Posthypothermic Circulatory Failure

I. Physiologic Observations on the Circulation

By Emil Blair, M.D., A. Vernon Montgomery, Ph.D., and Henry Swan, M.D.

Certain aspects of cardiovascular function were studied in dogs that were cooled to 30 C. without ventilatory assistance, and rapidly rewarmed in warm water. While in the hypothermic state, the animals appeared to make an adequate cardiovascular adjustment to the lowered body temperature. Upon rewarming, however, each animal incurred an acute circulatory collapse, which was characterized by a low cardiac output, diminished ventricular work, hypotension, hyperpnea, and increased arteriovenous oxygen difference. It is uncertain whether this circulatory failure is central or peripheral in origin.

Following experimental hypothermia in the dog cooled to temperatures as low as 20 C., the animal will return to a normal physiologic state upon rewarming.1-7 The deaths that did occur were categorized into essentially 3 groups: (1) ventricular fibrillation or cardiac asystole, (2) circulatory collapse, and (3) respiratory collapse.

On the other hand, some animals were not normal physiologically for some time after rewarming even if they survived. Bigelow3 found a low cardiac output in 1 animal for one hour following rewarming. Reduced cardiac output has also been shown by Prec and co-workers,9 by Ross,10 and by Sabiston and associates.11

The present report concerns the cardiovascular status of the dog cooled to the moderate level of 30 C. and rapidly rewarmed. It has been found that the animal rapidly rewarmed develops acute circulatory failure, which persists for at least three hours.

Method

Apparently healthy mongrel dogs in the weight range of 12 to 38 Kg. were used. The experiments were done from October 1954, through April 1955.

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Food and water were withheld for a period of 12 hours prior to the study. No premedication was administered. The animals were anesthetized with chloralose, 100 mg./Kg. The agent was dissolved in boiling saline solution, cooled to body temperature, and kept in a warm bath to prevent crystallization. Under fluoroscopic vision two 8 cardiac catheters were introduced into the right heart. One of these was placed into the right or left pulmonary artery and the other into the right atrium. A femoral artery was cannulated with a no. 18 Cournard needle. An endotracheal catheter was made airtight by a ligature around the trachea placed through a small wound in the neck. The animal was heparinized, 3 mg./Kg. A rectal thermometer was inserted into the sigmoid for recording of temperature changes. Lead II of the electrocardiogram was monitored continuously on an oscilloscope. Respirations were unassisted, but were recorded at regular intervals.

Pressures were transmitted to a strain-gage amplifier and recorded on a multichannel oscilloscope-type recorder. Mean pressures were either electronically integrated or computed with a compensating planimeter. Expired air samples were analyzed by the Scholander method, duplicate samples were accepted if within an error of 0.06 volumes per cent. Blood gas determinations were done by the Van Slyke-Neill method, with duplicate samples falling within a margin of 0.2 volumes per cent. The expired air from the tracheal catheter was collected in Douglas bags, measured in a Tissot spirometer, and corrected for volume at standard conditions (STPD). The pH was determined with a Beckman pH meter with the water bath adjusted to the temperature of the animal. Cardiac output was calculated by the Fick principle, and stroke volume was computed from the output and the rate. From the output and the mean arterial pressure, the total peripheral resistance

* Manufactured to our specifications by Electronics for Medicine, Inc., White Plains, New York.
(TPR) and the work of the left ventricle (LVW) were computed as follows:

1. \[ TPR = \frac{BPm}{Q/T} \quad (1332) \]  
   wherein,

   \[ TPR = \text{resistance in dynes seconds/cm}^5 \]
   \[ BPm = \text{mean pressure in systemic artery in mm. Hg} \]
   \[ Q/T = \text{cardiac output in ml./sec.} \]
   \[ 1332 = \text{conversion factor from mm. Hg to dynes/cm}^5 \]

2. \[ LVW = \frac{(CI \times 1.055)(BPm \times 13.6)}{1000} \]  
   wherein,

   \[ LVW = \text{work in Kg. M./min./M}^2 \]
   \[ CI = \text{cardiac index} \quad \text{in L./min./M}^2 \]
   \[ 1.055 = \text{specific gravity of blood} \]
   \[ BPm = \text{mean blood pressure in mm. Hg} \]
   \[ 13.6 = \text{specific gravity of Hg} \]

Following anesthetization, a period of 30 minutes was allowed in order to reach a steady state before baseline normothermic studies were made. Then the animal’s hair was clipped (no depilation was done), and the animal was immersed in a bath of ice water up to its neck. It was removed from the ice bath when the rectal temperature dropped to 32 C. The temperature continued to fall another 2 C. Observations were made again at this time and also an hour later at the same temperature (30 C.). The animal was then placed into a warm bath 42 to 45 C. and rewarmed rapidly. When the rectal temperature returned to 35 C., the animal was removed and dried thoroughly. Studies were made at the end of the rewarmin period and again three hours later when the temperature had risen another degree to 36 C.

Blood was replaced, milliliter for milliliter, immediately after withdrawal of samples. The blood was not previously cooled. The amounts of transfusion were so small that they did not noticeably affect the blood gas content or rates of cooling.

During cooling, anesthesia was maintained at a level sufficient to depress shivering because shivering markedly prolongs the process and predisposes the animal to cardiac irregularities, particularly ventricular fibrillation. During the period of cooling, muscle relaxation must be complete to permit rapid induction of the state of hypothermia. Curare or curare-like agents were not employed because artificial or assisted respiration was not used, and partial or complete respiratory arrest in early stages of cooling is undesirable.

During the rewarmin period no attempt was made to control shivering, and only enough anesthetic agent was supplied to keep the animal asleep during the technical manipulations of the study. Shivering was not controlled at this time for several reasons: (1) interest was centered on the effect of rapid rewarmin and, consequently, the process of shivering, a normal response of the temperature-regulating mechanism of the dog, was permitted; (2) the procedure currently used in cooling and rewarmin patients was followed; (3) in the dog shivering during rewarmin is very active so that its depression would require massive supplemental anesthesia, possibly resulting in marked alterations in physiologic chemistry and circulatory dynamics.

A control series of dogs studied under chloralose anesthesia alone revealed none of the cardiovascular changes to be described.

**RESULTS**

Acceptable data were obtained in 15 animals. Of these, studies were done three hours after warming in 8. Five deaths occurred in the entire group at intervals of 1 to 12 hours after rewarmin. All the data are tabulated in table 1.*

Considerable variation was observed from animal to animal and during the periods immediately following a change in temperature; there was much less variation during a steady environmental state. Upon cooling and also on rewarmin, there was considerable scatter in the measured values, especially in the A – V \( O_2 \) difference and in the \( TPR \). There was less variation from one animal to the other upon entering a steady state.

Upon cooling to 30 C., there was a significant decrease in mean femoral artery pressure with little change noted after one hour of a steady state of hypothermia (fig. 1). At the same time, the peripheral resistance also became elevated. The heart rate declined. Upon rewarmin, the hypotension persisted although the peripheral resistance remained high. The heart rate returned to normal levels, but did not exceed them, despite the persistent hypotension.

The cardiac index declined considerably upon cooling with no significant change in A – V \( O_2 \) difference (fig. 2). No change was noted an hour later. On cooling, the work of the heart (LVW) decreased approximately 60 per cent. Upon rewarmin, the A – V \( O_2 \) difference increased immediately often to a

* In comparing any two groups of data in this study, a \( p \) value of < .05 was accepted as significant.
Table 1.—Summary of Data—Cooling to 30 C. and Rewarming

<table>
<thead>
<tr>
<th></th>
<th>Normothermia</th>
<th>Hypothermia</th>
<th>Rewarmed</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>36 C.</td>
<td>30 C.</td>
<td>30 C. 1 hour</td>
</tr>
<tr>
<td></td>
<td>Mean S.D.</td>
<td>Mean S.D.</td>
<td>Mean S.D.</td>
</tr>
<tr>
<td>Femoral artery pressure mm. Hg</td>
<td>120 ± 28</td>
<td>92 ± 20</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Right atrial pressure mm. Hg</td>
<td>2 ± 2</td>
<td>0.5 ± 1.9</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Heart rate per minute</td>
<td>140 ± 40</td>
<td>98 ± 35</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>A-V O₂ difference vol. %</td>
<td>4.30 ± 1.30</td>
<td>4.90 ± 2.20</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Cardiac index L/min./M²</td>
<td>4.26 ± 0.80</td>
<td>1.62 ± 0.57</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Left ventricular work Kg.M./min./M²</td>
<td>7.76 ± 1.87</td>
<td>2.31 ± 0.87</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Minute ventilation L./min./M²</td>
<td>4.64 ± 1.48</td>
<td>1.56 ± 0.65</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Oxygen consumption ml./min./M²</td>
<td>161 ± 23</td>
<td>70 ± 20</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Total peripheral resistance dynes cm.²/M²</td>
<td>2600 ± 700</td>
<td>5900 ± 3000</td>
<td>&lt;.005</td>
</tr>
</tbody>
</table>

* Compared with normothermia
† Compared with initial hypothermia
POSTHYPOTHERMIC CIRCULATORY FAILURE

FIG. 1. Vascular physiologic effects during hypothermia and rewarming (mean values). The arterial pressure and the peripheral resistance fail to return to normal on rewarming.

FIG. 2. Cardiac index, atriovenous oxygen difference, and left ventricular work during hypothermia and rewarming. On rewarming the cardiac index is low, the arteriovenous oxygen difference increases, and the left ventricular work is below normal.

greater than normal figure, with a persistent low cardiac index. At this time, the LVW increased, but not to normal. Three hours after rewarming the A – V O₂ difference continued to increase, with a continued low cardiac index and decreased LVW. In short, no significant improvement occurred in the circulation during the three hours following rewarming.

As might be expected with unassisted respiration, respiratory acidosis developed, but it disappeared on rewarming (fig. 3).

The total oxygen consumption decreased about 50 per cent on cooling to 30 C. (fig. 4). One hour later there was no significant change. Upon rewarming, however, the consumption rose to levels above control and three hours later was even greater.

Figure 5 illustrates these characteristic changes in one animal. In some animals the changes were less extreme and the return to normal on rewarming was more pronounced; in others, the changes were greater and the animals succumbed.
A linear correlation was found between total oxygen consumption and cardiac output in normal, hypothermic, and rewarmed animals (fig. 6). Both variables decreased proportionately in the cold state, indicating that circulation was adequate for the oxygen demand. As seen in figure 7, however, in the rewarmed animal the output rose relatively less than oxygen consumption. The circulation was therefore inadequate for the oxygen demand.

**Discussion**

A major physiologic effect of cooling is lowered body metabolism.\(^5,^{12}\) In consequence ventilation is reduced, as is cardiac activity (manifest by slow heart rate, low cardiac index, reduced ventricular work, and lower blood pressure) with subsequent decrease in blood flow in both the greater and lesser circuits. With some exceptions,\(^9,^{11}\) investigators generally observed that animals tolerated cooling and rewarming well and returned to normal in all respects upon rewarming.

Data from the present study concerning hypothermia at 30 C. of one hour's duration, corroborated part of this view: that the animal adjusts adequately to a state of hypothermia. Upon rapid rewarming, however, a striking abnormality, which can be described as circu-
latory failure, persisting for at least 3 hours, was observed consistently in every animal.

Upon rewarming to normothermia, the animal became hyperpneic and oxygen consumption increased. During this period of time shivering was active. The blood pressure, which fell during hypothermia, failed to rise, although the heart rate returned to the control level. Clinical signs of circulatory collapse appeared, indicated by a pale dry tongue and overbreathing. The A – V O₂ difference widened markedly and there was a low cardiac index, decreased left ventricular work, and persistently elevated resistance to blood flow. At this time, the circulation was not adequate; survival depended on maximal extraction of oxygen from the hemoglobin. We believe this phenomenon results from serious decrease in effective circulating blood volume or myocardial failure.

During the cooled state, it seems probable that blood is shunted into reservoirs and the reduced cardiac output is adequate during the hypothermic state. Upon rewarming the cardiac output and blood flow do not return to normal, but a state of circulatory shock develops, with continued low output. The mechanisms involved in reduction of effective circulating blood volume may be a failure of homeostatic mechanisms to release blood from reservoirs into the effective circulation and an overexpansion of the capillary bed with a peripheral trapping of blood. Despite the severe degree of hypotension, tachycardia that is ordinarily seen in states of low volume circulatory collapse was absent. The state of the heart during hypothermia should be reviewed before consideration of possible myocardial dysfunction in the rewarmed state. Anoxia of the heart during hypothermia has been reported with resultant circulatory collapse. Adequate myocardial oxygenation has been indicated, however, by other investigators and ourselves in finding no change in the A – V O₂ of the myocardium. Our observations confirm the latter view. Furthermore, even with unassisted ventilation, there was adequate oxygenation at the temperature level studied. There appears to be no myocardial inadequacy during hypothermia.

It has previously been demonstrated that in acidosis the myocardium enters a positive K+ balance. According to Szent-Györgyi, this positive balance leads to a decrease in the tension developed during ventricular contraction. The net result of these myocardial metabolic derangements would be a reduced ventricular efficiency, manifest by a lowered ability to work and a consequent low output. This sequence has not yet been definitely established, however. The oxygenation and potassium balance of the myocardium at this stage of the posthypothermic state will be the subject of a subsequent report.

The normal right atrial pressure in the rewarmed animal is inconsistent with myocardial insufficiency; with prolonged reduction of cardiac output the venous return should become overpowering if the effective circulating blood volume has been restored. Furthermore, pulmonary hypertension, which is a frequent accompaniment of acute myocardial failure, was absent in the present study.

It is possible, of course, that even in the absence of direct myocardial muscular derangements during rewarming, the circulatory collapse might affect the myocardium secondarily with the same net results.

The nature of this posthypothermic circulatory failure is unclear at present. The problem is of great importance, however, for the proper understanding and management of general hypothermia. Further studies are in progress in this laboratory.

**SUMMARY AND CONCLUSIONS**

Dogs under chloralose anesthesia with unassisted respiration were subjected to a rectal temperature of 30 C. for one hour and rewarmed rapidly.

In the hypothermic state the cardiovascular system in the majority of the animals appeared to adjust adequately to the change in environment for the period observed.

Upon rewarming, every animal developed acute circulatory collapse, characterized by low cardiac output, diminished ventricular work, hypotension, hyperpnea, increased A – V O₂ difference, and increased total oxygen consumption.

The exact mechanisms for the circulatory
failure are not known, although it is suggested they may involve diminished effective circulating blood volume or myocardial insufficiency or both.

**Acknowledgment**

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**Summario in Interlingua**

Canes sub anesthesi a chloralosa sin assistentia respiratoria eseva subjicte durante un hora a un temperatura rectal de 30 C e recetafacite rapidemente.

In le stato hypothermic le sistema cardiovascular del majoritate del animales pareva adjustar se adeguatemente al ambiente alterate durante le periodo del observation.

Post recetafactione, omne le animales developpava un acute collapso circulatori, caracterisate per basse rendimentos cardiaci, reducite labor ventricular, hypotension, hyperpnea, augmentate differentia atrio-ventricular de O₂, e augmentate consumption total de oxygeno.

Le exacte mecanismos del disfallimento circulatori non es cognoscite, sed nos postula le possibilitate que illos involve un reduce effective volumine de sanguine circulante o insufficientia myocardial o ambe iste factores.

**References**

Posthypothermic Circulatory Failure: I. Physiologic Observations on the Circulation

EMIL BLAIR, A. VERNON MONTGOMERY and HENRY SWAN

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