The Effect of Immersion Hypothermia on Coronary Blood Flow

By ROBERT M. BERNE, M.D.

In severe hypothermia resistance in the coronary vascular bed is reduced and flow continues despite very low aortic pressure. Moderate artificial acceleration of the hypothermic heart at constant coronary perfusion pressures produces a decrease in coronary blood flow. This decrease in flow is roughly proportional to the increase in heart rate and is due to the longer periods of extravascular compression in each cardiac cycle. Epinephrine produces transient improvement in blood pressure and coronary blood flow but is followed in a matter of minutes by ventricular fibrillation.

The low blood pressure, the prolonged state of ventricular contraction and the increase in blood viscosity in hypothermia have led some investigators to postulate that coronary blood flow is greatly reduced at low temperatures. However, the marked bradycardia and the possible dilating effect of cold on the coronary vessels, as seen in vitro and in the heart-lung preparation, would augment coronary flow. In this investigation an attempt has been made to assess the relative importance of these various factors in contributing to the changes observed in coronary flow in the hypothermic dog.

METHODS

Experiments were completed on 13 dogs weighing between 14 and 22 Kg. The animals were anesthetized with intravenously administered pentobarbital (30 mg. per kilogram). The chest was opened in the third left intercostal space and respiration was maintained artificially. Following the administration of heparin, the circumflex branch of the left coronary artery was cannulated near its origin and perfused via the subclavian artery. A pump perfusion system was placed in parallel with the arterial perfusion system, thereby permitting adjustment of perfusion pressure to any desired level at different stages of hypothermia regardless of aortic pressure. Coronary blood flow was measured by an optically recording rotameter. Mean coronary perfusion pressure and phasic aortic pressure were recorded by modified Gregg manometers. In some experiments, left ventricular and left atrial pressures were also registered. Temperatures in the coronary inflow cannula, the right atrium, and the rectum were recorded by a Leeds and Northrup Micromax instrument. The blood cell/plasma ratio was determined periodically throughout the experiment and kept reasonably constant by the administration of appropriate quantities of 0.9 per cent sodium chloride solution. This was done because the degree of hemoconcentration reached during severe hypothermia was found to be greater in open chest than in closed chest dogs. Unless hemoconcentration was avoided altogether it would be impossible to assess how much would be attributable to hypothermia alone.

Following control observations, approximately two-thirds of the body surface of the dog was immersed in ice water, care being taken to prevent either ice or water from entering the chest cavity. Cold narcosis obviated the need of additional pentobarbital.

RESULTS

Aortic Pressure and Coronary Blood Flow.

After immersion of the dog in ice water, observations were made of body temperature, heart rate, blood pressure and coronary flow until death occurred two to four hours later. In figure 1 the heart blood temperature, arterial pressure, and coronary blood flow are plotted against time for a representative experiment. It is evident that as right atrial temperature declined from 39.5 C. to 28 C., aortic pressure decreased slowly, whereas below 28 C. it dropped sharply. In this experiment pulse pressure diminished during the first 87 minutes of immersion, remained essentially unchanged during the succeeding hour, and then increased...
slightly in the late stages of hypothermia at temperatures of 20 to 22 C.

In contrast to aortic pressure, coronary blood flow decreased sharply in the early stages of hypothermia, declined more gradually as blood temperature fell from 33.5 C. to 21.5 C., and then remained relatively constant in the late stages of hypothermia when blood temperature was reduced to 20 C. This constancy of coronary blood flow occurred during the last half-hour of the experiment despite a further decrease in aortic pressure.

In figure 2, data from all 13 experiments are plotted as pressure/flow curves for the duration of the experiments. The average values of all experiments are represented by the heavy line. Although there are numerous differences in the contours of the pressure/flow curves, it is apparent that at low pressures (severe hypothermia) the rate of decline of coronary blood flow is less per unit decrement of perfusion pressure than at higher pressures (moderate hyperthermia).

Elevation of Perfusion Pressure. In order to determine to what extent the great reduction in coronary blood flow is dependent upon the decrease in arterial pressure, perfusion pressure was increased toward or to control levels by means of the pump perfusion system. A representative experiment is depicted in figure 3 in which the perfusion pressure was elevated in a stepwise fashion when heart blood temperature had reached 21 C. Curve A represents the pressure/flow relationship as hypothermia developed, and curve B the coronary blood flow obtained at 21 C. when perfusion pressure was artificially elevated. It can be seen that at comparable pressures coronary blood flow was

![Figure 1](image1.png)  
**Fig. 1.** Effect of reduction in body temperature on aortic pressure and coronary blood flow (C.B.F.) in a representative experiment.

![Figure 2](image2.png)  
**Fig. 2.** Pressure/flow relationships in hypothermia in all experiments. Heavy line represents the average values.

![Figure 3](image3.png)  
**Fig. 3.** Effect of increasing coronary perfusion pressure in severe hypothermia. Curve A is the pressure/flow curve in progressive hypothermia. Curve B represents the flows obtained at blood temperature of 21 C. when perfusion pressure was artificially elevated.
TABLE 1.—Effect of Elevation of Perfusion Pressure on Coronary Blood Flow, Aortic Pressure and Heart Rate in the Hypothermic Dog

<table>
<thead>
<tr>
<th>Exp.</th>
<th>Right Atrial Temperature (°C)</th>
<th>Coronary Perfusion Pressure (mm. Hg)</th>
<th>Coronary Blood Flow (cc./min.)</th>
<th>Aortic Pressure (mm. Hg)</th>
<th>Heart Rate (beats/min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>21.0</td>
<td>Without pump, 37</td>
<td>4.0</td>
<td>45/30</td>
<td>75</td>
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<tr>
<td></td>
<td>21.0</td>
<td>With pump, 112</td>
<td>36.0</td>
<td>48/30</td>
<td>76</td>
</tr>
<tr>
<td>9</td>
<td>21.0</td>
<td>Without pump, 62</td>
<td>18.5</td>
<td>80/51</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>21.0</td>
<td>With pump, 87</td>
<td>38.5</td>
<td>81/51</td>
<td>46</td>
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<tr>
<td>13</td>
<td>25.5</td>
<td>Without pump, 58</td>
<td>11.0</td>
<td>65/54</td>
<td>57</td>
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<tr>
<td></td>
<td>25.5</td>
<td>With pump, 121</td>
<td>37.5</td>
<td>67/52</td>
<td>60</td>
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<tr>
<td>16</td>
<td>19.0</td>
<td>Without pump, 46</td>
<td>14.0</td>
<td>67/40</td>
<td>31</td>
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<tr>
<td></td>
<td>19.0</td>
<td>With pump, 117</td>
<td>74.5</td>
<td>68/41</td>
<td>32</td>
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<tr>
<td>18</td>
<td>21.5</td>
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<td>10.5</td>
<td>55/29</td>
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<td>With pump, 58</td>
<td>74.5</td>
<td>54/28</td>
<td>37</td>
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<tr>
<td>26</td>
<td>20.5</td>
<td>Without pump, 106</td>
<td>18.0</td>
<td>118/92</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>With pump, 124</td>
<td></td>
<td>32.0</td>
<td>110/93</td>
<td>26</td>
</tr>
</tbody>
</table>

greatly in excess of that observed during the reduction of blood temperature from 40 to 20 C. Coronary blood flow at 122 mm. Hg was too great to be recorded by the optical system employed.

Because of (1) the limited oxygen reserve of coronary venous blood, (2) the shift of the oxyhemoglobin dissociation curve to the left with cold, and (3) the low coronary blood flow that obtains in hypothermia, the effect of increasing coronary flow on cardiodynamics was also studied. In severe hypothermia, coronary blood flow was increased as much as ninefold by elevation of perfusion pressure (table 1).

We were surprised to find that in none of the six experiments in which this was done was a significant change in aortic pressure or heart rate observed.

Cardiac Acceleration. Since heart rate determines the temporal ratio of systolic to diastolic coronary flow, the effect of acceleration of the hypothermic heart on mean flow was examined. This is illustrated in figure 4. The solid line represents the terminal segment of the pressure/flow curve (A) of figure 3, that is, when flow was diminishing from 22 to 10 cc.

per minute. When the heart rate had decreased to 19 beats per minute (encircled number) at 20 C., an increase in rate to 55 beats per minute by artificial stimulation of the left auricle caused coronary blood flow to decrease to zero (downward arrow at right). With resumption of a heart rate of 20 beats per minute, perfusion pressure was elevated to 63 mm. Hg pressure, which raised coronary flow to 33 cc. per minute. An increase in heart rate to 46 beats per minute at this time reduced flow to 21 cc. per minute (middle downward arrow). When heart rate was permitted to return to a control rate of 20 beats per minute, a further increase in perfusion pressure to 77 mm. Hg elevated coronary flow to 43.5 cc. per minute. Cardiac acceleration to 42 beats per minute resulted in a fall of flow to 33 cc. per minute (left downward arrow). In the first two instances in which the heart rate was accelerated there occurred a slight decrease in perfusion pressure. However, the depression of coronary blood flow was proportionately greater than the reduction in perfusion pressure. Furthermore, at the perfusion pressure of 77 mm. Hg coronary flow decreased with cardiac acceleration despite a slight rise in perfusion pressure.

In each of the four experiments in which the cooled heart was accelerated, a reduction in
coronary flow occurred, and the magnitude of this reduction was roughly proportional to the increase in heart rate. Cardiac acceleration of from 50 to 70 beats per minute reduced coronary blood flow to zero and was frequently accompanied by a decrease in aortic pressure and an increase in left atrial pressure. Attempts at greater cardiac acceleration produced arrhythmias, a drastic fall in aortic pressure, and in one instance, ventricular fibrillation.

**Effect of Epinephrine.** In five experiments at blood temperatures of 19 to 21.5 °C, epinephrine was administered intravenously and produced an increase in coronary blood flow, aortic pressure, and heart rate (table 2). However, in each instance ventricular fibrillation ensued within a few minutes. Left ventricular pressure curves were recorded in experiments 13 and 14 and showed that epinephrine approximately doubled the rate of ventricular relaxation.

**DISCUSSION**

The first question that arises in connection with these observations is; how do coronary flow and arterial pressure alter in control open chest experiments, two to four hours in duration? While this naturally depends on the condition of the dog and on technical precautions, it has been found in previous studies in this department that animals in good condition maintain a reasonably constant circulatory state for at least four hours. Opdyke and Foreman have published pertinent data of control experiments employing techniques essentially similar to those in the present study.

In the early stages of hypothermia coronary blood flow decreased sharply at a time when mean arterial pressure was relatively well maintained. However, in the late stages the slope of the coronary pressure/flow curve (fig. 2) indi-
cates a proportionately greater decrease in blood pressure than in coronary blood flow. In order to interpret these findings, it is necessary to consider the individual factors that may affect coronary blood flow in hypothermia.

Perfusion pressure is a major determinant of coronary blood flow. In the normothermic open-chest dog in which heart rate and cardiac work remain constant, abrupt changes of perfusion pressure produce equally abrupt changes of flow in the same direction. However, despite the maintenance of perfusion pressure at the new height, flow returns toward control levels within a few seconds and stabilizes near or at these levels depending upon the degree of pressure change produced. It appears that in the normothermic dog coronary blood flow is intrinsically adjusted to cardiac metabolic needs. Such an adjustment of flow to the myocardial needs can be invoked to explain the sharp decrease in coronary blood flow in the early stages of hypothermia when the decline in arterial pressure is small. With moderate reduction of body temperature cardiac work is decreased by virtue of the diminished cardiac output as evidenced by bradycardia and reduced stroke volume and the slight reduction in aortic pressure.

It need not be construed that metabolic factors are responsible for the maintenance of flow in severe hypothermia. In fact this is clearly shown not to be a factor of any importance, since elevation of perfusion pressure in severe hypothermia yielded coronary blood flows greatly in excess of those obtained at identical pressure during the earlier stages of temperature reduction. Were metabolic requirements the primary regulators of coronary blood flow in severe hypothermia, the reduced metabolic rate should have resulted in lower rates of flow than those obtained at the same perfusion pressure but at higher body temperatures and greater cardiac work loads.

Blood viscosity increases in hypothermia owing to the decrease in temperature of the blood and because of an increase in the blood cell/plasma ratio. The latter was not a factor in our experiments, since this ratio was kept relatively constant by the intravenous administration of isotonic sodium chloride solution. However, cooling of blood from normal body temperature to 20°C produces about a twofold increase in relative apparent viscosity. Since no valid data on the effect of increased blood viscosity on coronary flow are available, the extent to which this increase in viscosity would retard coronary flow at low blood temperatures cannot be accurately estimated.

The degree of extravascular compression is significantly altered in severe hypothermia and therefore is capable of influencing coronary blood flow. On the one hand, the reduced ventricular pressure and the longer periods of diastole offer less impedance to coronary inflow; on the other hand, the low aortic pressure that obtains with long diastolic pauses and the extended periods of systole and isometric relaxation tend to reduce coronary inflow. It is possible that the long diastole accounts, in part, for the relatively greater coronary flow at very low temperatures and pressures. However, it cannot be of major importance, since only slight increase in heart rate, produced by stimulation of the left atrium, resulted in marked reduction in coronary blood flow. This decrease in coronary flow which accompanied cardiac acceleration may be due to the total prolongation of extravascular compression per minute. At heart rates of 50 to 70 per minute, coronary flow was completely throttled, since the hypothermic ventricle was in a state of partial contraction throughout the cardiac cycle.

It is evident from the experiments in which perfusion pressure was restored to control levels that in severe hypothermia the resistance of the coronary bed is decreased and none of the factors so far discussed can adequately account for it. Cruickshank and Subba Rau have presented evidence that segments of coronary arteries, perfused with Ringer's solution or defibrinated blood, are contracted at normal body temperature and relax upon cooling, whereas systemic arteries exhibit the opposite response. Anrep and Häusler, employing the hot wire anemometer to measure coronary blood flow in the dog heart-lung preparation, reported that cooling of the blood perfusing the cannulated coronary artery produced an increase in flow. Therefore, in our experiments one must scri-
ously consider the possibility that the reduced temperature of the blood acts directly on the coronary vessels to produce vasodilatation.

Since coronary blood flow is reduced to about one-fourth of its control level in hypothermia and coronary resistance is diminished, the question arises whether the heart is in a state of chronic anoxia due to an insufficient blood supply. The fact that as much as a ninefold increase in blood supply to the major part of the left ventricle failed to alter heart rate or aortic pressure, plus the observation of Penrod that the hypothermic heart is capable of extracting oxygen from blood as effectively as the normothermic heart, strongly suggest that the heart is receiving an adequate blood supply for the work it is performing. Furthermore, the vessels of the cooled heart show a decrease in resistance with anoxia. This can be demonstrated by temporarily interrupting the coronary flow. When coronary circulation is re-established, flow increases above that observed prior to the interruption of flow. Although the subsequent return of flow to previous levels is slower than that seen in the normothermic heart the response to anoxia is qualitatively the same.

The intravenous administration of epinephrine proved to be a hazardous procedure in severe hypothermia. Circulatory dynamics were temporarily improved, but ventricular fibrillation soon supervened. The onset of ventricular fibrillation is possibly due to a discrepancy between oxygen requirements and supply induced by epinephrine in the presence of a lowered threshold to ventricular fibrillation produced by cold. The moderate increase in heart rate caused by epinephrine did not interfere with ventricular filling, as when the cooled heart is electrically stimulated, because the rate of cardiac relaxation was accelerated by epinephrine to the point where relaxation was complete before the onset of the next systole. This effect of epinephrine on the rate of relaxation has been previously described by Opdyke in the normothermic heart.

Cardiac acceleration in the hypothermic rat, accomplished by means of warming the S-A node via the esophagus, was found by Crismon and Elliott to increase arterial pressure. However, a similar procedure in the dog was ineffective. It is possible that this failure to improve circulatory dynamics in the dog by warming the S-A node may have been due to the detrimental effect of cardiac acceleration of the cold heart on cardiac filling and on coronary blood flow.

Application of these findings to hypothermic man suggests that epinephrine is contraindicated, and that an increase in ventricular rate, as might occur with atrial fibrillation (a relatively frequent complication in hypothermic man) may precipitate acute circulatory failure.

**SUMMARY**

Progressive generalized hypothermia was produced experimentally in the anesthetized open-chest dog by immersion in ice water. Coronary blood flow decreased proportionately more than arterial pressure in the early stages, whereas the reverse was true when blood temperature was reduced below about 28°C. The initial disproportionate reduction in coronary flow appears to be related to the decrease in cardiac work (cardiac slowing, diminished pulse pressure and slightly reduced blood pressure), and possibly represents an intrinsic adjustment of coronary blood flow to cardiac metabolic needs.

In severe hypothermia coronary resistance was reduced since artificial elevation of coronary perfusion pressure yielded flows much greater than those obtained at identical pressures in the early stages of hypothermia. This decrease in coronary resistance could not be adequately explained by the bradycardia and the possibility remains that it is due to a direct effect of cold on the coronary vessels.

With coronary perfusion pressure held constant, attempts to restore heart rate to control levels by means of electrical stimulation of the left atrium were attended by decreases in coronary blood flow. In severe hypothermia cardiac acceleration to 50 to 70 beats per minute completely abolished coronary blood flow and seriously interfered with cardiac filling.

Administration of epinephrine increased heart rate, blood pressure, and coronary blood flow, but was shortly followed by the onset of ventricular fibrillation.
REFERENCES


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