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THE EFFECTS OF HYPOTHERMIA ON THE CARDIOVASCULAR SYSTEM

BY

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I. Preface:

In this day of diverse and excellent anesthetics hypothermia has its importance in the slowing of metabolism. With hypothermia the need for anesthesia is minimized, operative blood loss is lessened and a hypotensive effect is achieved. The most dramatic use of cold has been in cardiac surgery where opening of the heart is a procedure limited as to time (from three to eight minutes before there is damage to the central nervous system and risk to life) unless some provision can be made for an alternative circulatory system, or, a reduction in metabolic requirements. With hypothermia open heart surgery by direct vision is now possible. Hypothermia, as an adjunct to anesthesia, has also found value in thoracic, vascular, central nervous system, liver and other abdominal operations, as well as in cardiac operations.

Since it was first discovered that hypothermia could be used as a valuable adjunct to anesthesia and surgery, problems in its use rose in rapid succession. This paper will be largely confined to the physiologic and pathologic changes the cardiovascular system undergoes as body temperature is lowered. The majority of the experimental work and the conclusions drawn have been with the use of dogs and other smaller warm blooded animals.

II. Physiological Effects:

A. Circulatory effects:

As the body temperature falls, changes in the heart rate and blood pressure occur. Studies have shown that in dogs, there is an initial rise of ten to fifteen beats per minute on first exposure to cold and then a gradual fall to a final rate, at 18 to 20 degrees centigrade, of from fifteen to thirty beats per minute.[1] In hypothermia produced in rats and kittens without anesthesia, as noted by Hamilton and Dresbach,[2] there is a linear relationship between the decrease in heart rate and the lowering of the body level of heat. Body temperatures as low as 20 degrees centigrade caused a slowing of the heart rate to one-third the normal rate.

Bigelow[1] and other workers with hypothermic animals agree that the blood pressure tends to diminish as the temperature is lowered. The arterial pressure may show an initial rise when the animal is first exposed to the ice bath, but the pressure will then fall and become stabilized at temperatures between 32 and 24 degrees centigrade. It will then decrease rather sharply, usually in the temperature zone of 24 to 20 degrees centigrade.

The pressure will not fall to zero unless the heart rate becomes irregular or stops. As the animals are rewarmed the pulse and blood pressure rise in a fashion almost exactly the reverse of the change during cooling.

As the body temperature falls the cardiac output also gradually falls and the peripheral vessels undergo a gradually increasing vasoconstriction.[1] Hegnauer and D'Amato[3] observed that at 17 degrees centigrade, the cardiac output of dogs was only ten per cent of normal. They calculated that the work of the heart diminished to eight per cent of normal.[3] Cardiac output also returns toward normal as the animal is rewarmed.[1] It has also been shown that circulation time is reduced and that venous pressure rises or diminishes as cooling or warming occurs.[1]

B. Electrocardiographic changes:

Probably the most interesting and least well understood phenomena are the electrocardiographic changes seen with the use of hypothermia. The usual changes seen include slowing of the rate, widening of the complexes, and changes in the ST segment and the T wave. The changes often resemble those seen with myocardial hypoxia. Various degrees of heart block and ventricular extrasystoles are common below 25 degrees centigrade as are also auricular and ventricular fibrillation.[4,5] Provided ventricular fibrillation or other normally irreversible changes have occurred, the electrocardiographic pattern will usually return to a normal sinus rhythm as normal body temperature is regained.

The chief hazard in the clinical use of hypothermic anesthesia is ventricular fibrillation. Hypothermia increases the incidence of ventricular fibrillation, especially when the body temperature is lower than 26 degrees centigrade.[6] In order to avoid this complication, the level of hypothermia induced during surgical procedures is usually restricted to rectal temperatures above 28 degrees centigrade. The advantages of hypothermia in surgery, however, increase in proportion to the lowering of body temperature.[7]

The etiology and pathophysiology of ventricular fibrillation is not yet elucidated. There are two main hypothesis opposed to each other. One is the "Dissociation Theory", the followers of which postulate the presence of multifocal stimuli in a number of dissociated centers; and the second, the "Theory of Tachysystole" which presupposes a very rapid formation of impulses in a heterotope center (or in the sinus node) where ventricular fibrillation is taken to be a final stage of a still more rapid extrasystole formation. The problem of why ventricular fibrillation occurs so frequently in deep hypothermia, factors in its production, and electrocardiographic changes preceding it, will comprise most of the remaining discussion.

III. Electrocardiographic changes preceding ventricular fibrillation:

Milstein and Brock,[8] in 1954, described three kinds of electrocardiographic changes which they considered indicate stages preliminary to ventricular fibrillation in humans under hypothermia. They include: (1)increased irritability in the form of ventricular extrasystoles and paroxysmal ventricular tachycardia; (2)signs of increased myocardial depression in the form of bundle branch block and constantly increased ST depression with eventual bradycardia; and (3) asystole. In 1957 Johansson, Haeger and Sjostrom[5] reviewed these studies and performed a similar study on dogs anesthetized with pentobarbital under deep hypothermia. The comparison of the electrocardiograms of the dogs that later had ventricular fibrillation with those that had not, resulted in the conclusion that they could not point to any electrocardiographic change which indicated ventricular fibrillation was imminent. The finding of a diagnostic electrocardiographic change revealing imminent ventricular fibrillation would be of obvious clinical significance and much work has been done on this subject.

One electrocardiographic pattern which has appeared rather constantly in experimental work, but which is still debatable as to its prognostic value, is what has come to be known as the "Osborn wave"(since it was first described in detail by Osborn in 1953).[9] It was originally described as a secondary wave closely following the S-wave; so closely in fact that it appeared to be a part of the QRS complex. Osborn felt that this "abnormal" wave following the S-wave represented a current of injury rather than a widening of the ventricular complex due to a conduction defect. He found this current of injury in the electrocardiographic pattern of every animal, but one, under hypothermia that later developed ventricular fibrillation. It usually appeared one-half hour before fibrillation, at rectal temperatures of 25 degrees centigrade, and gradually increased in degree until the usual termination by ventricular fibrillation. He concluded that it was, thus, a bad prognostic sign. Ross,[4] in 1954, from a series of hypothermic dogs, described a similar wave phenomenon which he did not report as the "Osborn wave" but which was followed on a number of occasions by ventricular fibrillation. The objection to the prognostic value of the "Osborn wave" has been the fact that it has also been observed in dogs that did not fibrillate. Haeger, Johansson and Sjostrom[5] observed the "Osborn wave" and found that it appeared constantly in all their animals whether they developed ventricular fibrillation or not. Siebecker and Steinhaus,[10] in 1958, adding mechanical stimulation of the heart during hypothermia, observed the "Osborn wave" in dogs whose hearts did not fibrillate. They also reported that none of the dogs had ventricular fibrillation without exhibiting this wave. They observed the previously mentioned electrocardiographic changes such as bundle branch block, mild deviations of the ST segment, bradycardia and occasional premature systoles. They could conclude no prognostic value from any of these changes. The significance of the "Osborn wave" is thus unknown.

Milstein and Brock,[8] in the "Guy's Hospital Report" of 1954, reported that atrial fibrillation is probably significant when it develops during hypothermia since it is otherwise rare during cardiac operations and was followed by ventricular fibrillation in their cases. Swan,[6] in 1953, reported atrial fibrillation in seven out of fifteen cases using hypothermia for cardiac surgery, but ventricular fibrillation developed in only two. In 1956, Gunton, Scott, Lougheed and Botterell[11] studied electrocardiograms from 29 adult patients in whom hypothermia was induced for neurosurgical procedures. Observations made in this study suggested that auricular arrhythmias are common in human subjects at body temperatures in the range of 28 to 30 degrees centigrade. They found that auricular fibrillation appeared to be a common benign arrhythmia which was limited to the period of lowered body temperature and that it did not produce important hemodynamic disturbances. Auricular fibrillation or other auricular arrhythmias, occurred in nineteen patients two of which developed ventricular fibrillation at 28 degrees centigrade. In conclusion the prognostic value of the electrocardiographic changes preceding ventricular fibrillation are yet to be determined.

IV. Factors in the production of ventricular fibrillation and other arrhythmias with hypothermia:

A. Changes in blood pH and hypoxia:

It is well known that when blood is cooled in vitro it becomes more alkaline. The pH of dog whole blood in vitro increases 0.0147 units per degree centigrade increase in temperature. Fleming,[12] in 1954, made the following observations as regards the acid-base balance in dogs at reduced body temperatures: He found that the average pH of ten dogs prior to cooling was 7.35 while at 20 degrees centigrade it was 7.03. This represented an average drop of 0.016 units per degree centigrade, a change opposite the in-vitro change towards alkalinity. In these same dogs a retention of carbon dioxide was shown by an elevation of the carbon dioxide content of the plasma from 22 milli-equivalents per liter at normal body temperature, to 30 milli-equivalents per liter at 20 degrees centigrade. The pCO_2 rose from 45 to 130 milli-meters mercury. He concluded this change as obviously due to two factors; the diminished respirations and the increased solubility of carbon dioxide in blood at lowered body temperatures. Of what importance then is the relationship of blood pH and ventricular fibrillation?

Swan,[6] in 1953, found that the retention of carbon dioxide had a profound effect upon cardiac action in dogs under hypothermia, presumably due to the associated changes in the blood pH. He reported that dogs made hypercapnic by breathing a 30 percent carbon dioxide mixture for two hours, almost invariably developed ventricular fibrillation if suddenly placed in room air and hyperventilated. On the other hand, if these dogs were slowly brought back to a normal pH by being graduated through stages of serially reduced carbon dioxide in the breathing mixture, no fibrillation occurred. From his data he concluded that ventricular fibrillation may be initiated by sudden rises in the pH from abnormally low levels. Cardiac inflow occlusion was also included in the study and it was shown that if the dogs were not only prevented from becoming hypocapnic during the cooling, but indeed were rendered hypercapnic by over-ventilation, the carbon dioxide did not increase to abnormal heights during the period of cardiac inflow occlusion and the lethal effect of the rapid fall from hypercapnia was prevented. Swan further went on to say that it is not the carbon dioxide per se, but rather its effect on the pH which causes the arrhythmia; the carbon dioxide content of the circulating venous blood (and thus the pH) being merely a mirror of changes going on in the tissues.

Osborn,[9] in 1953, observed a somewhat similar phenomenon. He found that the current of injury that he observed ("Osborn wave") and which he concluded as a bad prognostic sign in production of ventricular fibrillation, was mininal or absent in hypothermic animals in whom he maintained the arterial pH constant by manipulation of the respiration. When the injury current appeared in animals receiving increased respiratory carbon dioxide, he was repeatedly able to cause the wave to decline or disappear by decreasing the concentration of carbon dioxide in the inspired air, or by increasing the resiratory minute volume. From this evidence he concluded that the electrocardiographic changes associated with hypothermia, particularly of the injury current type, may not be associated with the low temperature directly, but rather with the faulty elimination of carbon dioxide under hypothermic conditions. In his animals major changes in pH during hypothermia were significantly associated with high mortality from ventricular fibrillation.

Fleming[12] has also reported studies using increased ventilation in an effort to prevent acidosis in hypothermic dogs. From the moment the dogs were anesthetized until the termination of the experiment, oxygen administered by an endotracheal technique was given under strong positive pressure at a rate varying from ten to twenty breaths a minute. By this means blood pH could be kept constant or made to rise with a simultaneous decrease in the carbon dioxide content of the plasma. The carbon dioxide content could be kept constant or decreased and the pCO_2 decreased slightly. Although minor cardiac irregularities were noted, ventricular fibrillation did not occur in any of the hyperventilated dogs and there was a better survival rate than in the acidotic control dogs.

The above reports seemed to agree almost exclusively that hyperventilation did indeed help prevent ventricular fibrillation in hypothermic dogs. However, in 1954, Niazi and Lewis[13] reported studies the results of which were somewhat controversial to the above. They noted that in hypothermic rats and dogs heart block was common when the temperature dropped below 20 degrees centigrade. They also noted that this complication could be prevented or successfully treated by adding carbon dioxide to the inspired air or oxygen. Of further importance was the observation that ventricular fibrillation in hypothermic dogs could also be significantly reduced by adding carbon dioxide to the inspired air or oxygen. Of ten dogs given oxygen alone during cooling, 40 per cent developed ventricular fibrillation and 70 per cent had heart block. When 2.5 to 11.4 per cent carbon dioxide was given with the inspired oxygen continuously during cooling, in eleven dogs ventricular fibrillation and heart block did not occur. In nineteen dogs when carbon dioxide was given in the first part of cooling and then discontinued, ventricular fibrillation occurred in 21 per cent and heart block in 47 per cent. It was found that when oxygen was given alone for breathing, the pH rose as high as 8.4 even without hyperventilation. This rise in pH was found to be more marked as the temperature dropped below 20 degrees centigrade. The carbon dioxide content of the blood was found as low as 9.0 milli-moles per liter at 10 degrees centigrade. When carbon dioxide was given, this rise in pH was avoided and the pH was either kept within normal limits or decreased. These observers felt that the two extremes of hypo- and hyperventilation could both produce tissue hypoxia and cause cardiac arrhythmias. They implied the best procedure was not to hyperventilate but to give adequate amounts of oxygen plus carbon dioxide and thus avoid both direct anoxia and alkalosis. Lewis suggested that the basic cause of cardiac arrhythmias during hypothermia was hypoxia, whether it followed hypoventilation directly, or whether it resulted as a consequence of alkalosis.

Electrocardiographic changes do occur with hypothermia that resemble those seen with myocardial hypoxia as in coronary occlusion. Swan,[6] in 1953, had already firmly stated that agreement of opinion existed that tissue hypoxia was not a cause of ventricular fibrillation in general hypothermia in the dog. He referred to the work of Bigelow,[14] in 1950, and of Penrod,[15] in 1951, who could find no difference in the arterio-venous oxygen content difference of the coronary blood flow in the normothermic and hypothermic dogs; nor did any change occur when the animals breathed 100 per cent oxygen. These studies were further confirmed by Hegnauer and D'Amato[3] whose studies of oxygen consumption and arterio-venous oxygen difference pointed to the hearts oxygen supply as being adequate until the moment of cardiac arrest or ventricular fibrillation.

Much work has been done since Swan's initial observations in an attempt to determine the best method of ventilation in the hypothermic animal. Fisher and co-workers,[16] in 1955, used self ventilation in their studies and reduced their incidence of ventricular fibrillation.

Covino and Hegnauer,[17] in 1955, using hypothermic dogs under pentobarbital anesthesia, found that without hyperventilation for controll of the systemic pH near normal limits, the incidence of ventricular fibrillation was greater than 60 per cent even without any additional trauma such as ventriculotomy. Moulder and Thompson,[18] in 1956, using hypothermia in cardiac surgery in dogs, found that hyperventilation to a state of alkalosis was associated with considerable pre-surgery ventricular fibrillation and that this phenomenon increased in frequency at the lower body temperatures. They found that maintenance of a near normal acid-base balance, even though it might require self-ventilation during cooling and minimal respiratory assistance when the chest was open, gave them the best results in preventing ventricular fibrillation. The significance of all these observations is dependent on the wide variety of variables that exist in these studies.

B. Electrolyte changes:

After Swan and others reported that prevention of acidosis during cooling was capable of controlling ventricular fibrillation, the suggestion was made that acidosis may exert its deleterious effects via a change in the electrolyte balance of the heart. The serum potassium levels have a profound effect upon the function of cardiac muscle. The reciprocal relation of calcium and potassium in their effect on cardiac muscle has been repeatedly demonstrated. It was important therefore to rule in or out electrolyte changes as a related factor in the production of ventricular fibrillation in the hypothermic animal.

Swan,[6] in 1953, found that the serum potassium levels in the cooling hyperventilated dog consistently fell. When fifteen minutes of coronary inflow occlusion was added the potassium levels fell during cooling but following occlusion were considerably higher than before. Swan postulated that during the circulatory arrest the potassium must accumulate in the tissue spaces and upon resumption of the blood flow appear rapidly in the serum. From his studies, Swan concluded that during hyperventilation and cooling there was a shift of potassium within the body since more of the ion leaves the extracellular space during the cooling period than appears in the urine. He presumed that the potassium must enter the cells since it was not in the urine. He also noted that this shift of potassium ion was more profound as temperatures decreased further. Hyperventilation alone, without the influence of hypothermia, depressed the serum potassium but the exact relationship was not clear. Then in 1954, Swan[19] repeated studies on pH and the potassium concentration of the myocardium. He observed that regardless of whether the animal is started on hyperventilation and switched to hypoventilation (low pH), the heart during cooling is taking up potassium; whereas when the animal remains on hyperventilation (high pH) throughout the cooling process, the heart maintains potassium balance, neither gaining nor losing significant amounts. This was determined by measuring the arterio-venous difference in plasma potassium concentration across the coronary circulation in the hypothermic dog. He concluded that an acidotic, hypoventilated, hypothermic myocardium gains potassium and is subject to fibrillation; and whenever the myocardium enters fibrillation, potassium is released from the heart.

In 1955, Covino and Hegnauer[20] studied the electrolyte changes and their possible role in production of arrhythmias during hypothermia in dogs. They found that sodium, chloride and magnesium apparently played no observable role in the production of ventricular arrhythmias in dogs at low temperatures, but that potassium, calcium and hydrogen ions did. Their data suggested that the ventricular excitability and the extrasystolic activity observed in acidotic hypothermic dogs was the result of a myocardial exchange between intracellular potassium and hydrogen ions and extracellular calcium ions. In this study, arterial and coronary venous concentrations of sodium, chloride, magnesium, potassium, calcium and hydrogen ions were measured in normo- and hypercapneic dogs subjected to immersion hypothermia. Myocardial exchange between intracellular potassium and hydrogen ions and extracellular calcium ions was observed only in those hypothermic acidotic dogs that succumbed to ventricular fibrillation. All dogs suffering fibrillary deaths exhibited a positive calcium coronary arterio-venous difference and a negative hydrogen ion difference. From the above studies it has been concluded that during hypothermia a shift of potassium ions does take place in an intracellular direction and continuing until interference with coronary flow or ventricular fibrillation occurs. This hypothesis is supported by the observation of reduced serum potassium levels without corresponding increase in urinary potassium excretion. A shift of potassium distribution points to its contributing to the high frequency of fibrillation—the more so as other ions which could be thought to be of significance (sodium, and magnesium for example) are only slightly, if at all, influenced by hypothermia.[21]

C. Mechanical stimulation:

There are many other factors which act as variables in the production of cardiac arrhythmias during hypothermia. One of these which has been observed for a long time is mechanical stimulation of the heart. This is obviously a very important factor and one not avoidable during cardiac surgery. Swan,[6] in 1953, stated that in his experience there were three periods during hypothermia when animals are prone to develop ventricular fibrillation: (1) during cooling below 26 degrees centigrade without cardiac manipulation, or circulatory arrest; (2) during cardiac manipulation, particularly ventricular incision; and (3) immediately following restoration of circulation after inflow occlusion. There seems to be no doubt that in the cold state, the dogs myocardium is extremely irritable and mechanical stimuli can produce fibrillation. Siebecker and Stienhaus,[10] in studying the effects of mechanical stimulation, felt that many of the hypothermic dogs in their series developed ventricular fibrillation upon stimulation, whereas they would have progressed to deeper levels of hypothermia without ventricular fibrillation if the stimulation had been omitted.

Covino and Beavers[22] attempted to measure ventricular fibrillary thresholds by determining the minimum electrical stimulus needed to induce a fibrillary state in dogs subjected to immersion hypothermia. In their studies the fibrillary threshold represented the mininal stimulus, in terms of strength of current and duration, which could produce ventricular fibrillation when applied during the prediastolic period of the cardiac cycle. Direct quantitative measurements of both the basic ventricular threshold and the ventricular fibrillary threshold were made in dogs prior to and during progressive immersion hypothermia. No change in basic ventricular threshold was observed as rectal temperatures fell from 38 to 22 degrees centigrade, while at the same time, the ventricular fibrillary threshold showed a five-fold dedrease.

The best fibrillary stimulus in dogs seems to be ventriculotomy.[6] Radigan and Lombardo[23] found that mechanical stimulation of the interventricular septum was an important factor in consistently producing ventricular fibrillation in hypothermic dogs. In spite of this they did observe an occasional dog's heart which would tolerate the procedure without fibrillation.

D. Age of the animal and other factors:

Another interesting but not easily explained phenomenon, has been the not infrequent observation that the age of the dog will affect the mechanism of death and the ability to tolerate acute hypothermia. Maquire[24] did the most complete studies on this problem using two groups of mongrol dogs, one group of adult and the other juvenile (those with deciduous teeth). The animals were cooled until death occurred, the end point estimated by electrocardiographic evidence of ventricular fibrillation or cardiac arrest. Results showed that the terminal event in all of the mongrol adult dogs was ventricular fibrillation, whereas the terminal event in the juvenile dogs was cardiac arrest in all. This was explained on the basis of a difference in the metabolic activity of the myocardium of each age group.

There is some evidence that man too may vary in his response to hypothermia in different age groups. Gunton and Scott,[11] in 1956, studied the electrocardiograms of twenty-nine adult patients in whom hypothermia was induced for neurosurgical procedures. They found that patients who maintained sinus rhythm throughout the period of hypothermia tended to be in a younger age group than those who developed cardiac arrhythmias. Also Bailey[25] has suggested that in the human, the age of five years is the best age for hypothermic anesthesia since he found a lower incidence of ventricular fibrillation in this age group.

Choice of the anesthetic agent is involved in the production of cardiac arrhythmias in animals under hypothermia. Animal studies suggest that ventricular fibrillation is less common with one type of anesthetic than another. This has not been conclusively established in man. Covino, Charleson and D'Amato[26] state that ventricular fibrillation occurs less frequently in dogs receiving theopental or ether than in those receiving pentobarbital in the hypothermic state. Further McCrory and Virtue[27] indicate that sodium pentobarbital may have a protective effect on cardiac irritability during hypothermia while cyclopropane showed no such effect. The effects of ether were somewhat intermediate between those of the other two agents. Examples of studies concerning this problem are many and will not be included here.

Just to mention some of the other factors that have been observed and speculated upon as important in the production of cardiac arrhythmias during hypothermia include: the rate of cooling of the animal, cold acclimatization,[22] presence of shivering during the cooling period, circulatory stasis, high venous pressure,[26] increase in sympathetic impluses to the heart, changes in enzyme systems and others much less incriminated.

V. Summary:

The effects of hypothermia on the cardiovascular system are many. Outstanding in importance, from a clinical aspect, is the incidence of serious cardiac arrhythmias as body temperature falls. The problem as it stands today is whether hypothermia, as a valuable adjunct to anesthesia and surgery, can remain, or whether the adverse cardiovascular effects it can produce in the range of usefulness will outweigh its value. Research continues for a better understanding of the effects of hypothermia so that it might be applied clinically more advantageously and with greater safety to the patient.

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