also found a rise in K and an inconstant rise in Ca in their hypercapnic non-shivering dogs. In our studies, we too have found that changes in K levels have been one of the most marked aberrations from normal physiology that we have observed. Somewhat to our surprise, however, in our animals the change was in the opposite direction; serum potassium levels in the cooling hyperventilated dog consistently fell.

TABLE II.

Dog 444, cooled to 25° C. circulatory arrest for 15 minutes, hyperventilation

Time	Event	Temp.	Venous O_2 (Vol.%)	Venous CO_2 (Vol.%)
10:05	Control	38.5°	15.9	43.4
12:45	2 min. before occlusion	25°	18.4	31.7
13:06	2 min. after occl. released	25°	4.8	43.6
13:09	5 min. of resumed circulation	25°	18.1	40.9
13:17	13 min. of resumed circulation	25.2°	21.2	34.5

The data on our studies of potassium levels in hypothermic dogs under various conditions are presented in Figure 5. It is apparent in (A) that in the cooled dogs with hyperventilation (high pH), but without circulatory arrest, the blood K levels rather uniformly fell from 10 to 40 per cent of their control value and tended to remain low during the cooling period. When 15 minutes of inflow occlusion is added (B), the levels are the same during the cooling period, but apparently during circulatory arrest, K accumulates in the tissue spaces and upon resumption of blood flow appears rapidly in the serum, as the serum levels immediately following occlusion are considerably higher than those just before (Cf. typical pattern shown in Figure 1). Adjustment to normal is not completed during the warming period. When the dogs were hypoventilated (low pH), cooled to 25° C. and occluded (C), the K also tended to be low. Further reference to this scattergram will be made below.

TABLE III.

Carbon dioxide content does not rise in venous blood during arrest of circulation

Time	Event	Temperature	Venous CO_2 Vol. %
11:15 a.m.	2 min. before occlusion	23° C	41.9
11:31 a.m.	1 min. before release of occlusion	23 °C	42.7
11:33½ a.m.	90 seconds after occlusion released	23° C	48.3

It appeared from this data that K was leaving the extra-cellular fluid space under the conditions of our experiments. Was it crossing the renal barrier into the urine? Quantitative measurements failed to account for the apparent loss during cooling. Figure 6 presents this data in composite

form. The effect of the changes occurring following occlusion are not shown, since the computations on a system changing so rapidly at this time were not thought to be sufficiently documented to be reliable. Figure 6, therefore, describes the observations on the effect of hyperventilation and cooling without circulatory arrest. The computations on the amount of K leaving the extra-cellular fluid space are based on the estimated size of this compartment in terms of body weight and its changes, as observed by thiocyanate and the stable serum Na during the experiments, and the observed serum levels of K during the same period.

It would appear that during hyperventilation and cooling, there is a shift of K within the body, since more of the ion leaves the extracellular space during the cooling period than appears in the urine. In the warm dog and at 25° C., these relations readjust themselves during the warming period so that by the end of the experiment the loss can be accounted for in the urine. At 20° C., however, it appears that the shift is more profound, and within the time of the observations, re-adjustment does not occur. The lower temperature (20° C.) is recognized as being more apt to produce ventricular fibrillation than 25° C.[29] It is interesting that the K shift is also greater. One presumes that the K must enter the cells, since it is not in the urine. Whether it enters liver, skeletal muscle, heart or brain, one does not know. Mackay[30] has suggested that liberated K deposits in muscle. The mechanisms controlling the shift have not yet been elucidated in this work, but its possible relation to glucose metabolism is under investigation.

In the light of the observations of the variations from normal in the serum potassium level, our interest became directed toward the possible use of this ion in the prevention or management of ventricular fibrillation in the cool dog. A standard stimulus to produce fibrillation in a hyperventilated dog at 25° C. with inflow occlusion proved to be an incision in the right ventricle. In early experiments on five dogs, ventricular incision (unlike auricular incision) initiated fibrillation in all five. In none of these animals were attempts at resuscitation successful.

With this group as a control, a series of seven animals was again subjected under

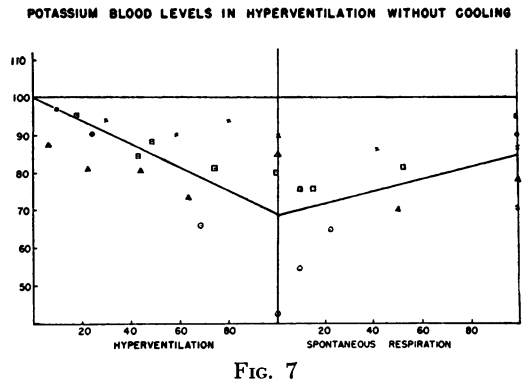

FIG. 7

identical conditions to the fibrillatory stimulus, ventricular incision. All seven responded by entering ventricular fibrillation. Conversion of rhythm was now attempted as follows: The incision was completed and sutured, flooding the chest with Ringer's solution to avoid air embolism,[44] and with the noncrushing clamp in place across the aorta and pulmonary artery through the transverse pericardial sinus, KCl solution (½ mEq. per cc.), 2 cc. at a time was injected into the aorta proximal to the clamp. Two or three manual compressions of the heart now forced the KCl solution through the coronary system to the myocardium. Almost immediately, the ventricular fibrillation ceased, and the heart lay flaccid in the hand. A 2 per cent solution of $CaCl_2$ was now cautiously and intermittently injected in the same manner, introducing 0.1 cc. at a time followed by manual pumping of the heart to send the agent to the myocardium. Soon an organized cardiac beat would be resumed, the contractions gradually becoming more and more forceful. Release of the

inflow tapes was now gradually performed allowing progressive resumption of blood flow as the cardiac action improved. For some time the heart continued to beat with a ventricular rhythm, but this would change to sinus rhythm in about 30 minutes as the dog was beginning to warm (See Fig. 9).

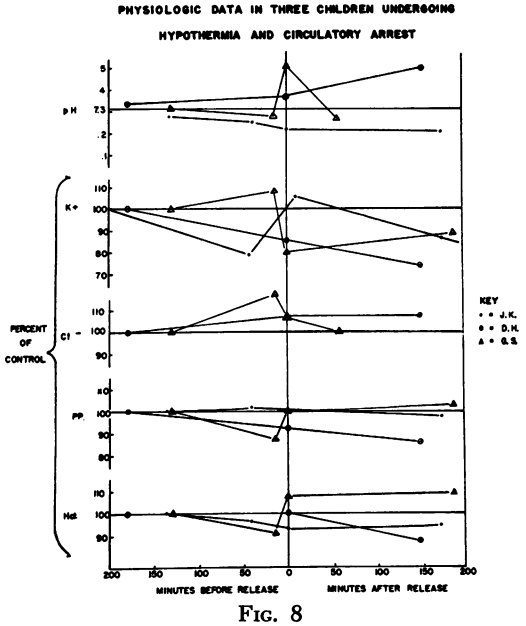

FIG. 8

Successful reconversion of the fibrillation to normal rhythm was accomplished in six of these seven animals.

From these studies, it appears reasonable to conclude that potassium undergoes significant changes in the body of the dog during hypothermia, and that these changes are in some way related to the frequent occurrence of ventricular fibrillation under these conditions. By the use of a potassium solution, it has become possible for the first time in our hands to defibrillate the cold heart. Further studies on the relation of potassium to fibrillation are in progress.

IS THERE A RELATION BETWEEN CARBON DIOXIDE AND POTASSIUM

It has occurred to us that the opposed findings in relation to potassium levels in the serum of cold dogs observed by Bigelow *et al.*[4] and ourselves might be due to the fact that most of our dogs, being hyperventilated, had a high blood pH while his were deliberately made lower. We found that hyperventilation alone in the warm dog tends to depress the serum potassium levels. This data is presented in Figure 7, which shows observations on serum K levels of four anesthetized dogs subject to hyperventilation only. The fall in K appeared to be progressive throughout the period of over-breathing, reverting toward normal on resumption of spontaneous respiration.

Mackay's[30] observations in normal and adrenalectomized cats were also suggestive of a correlation between hypercapnia and K. Both groups showed a marked rise of serum K within five minutes of being exposed to 34 per cent CO_2 breathing mixtures. This high level gradually falls in about one-half hour, even though the mixture is maintained. When the animal is put back on air, the serum K again rises as the excess CO_2 is blown off. If the cat were eviscerated so there was no blood flow through the liver, the K changes did not occur. She suggested the source of the K in hypercapnia might be the liver.

In spite of these observations, a straight line correlation between CO_2 and serum K levels did not appear in our studies, which included hyper- and hypoventilation, cooling to 25° C., and interruption of circulation. Reference again to Figure 5 (B) and (C) shows that the serum K levels with hypocapnia (B) were essentially the same as those with hypercapnia (C). It is to be admitted that the number of pre-occlusion observations in hypercapnia are too few to establish positively the trend.

Thus, although there appears to be a correlation between CO_2 content (blood pH) and serum K levels, and although there is little doubt that hyperventilation alone depresses serum K, the exact relationship between these ions is not yet clear.

HUMAN OBSERVATIONS

Recent experience in the application of general hypothermia to the clinical patient has given us the opportunity to record similar observations in the human. Three children who successfully underwent radical pulmonary valvulectomy under direct vision with cessation of blood flow were studied. The operative technic and the management of the patient will be the subject of a later report, but the observations obtained are detailed in Figure 8. The results appear to approximate those observed in the dogs. Although the intent was to effect hyperventilation throughout, the effort was clearly unsuccessful in patient J. K., whose pH fell to dangerous levels. Interestingly, in all three patients the blood K determinations maintained a reciprocal relation to blood pH. Blood chloride in two patients showed a slight rise similar to that seen in the dogs. Changes in blood volume and body water of these and other patients will be the subject of future analysis. All of these patients made uneventful recoveries, with no untoward operative reactions, although their circulation was totally arrested for seven and one-half, three and one-half, and three and one-half minutes respectively.

COMMENT

By and large, in our experience, there are three periods during hypothermia when the animals are prone to go into ventricular fibrillation: (1) during cooling below 26° C. without cardiac manipulation or circulatory arrest; (2) during cardiac manipulation, particularly, ventricular incision; and (3) immediately following restoration of circulation after occlusion. There seems to be no doubt that in the cold state, the dog's myocardium is extremely irritable and minimal stimuli will send it into fibrillation. The stimulus for fibrillation in period (1) is unknown; that for period (2) is clearly local mechanical trauma; while that for period (3) may well be rapid change in tissue pH. The first must be discovered and the second overcome. The third can be successfully combated by ventilation control.

Since 25° C. appears to be a little safer from the point of view of fibrillation than 20° C., this temperature would be preferable if it is adequate to protect the brain against damage during prolonged circulatory arrest. Of 40 animals surviving 15 minutes of complete arrest, four showed evidence of slight to moderate cerebral damage. Although this incidence is low and the damage not severe, it would appear at this time that in the human at this temperature (25° C.), inflow occlusion for periods exceeding 10 minutes should be approached with caution. Repeated occlusion with a rest interval between might prove to be a safer course.

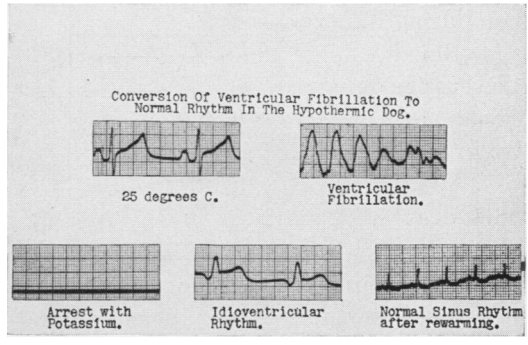

FIG. 9

SUMMARY

1. Observations on the changes occurring in certain physiologic variables in many dogs and three humans undergoing general hypothermia with and without circulatory arrest are presented. These include data on pH, serum sodium, chloride, potassium and phosphorus, plasma protein and hematocrit levels. Total body water, extra-cellular fluid space and blood volume changes are re-

corded. Urinary output of some of these materials was also determined.

2. Dogs were cooled in ice water to temperatures between 20° and 25° C. No cardio-circulatory drugs were used. Hypothermic dogs undergoing circulatory arrest by occlusion of cardiac inflow for 15 minutes were routinely subjected to auricular cardiotomy during this period.

3. Serum sodium levels remain constant; serum chlorides show a consistent slight rise during the experiment.

4. Blood volume tends to decrease, but the change is not excessive and is proportionate to a moderate overall loss of body water.

5. Since ventricular fibrillation is the chief cause of death in the hypothermic dog, aberrations of physiology which might affect this complication were sought. Blood pH and potassium both appear to be of importance.

6. Since adequate spontaneous respirations cease in hypothermia, a choice of rate and depth of artificial respiration must be made. Data are presented which suggest that ventricular fibrillation may be initiated by sudden rises in pH from abnormally low levels, and that this stimulus to fibrillation may be avoided by vigorous hyperventilation throughout the cooling period.

7. Contrary to observations by previous investigators, our studies consistently revealed a fall in the serum potassium during cooling. It appears there is a shift of this ion from the extracellular fluid space during this period, possibly into body cells.

8. Although the significance of this change is not yet clearly understood, the use of a potassium solution as an agent to defibrillate the cold heart has proved successful, whereas previously all other methods have been unavailing in our hands.

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DISCUSSION.—DR. CHARLES RIPSTEIN (4802 10th Avenue, Brooklyn): I would like to express my thanks for the privilege of the floor.

We have been very interested in the problem of hypothermia and its relationship to cardiac surgery, and also in trying to lower body temperature in severe septic infections and intractable pain. There are one or two technical points that have come up in dealing with low body temperature in humans that may be of interest.

(Slide) We have attempted to lower body temperature by use of the refrigeration blanket, with a circulation of refrigerant fluid through the blanket, and as you see on your right of the slide, there is a new type of thermometer that we have adapted for this purpose. This is an adaptation of a standard vapor-actuated industrial thermometer, which gives a constant record of body temperature. It is foolproof and very easy to use.

(Slide) This represents a fairly typical example of lowering body temperature in a dog. There is a long period of resistance on the part of the warm-blooded animal, with trembling and shivering, and by the time we get the dog down to a hypothermic state, there has been a depletion of the liver glycogen and the cardiac muscle glycogen in the exhausted animal.

(Slide) Recently there have been reports in the French literature of the effect of certain antihistaminic drugs on the thermal regulation. One of these with which we have had experience you see depicted here. The generic name for this is *chlorpromazine*. With the use of chlorpromazine in a dog, the body temperature falls much more rapidly and smoothly. The shivering effect is avoided, and the dog is rapidly and easily warmed.

(Slide) And here is a human patient who was refrigerated on two occasions with the drug and without it, with the same degree of cold applied to the body surface and the same depth of anesthesia.

With the drug, there was a much greater drop in temperature, and the lower temperature levels were reached more quickly.

I might add that refrigeration is not without danger. There have been four deaths in some 20 cases we have done, due to cardiac arrhythmias, and only two of those patients have been subjected to cardiac operations. The others have died from the effects of cold alone, and certainly more work of the type described by Dr. Swan is necessary before this method of treatment should be used in any case that can be treated without it.

DR. FRANCIS D. MOORE (Peter Bent Brigham Hospital, Boston 15, Mass.): I would like to congratulate Dr. Swan, Dr. Holmes and their group on a remarkably beautiful piece of biochemical research.

The reason I would like to comment on it is not that I have had any experience with hypothermia, because I have had none. I would simply like to point out that they have shown that changes in plasma K concentration may be due to changes in acid-base balance rather than loss from the body. The same thing is true of certain other metabolic situations wherein one can produce a drop in K and then a restoration to normal plasma K without any alteration in net external balance at all. The mechanism of this is not known. It may well be due to shifts across the cell. It may be due to an alteration in the physicochemical state of potassium within the cell. It may be dilution. But