THE CARDIOVASCULAR EFFECTS OF ACUTELY INDUCED HYPOTHERMIA [1,2]

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Under the conditions of relatively constant body temperature which exist in warm blooded animals including man, the physiological variations occurring in circulatory functions such as blood pressure, cardiac output, and circulatory rate are small. This relative constancy has led to the development of the concept of circulatory homeostasis. In recent years there has been a growing appreciation that the warm blooded animal may survive at greatly reduced body temperature during which marked circulatory changes may occur. The interdependence of the several cardiovascular functions has indicated the need for a correlation of the circulatory adjustments which occur during such progressive hypothermia. Only in this manner would it be possible to interpret the significance of the changes and their respective roles in the integration of the animal under the stress imposed by the hypothermia. Such studies may also have value in the development of rational therapy for individuals who have undergone prolonged exposure to cold.

METHOD

Fifteen heparinized dogs were anesthetized with intravenously administered sodium pentobarbital. Three animals were used as controls and 12 were cooled. Nine of these latter were maintained in a lighter and three in a deeper plane of anesthesia. The results were compared with those of six other dogs, in a parallel study (1), subjected to hyperthermia.

Respiratory rate and oxygen consumption were recorded with a basal metabolism apparatus attached to a tracheal cannula. Kymographic tracings of arterial blood pressure were obtained from the femoral artery

with a mercury manometer. Pulse rates were obtained from electrocardiograms taken simultaneously with the other measurements.

Cardiac output was calculated from the oxygen consumption and the arteriovenous oxygen difference according to Fick's formula (2). Two radio-opaque cardiac catheters were introduced through the external jugular veins and, with the aid of fluoroscopy, the distal ends were placed in the right auricle and in the pulmonary artery, respectively. The proximal ends of the catheters were connected with saline manometers for the recording of mean pressures. The location of the catheters and their zero pressures were verified at post-mortem examination. To ensure maximal mixing of the blood returning to the heart, samples of venous blood were taken from the pulmonary artery. Arterial blood was obtained from the cannulated femoral artery. In the course of each experiment, 100 to 150 cc. of blood were withdrawn and replaced with isotonic saline solution. The Van Slyke-Neill technic (3) was used in the analysis of blood O_2 and CO_2. Hematocrits were determined by the Wintrobe method (4), arterial blood being employed.

Control measurements were made when the blood pressure and respiration of the animal became stabilized. The animals were then covered with chipped-ice packs. Body temperatures were recorded from thermometers placed deeply in the rectosigmoid area and protected from the ice packs. The mean cooling period was about two hours during which the body temperatures fell to 29° C. The animal was then dried, covered with thin sheets, and exposed to radiant heat. However, the body temperatures continued to fall to 27° C, before beginning to rise. The mean rewarming period lasted five to six hours, at the end of which body temperatures usually had returned to 37° C. Ten or 11 determinations were obtained in each experiment, measurements being taken after each 2 degree change of body temperature.

Evaluation of the method

Measurements of right auricular and pulmonary arterial pressures represent only the approximate mean values. The *changes* in pressure were considered to be of greater significance. During periods of extreme bradypnea resulting from severe respiratory center depression, great variations in concentration of blood gases occur during each respiratory cycle, and this produces errors in the direct Fick method. This inaccuracy is further increased by the fact that the usual means of collecting blood samples makes it impossible to obtain exactly
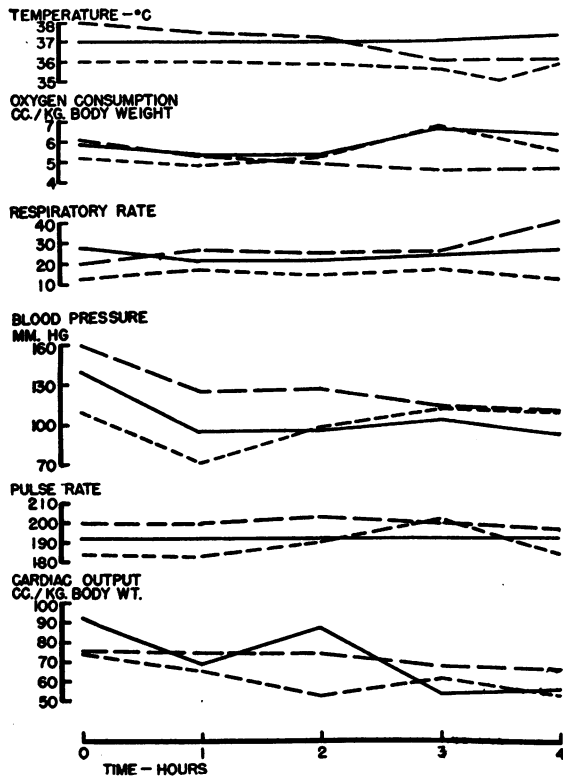
FIG. 1. COMPOSITE GRAPH OF DATA OBTAINED FROM THREE CONTROL DOGS, ANESTHETIZED BUT NOT SUBJECTED TO COOLING, DURING FOUR-HOUR PERIOD

Values for oxygen consumption and cardiac output are given in cc./kg./min. Respiratory and heart rates are in frequency per minute. The results in each individual dog are indicated by a different type of line.

simultaneously withdrawn arterial and mixed venous blood. These samples were drawn within 10 seconds of each other. This error is shown by the progressive accumulation of carbon dioxide in both arterial and venous bloods during apneic periods. Thus arterial blood taken at the end of apneic periods may contain more carbon dioxide than is found in venous blood withdrawn at the beginning of the respiratory cycle. For this reason, data obtained during marked bradypnea are not used in the conclusions of this study, although these are included in the tables.

Measurements similar to those described above were obtained over four-hour periods in a control group of three dogs, anesthetized but not subjected to cooling procedures (Figure 1).

The site from which true mixed venous blood can be obtained has been a controversial point, and has been discussed by many investigators in connection with the application of the direct Fick method in man. In the latter instance it has been demonstrated that there are only slight differences between blood taken from the right ventricle or pulmonary artery and that from the right auricle provided that the catheter tip is placed near

the tricuspid valve orifice. A different situation exists in dogs, our experience having shown that the oxygen content of blood taken from the right ventricle or pulmonary artery may differ markedly from that of the right auricle. We therefore adopted catheterization of the pulmonary artery as a more exact technic. Even greater errors may be introduced when venous blood is taken from the inferior vena cava due to the presence of more highly oxygenated renal venous blood which is poorly mixed with that from other viscera.

DISCUSSION OF RESULTS

Oxygen consumption

The initial values for oxygen consumption lay within a relatively small range, 4.0 to 6.6 cc./kg./min. In the control series no significant changes in oxygen consumption occurred during the four-hour period of observation (Figure 1). In eight cooled dogs there was a progressive decrease in oxygen consumption as body temperature fell. In two less deeply anesthetized animals the oxygen consumption increased from 4.7 to 10.8 and from 4.0 to 4.7 cc./kg./min. during shivering, and then suddenly decreased. In two other dogs the oxygen consumption did not vary significantly until body temperature fell to 31°C. Very little variation was noted in the pattern of change after the temperature fell below 31°C. The lowest oxygen consumption was 1.4 cc./kg./min. During rewarming periods there was a progressive increase in oxygen consumption in all instances. Data on three deeply anesthetized animals are given in Figure 2.

The direct relationship which was found between oxygen consumption and body temperature is similar to the results of other investigators in dogs (5). Variations in oxygen consumption up to 200% which we observed in the four less deeply anesthetized dogs mentioned above were associated with marked shivering and increase in pulse rate. There is general agreement that shivering causes an increase in oxygen consumption (6). Visible shivering occurred at temperatures as low as 29° C in our experiments and did not prevent further drop in body temperature. Figure 3 represents an experiment in which marked shivering did not prevent further fall in body temperature. It should be noted that the rate of temperature change during both the cooling and rewarming periods was not altered by marked shivering. The administration of 100% oxygen did not inhibit or delay the
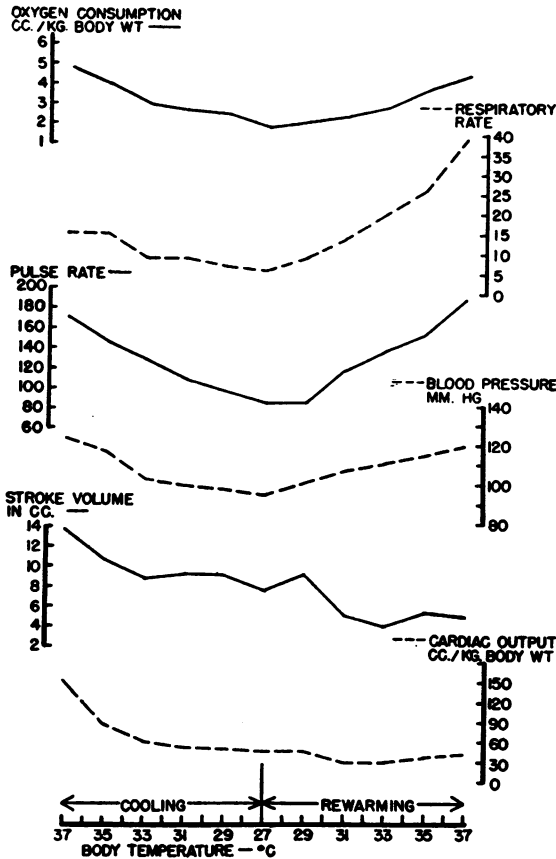
FIG. 2. A COMPOSITE GRAPH OF AVERAGE DATA OB-
TAINED FROM THREE DEEPLY ANESTHETIZED ANIMALS
DURING COOLING AND REWARMING

It should be noted that the cardiac output failed to
increase during the rewarming period despite the ac-
celeration of the heart rate. Values for oxygen consump-
tion and cardiac output are given in cc./kg./min., pulse
rate is in beats per minute.

onset of shivering although such effects have been
reported by others (7).

Respiratory rate

In the control series there was very little change
in the respiratory rate (Figure 1). During both
cooling and rewarming a close correlation between
the respiratory rate and body temperature was
found. This direct relationship was seen in the
three deeply anesthetized (Figure 2) and in most
of the less deeply anesthetized dogs. In two in-
stances transient increases in respiratory rate
from 28 to 40/min. and from 6 to 15/min. oc-
curred during the early cooling period. The ini-
tial rates varied from 6 to 28/min. and at the

lowest temperature varied from 0.5 to 7/min. ex-
cept in one dog. In this animal the lowest rate
was 22, this dog maintaining a high rate during the
entire experiment. In almost every case, the low-
est respiratory rate occurred at the lowest body
temperature. Following rewarming the range of
variation in the rates was greater than that prior
to cooling. Similar results have been obtained
by others in animals (4, 8).

Pulse rate

The direct relationship found between changes
in body temperature and pulse rate is shown in
Figure 2. During the induction of cooling, in-
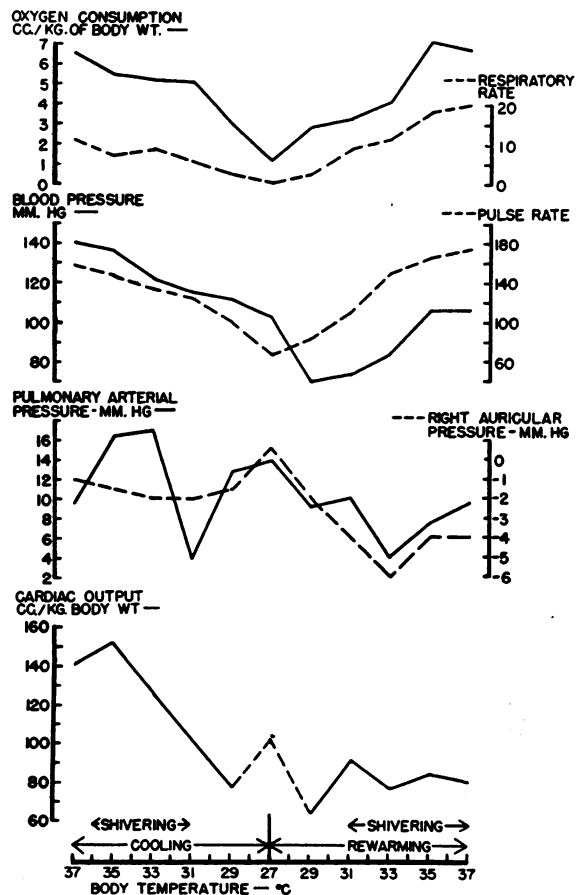creases in pulse rate occurred in the two animals

FIG. 3. A COMPOSITE GRAPH SHOWING THE EFFECT OF
SHIVERING IN ONE DOG

It should be noted that the curves obtained in this ani-
mal do not differ significantly from those obtained from
dogs in which shivering was absent (Figure 2). Values
of oxygen consumption and cardiac output are given in
cc./kg./min.

in which the rates were measured immediately after the ice was applied, although there was visible shivering in only one dog. In both there were transient increases in pulse and respiratory rates and blood pressure. After these initial changes an almost linear relationship was found, the changes in pulse rate closely paralleling the changes in body temperature. The lowest pulse rate was 59/min. occurring at 27° C. In the control series very slight changes were noted (Figure 1).

Similar results have been described by others (6). The direct effect of cold on the sinus pacemaker appears to be responsible for the variations in heart rate. The absence of changes in the control series lends support to the assumption that the changes are not due to the anesthetic.

Electrocardiogram

Electrocardiograms (Lead II) were taken simultaneously with other measurements in 11 dogs. The progressive sinus bradycardia occurring during cooling has already been discussed. There were no marked abnormalities of the P waves but the P–R intervals increased progressively as the heart rate slowed. A gradual widening of the ventricular complexes occurred during cooling, being maximal at the lowest temperatures in all but one dog. The average duration of the QRS complex was 0.062 seconds prior to cooling and this was doubled at 27° C. At the lowest temperatures an intraventricular block with notched S wave was noted in all but one animal. Figure 4 illustrates the relationship between the body temperature and QRS duration. Electrical systole, calculated from Bazett's formula (9), was progressively increased from a normal value for K of 0.33 to 0.43 at 29°C (Figure 4). An elevation of the S–T segment was observed in nine dogs and a depression in one dog. In two dogs the T wave reversed its direction and in four there was a decreased amplitude. No change in T wave was noted in four dogs. Ventricular premature beats were seen in three dogs and in two instances, ventricular fibrillation developed.

The initial effect of cooling is on the heart rate and on the duration of electrical systole. Change in contour and duration of ventricular complexes and S–T–T changes occur later. The effect of cooling on repolarization in the ventricles is seen

before the effect on depolarization. All these changes were entirely reversible during the rewarming phase. The observed abnormalities are probably a direct effect of cold on the metabolic processes in the myocardium, since similar changes occur with direct application of cold (10). A more severe hypothermia than we used has been reported to induce auricular fibrillation and A–V block (11), but we did not observe these effects.

Blood pressure

Sodium pentobarbital anesthesia induces a fall in blood pressure, apparently via a direct effect on the vasomotor center and this is often associated with a spontaneous fall in body temperature (12). In confirmation of this we noted in the control series a fall in temperature of as much as 2° C, associated with a decrease in mean blood pressure during the first two hours of anesthesia; after this, the pressure was maintained at the lower level in two dogs and returned to control values in the third (Figure 1).

A slight but transient rise in blood pressure usually occurred immediately after the application of the ice packs. Shivering usually elicited further increases as great as 25%, but in two dogs, despite shivering, mean blood pressures fell 6% and 17% respectively. The fall in blood pressure which occurred during the early phase was
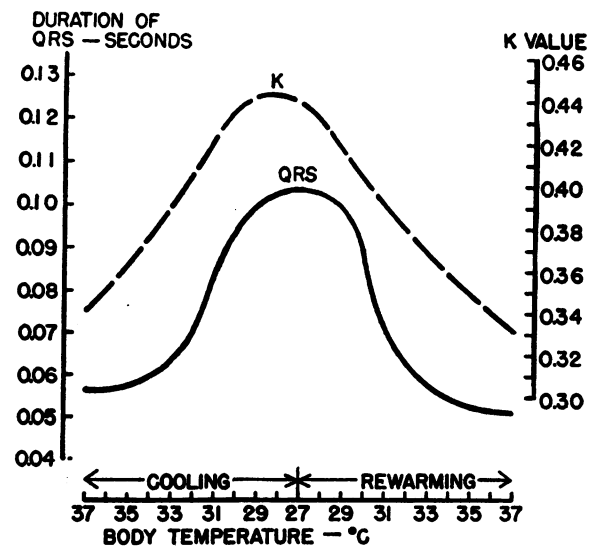

FIG. 4. RELATIONSHIP OF BODY TEMPERATURE TO ELECTROCARDIOGRAPHIC CHANGES
Discussed in text.

TABLE I

Cardiac output (cc./kg./min.) changes during cooling and rewarming

Dog no.	Cooling temperature ° C.								Warming temperature ° C.						
	38°	37°	35°	33°	31°	30°	29°	28°	27°	29°	31°	33°	35°	37°	38°
C2	150		70	59	56						36	34	46	49	
C7	175			43	47		39	30			30	29		46	
C11		144	100	83	66		63	35‡		73	29	29	35	31	
C1	82	98*	111*	76*		129*		22			21	30	18†		
C3	72		96*		121*		53		46	77*	43	44	144†		
C5	63		143*	92			104‡		80‡	95*	68	64	57	66	66
C8		112	65	86	88		40		101‡		78	67	82		
C9		75		39	173		42†			63					
C10	141		155	113*	168*		79		100‡	63			72	86	80
C12			200		77		†								

* Shivering.   † Dog died shortly afterward.   ‡ Extreme bradypnea. Estimation inaccurate.

not great in most instances and not markedly different from the changes observed in the control series. However, during prolonged cooling, there was a tendency to a progressive fall in blood pressure and at the lowest body temperature in the dogs that survived, mean pressures had fallen to as low as 54% of the original level (Figure 2). During rewarming there was a consistent rise in blood pressure, the latter returning almost to initial values when the body temperature returned to 37° C.

This laboratory has previously called attention to a relationship between body temperature and blood pressure which may be demonstrated in several species of animals. In these, lowering of the temperature is accompanied by a fall in blood pressure (13, 14). Certain data in the literature on the effect of cooling on the blood pressure of man (15), and animals (16) are in accord with this concept. However, other data (17) show that the blood pressure may be maintained at control levels in cooled anesthetized rats until the body temperature falls below 29° C. Proskauer *et al.* (18) found that in rats an initial decrease was followed after 30 minutes of cooling by a rise in blood pressure. These responses may be a part of the homeostatic mechanisms which maintain the body temperature at normal levels, and in the face of a falling temperature maintain the blood pressure for a period.

Cardiac output

Control values for cardiac output in these and other dogs that we have studied averaged 112 cc./kg./min. and varied from 60 to 175 (Table I).

In the deeply anesthetized dogs there was a marked decrease in output during cooling and a small increase during rewarming (Figure 2). The lowest outputs occurred, not at the lowest body temperatures, but during the early rewarming periods, and these ranged between 35% and 56% of the control values. There were greater variations in cardiac output in the six less deeply anesthetized dogs. In 10 of the 12 dogs, there was a definite increase in output as great as 126% during the first period of cooling. These changes were associated with shivering, increased oxygen consumption and pulse rate, or a combination of these factors. For example, dog C1, which shivered violently during early cooling, showed an increase of oxygen consumption from 64 to 146 cc./min., of respiratory rate from 28 to 40 and of pulse rate from 176 to 196. The sudden rise in output in dog C9 at 31° C was related to an acute fall in arterial oxygen content which persisted until sudden vasomotor collapse led to death. This sudden increase in output may have been due to the acute anoxia but the etiology of the sudden drop in arterial oxygen content could not be accounted for. Complete recovery from cooling was not achieved as can be seen from the fact that the final values for cardiac output during rewarming were only about 50% of the original values. Increases in output during rewarming of the less deeply anesthetized dogs were more rapid and of a higher order and almost returned to the original values.

In two dogs of the control group there was a fall in cardiac output coincident with a spontaneous fall in body temperature up to 2° C (Figure 1). The reduction in cardiac output may have been due

partly to an anesthetic action and partly to the reduction of body temperature. No change in either body temperature or cardiac output occurred in the third control dog.

Right auricular and pulmonary arterial pressures

The mean right auricular pressure was measured in 10 dogs during cooling and in three controls, and was found to lie in the range of ± 1 mm. Hg in the control state (compared to the atmospheric pressure). In the control group variations occurred, usually in a negative direction, the largest being − 2 mm. Hg. In the animals which were cooled the changes were as great as − 5 mm. Hg.

The mean pulmonary arterial pressure was measured in eight cooled and three control dogs. The initial values lay in a range of 7 to 12 mm. Hg except in one dog in which it was 15 mm. Hg. In both control and cooled dogs there were rapid and substantial variations in pressures as much as 6 mm. Hg. The pressure changes were not consistent and bore no relationship to pulse rate, blood pressure, stroke volume or cardiac output.

With the development of the direct Fick method in man, much attention has been paid to the right auricular pressure and its relation to cardiac output. McMichael and his group (19) have promulgated the idea that within physiological limits in the compensated heart, the cardiac output changes concordantly with right auricular pressure but this concept has recently been criticized (20, 21). In our experiments there was no relationship between mean right auricular pressure and stroke volume, pulmonary arterial pressure, blood pressure or work of the right heart in either the cooled or the control series. Changes in the mean right auricular and mean pulmonary arterial pressures usually occurred in the same direction but were not proportional and on occasion the direction of change was discordant.

Hemoconcentration

Hematocrits were taken periodically in 10 dogs. It should be noted that about 100 to 150 cc. of blood were withdrawn and replaced with isotonic saline solution during each experiment. There was an average increase in the hematocrit value of 10% at the lowest temperatures with a tendency to hemodilution during rewarming. Barbour (22) has demonstrated a reflex which originates in

chilled skin and is mediated via the hypothalamus, to produce a shift in the body fluids from the circulating blood to the interstitial spaces in hypothermic states.

Causes of death

Five animals died in the course of these experiments. Cardiac failure has been suggested as a cause of death in hypothermia in man (23), in dogs (5) and in rats (17). However, this view is not substantiated by our observations. One death was due to ventricular fibrillation which occurred early in the cooling period; ventricular premature beats were frequent from the onset of the experiment and in this case an irritating effect of the intracardiac catheter could not be excluded. In three dogs there was a sudden fall of blood pressure prior to the cessation of respiration. This occurred during rewarming at body temperatures of 35° C in one dog, at 34° C, in another, and in the third dog it occurred at 27.5° C. Marked bradypnea and respiratory irregularity developed soon after the blood pressure fell and respiration ceased shortly thereafter. In these dogs the pulse rates were 146, 120 and 90/min. respectively, and the cardiac outputs were at high levels during the period immediately preceding the fall in blood pressure. We must conclude that in such cases there was a sudden vasomotor paralysis. In the fifth dog there was a primary central respiratory arrest. A sudden anoxic rise in blood pressure occurred and this was followed by a progressive fall in pressure. In this case the vasomotor center was able to respond to anoxia in a normal manner. Artificial respiration was instituted and the heart continued to beat for about two hours after respiratory arrest. Therefore, in our cases death was due to failure in the central nervous system either of the respiratory or of the vasomotor centers, as stated in some other reports (5, 24). In more prolonged and more intense hypothermia employed by others, other causes may be involved.

GENERAL COMMENTS

The present studies, correlated with those of other investigators, make possible a more complete analysis of the hemodynamic changes occurring during hypothermic states. Figure 2 represents a composite graph in which the relationship between the hemodynamic factors which we have

studied and changes in body temperature can readily be seen. The general effect of cold on all body tissues is to reduce progressively all cellular metabolic processes in accordance with van't Hoff's Law. Early in the cooling period of a warm blooded animal such as the dog, reflexes are stimulated which tend to decrease the loss of heat and to increase the rate of endogenous heat production, thus tending to maintain the body temperature at normal levels. Some of these reflexes result in a reduction in peripheral blood flow, shivering and redistribution of body fluids. The cardiovascular response during this early period is manifested by tachycardia, elevated blood pressure and increased cardiac output, as was observed early in the cooling of the lightly anesthetized animals. Anesthesia tends to inhibit these protective reflexes to some extent but shivering can be seen in most anesthetized animals during cooling.

As cooling becomes more intense and more prolonged there develops a progressive bradycardia, bradypnea, decreased oxygen consumption, decreased cardiac output and hypotension. The metabolic demands of the tissues for oxygen and substrate are so markedly decreased that true anoxia must be minimal despite a reduced availability of oxygen. This accounts for the failure of the administration of 100% oxygen to be of benefit or to prolong life during hypothermia. At very low body temperatures a progressive respiratory center depression occurs, due to the effect of cooling, and in our experiments to the effect of anesthesia. This depression may markedly reduce the oxygen supply and lead to the death of the animal in anoxia. During this phase of respiratory failure, oxygen and artificial respiration should be of value.

The depressant effect of cold on all body tissues holds true for the myocardium itself. This is reflected by the development of progressive sinus bradycardia, abnormalities in depolarization and later in repolarization, prolongation of electrical systole and the development of intraventricular block, as well as prolongation of auriculo-ventricular conduction time. The direct effect of cold on the heart is well shown by the development in the isolated heart preparation of changes similar to those described above. We observed no evidence of an inability of the heart to deal satisfac-

torily with the venous return of blood from the periphery.

The marked decrease of cardiac output which occurred during cooling is primarily the result of changes in the peripheral circulation. There is a progressive decrease in the circulating blood volume with the development of hemoconcentration, due to a shift of body fluids from the vascular bed into the interstitial spaces. These factors tend to reduce the venous return to the heart and to decrease the cardiac output. There are certain compensatory mechanisms, however, as is shown by the maintenance of the blood pressure at relatively high levels in the face of a markedly reduced cardiac output. These facts may thus be considered as evidence that marked peripheral vasoconstriction occurs, partially compensating for the decreased blood volume and cardiac output. When these compensatory mechanisms fail to meet the stress produced by hypothermia, vasomotor collapse occurs and leads to death.

All the changes which we observed were entirely reversible upon rewarming, and the recovery of function was in general related to the degree of rewarming accomplished. Thus the heart and respiratory rates, the blood pressure and the cardiac output tended to return to control values as the animal approached its normal body temperature. This would suggest that the induction of hypothermia in a warm blooded animal such as the dog may not be an altogether unphysiological procedure, in the sense that the compensating adjustment patterns, which appear during the cooling and the rewarming periods, are ordinarily capable of coping with the situation, within limits.

SUMMARY

1. Circulatory changes and cardiac output were studied in 12 dogs during cooling induced by exposure to chipped ice packs and during rewarming, and in three control dogs.

2. During the early cooling period, thermogenic reflexes which cause shivering are set off which act to produce an increase in oxygen consumption, respiratory and heart rates, blood pressure and cardiac output. These reflexes may be inhibited to some extent by deep anesthesia.

3. As cooling continues, and the combined depressing effects of hypothermia and anesthesia act, hemoconcentration and a progressive fall in oxy-

gen consumption, in respiratory and heart rates, and in blood pressure occur. The cardiac output also falls. Marked prolongation of electrical systole, with the occurrence of intraventricular and A–V block, and changes in the S–T–T contour are seen. The changes in these values are related to the degree of hypothermia obtained.

4. During rewarming, these effects are reversed with a return of the blood pressure, respiratory rate, and pulse rate to normal, and with a tendency to a return to normal in the degree of hemoconcentration and cardiac output. Electrocardiographic changes were also reversed.

5. When it occurred, death in hypothermia was attributable to failure of the vasomotor or respiratory centers, rather than to failure of the heart.

6. No consistent correlated changes in right auricular pressure, on the one hand, and pulmonary arterial pressures, cardiac output, or the work of the right heart, on the other, were observed during either the cooling or rewarming periods.

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