Influence of Cooling the Heart on Reactive Hyperemia of the Coronary Bed in the Heart-Lung Preparation

By Henry S. Badeer, M.D.

The effect of cooling the heart on the characteristics of reactive hyperemia (RH) of the coronary vessels has not been investigated, although such studies have been conducted in the intact and sympathectomized limbs of man,\(^1,2\) and in the blood-perfused hindlimbs of cats (unpublished studies of Pappenheimer, Rapela and Badeer).

The purpose of the present study was to investigate the quantitative aspects of the RH of the coronary vessels at different hypothermic temperatures of the working myocardium. The dog heart-lung preparation (HLP) served as the experimental preparation.

Methods

Mongrel dogs of both sexes weighing 11 to 20 kg were anesthetized with pentobarbital sodium, (30 mg/kg iv). Bilateral vagotomy and mid-sternal thoracotomy were performed. The phrenic nerves were excised and the left coronary artery was dissected at its origin. Subsequently, the conventional HLP was established using defibrinated blood from donor dogs anesthetized with chloroform. The lungs were ventilated with 100% oxygen at a tidal volume of 150 to 200 ml and a frequency of 14 per minute. A Gregg coronary cannula was connected to the arterial side of the circuit with a recording Shipley-Wilson rotameter of 200 ml capacity interposed between the two. The left coronary artery was cannulated by way of the left subclavian artery. Aortic pressure was monitored with a mercury manometer connected to a Sanborn transducer, model 267A. Coronary flow and arterial pressure were recorded by means of a Sanborn polyviso recorder.

Cardiac output was set between 700 and 900 ml/min and the mean arterial pressure at 100 mm Hg. In a few pilot experiments, the temperature of the blood in the venous inflow cannula was compared with that of the left ventricular myocardium registered by means of a needle electrode of a Yellow Springs tele-thermometer. The values checked so well that in all the experiments to be reported the temperature of the blood in the venous cannula was recorded and taken to represent the myocardial temperature.

Under normothermic conditions, RH was induced by clamping the left coronary inflow for a period of 10 seconds. Subsequently, the temperature of the heart was lowered by cooling the water bath. At about 30°C, RH was again recorded in response to 10-second occlusion. The procedure was repeated at 25°C, which is the lowest temperature compatible with regular heart beats in the HLP. The experiments were concluded not later than 90 minutes after the completion of the HLP. During the cooling period, blood was taken for hematocrit determinations.

At the termination of each experiment the perfusing blood was used for the calibration of the rotameter. A Dale-Schuster pump served to deliver various flow rates. Calibrations were done at 37, 30, and 25°C blood temperatures. The wet weight of the whole heart and that of the left ventricle (including the septum) were determined.

Results

In a few preliminary experiments the influence of the duration of the heart-lung preparation (after completion) on the magnitude of RH was investigated. Figure 1 shows the results of such an experiment. The rectangular area between the occlusion (O) and release (R) of the coronary artery represents the "blood flow debt" incurred during the period of circulatory arrest and the area above the level of control flow represents the excess blood flow during the hyperemic period (RH) or the "repayment" of the blood flow debt. The hyperemic response was quantified by measuring the area of excess flow with a planimeter and comparing it with
Reactive hyperemia in response to 10-second occlusions (between "O" and "R") of the left coronary artery at various intervals after the completion of the HLP. Temperature 36.7°C. Heart weight 72 g. Note the progressive increase of control coronary flow and the constancy of peak flow during RH.

The influence of cooling the heart on the magnitude of RH of the left coronary artery is summarized in table 1. The results of a typical experiment are shown in figure 2. It is seen that cooling the myocardium from 37°C to 25°C reduces markedly the magni-
## Table 1

Heart-Lung Preparation: Effect of Hypothermia and Rewarming of the Heart on Reactive Hyperemia in the Left Coronary Artery in Response to Ten-second Occlusions

<table>
<thead>
<tr>
<th>Exp. no.</th>
<th>Dog weight &amp; sex</th>
<th>Heart weight Left ventricle</th>
<th>Heart temp.</th>
<th>Control left coronary flow</th>
<th>Blood flow RH</th>
<th>Repayment of blood debt</th>
<th>Peak flow during RH</th>
<th>Duration of RH</th>
<th>Hematocrit</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>11 M</td>
<td>73 kg</td>
<td>36.7 °C</td>
<td>3.8 ml/min</td>
<td>3.8 ml</td>
<td>13.4 ml</td>
<td>112 ml/min</td>
<td>21</td>
<td>%</td>
</tr>
<tr>
<td>5</td>
<td>15.5 M</td>
<td>115 kg</td>
<td>36.7 °C</td>
<td>5 ml/min</td>
<td>5.7 ml</td>
<td>8.7 ml</td>
<td>88 ml/min</td>
<td>12</td>
<td>%</td>
</tr>
<tr>
<td>6</td>
<td>14 F</td>
<td>91 kg</td>
<td>36.7 °C</td>
<td>6 ml/min</td>
<td>6 ml</td>
<td>18.7 ml</td>
<td>165 ml/min</td>
<td>24</td>
<td>%</td>
</tr>
<tr>
<td>7</td>
<td>16 M</td>
<td>111 kg</td>
<td>36.9 °C</td>
<td>14 ml/min</td>
<td>14 ml</td>
<td>30 ml</td>
<td>190 ml/min</td>
<td>17</td>
<td>%</td>
</tr>
<tr>
<td>8</td>
<td>18 F</td>
<td>127 kg</td>
<td>36.8 °C</td>
<td>9 ml/min</td>
<td>9 ml</td>
<td>31.7 ml</td>
<td>184 ml/min</td>
<td>32</td>
<td>%</td>
</tr>
<tr>
<td>9</td>
<td>15 M</td>
<td>135 kg</td>
<td>36.8 °C</td>
<td>11 ml/min</td>
<td>11 ml</td>
<td>33 ml</td>
<td>188 ml/min</td>
<td>30+</td>
<td>%</td>
</tr>
<tr>
<td>10</td>
<td>16.5 F</td>
<td>118 kg</td>
<td>37 °C</td>
<td>22 ml/min</td>
<td>22 ml</td>
<td>415 ml</td>
<td>175 ml/min</td>
<td>30</td>
<td>%</td>
</tr>
<tr>
<td>11</td>
<td>20 M</td>
<td>140 kg</td>
<td>38 °C</td>
<td>23 ml/min</td>
<td>23 ml</td>
<td>45 ml</td>
<td>28 ml/min</td>
<td>29</td>
<td>%</td>
</tr>
<tr>
<td>12</td>
<td>13 F</td>
<td>93 kg</td>
<td>38.7 °C</td>
<td>25 ml/min</td>
<td>25 ml</td>
<td>59 ml</td>
<td>146 ml/min</td>
<td>13</td>
<td>%</td>
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<tr>
<td>13</td>
<td>13 M</td>
<td>85 kg</td>
<td>36.7 °C</td>
<td>27 ml/min</td>
<td>27 ml</td>
<td>32 ml</td>
<td>188 ml/min</td>
<td>14</td>
<td>%</td>
</tr>
</tbody>
</table>

M = Male. F = Female. RH = Reactive hyperemia. Cardiac output = 700 to 900 ml/min. Arterial pressure = 100 mm Hg.
Effect of cooling (B, C) and rewarming (D) the heart on the magnitude and duration of reactive hyperemia of the coronary bed. Ten-second occlusions between "O" and "R."

Figure 2

Magnitude, duration, and peak flow of the hyperemic response. In normothermia, the repayment is far in excess of the debt. With 10-second occlusions, RH averaged 431% of the coronary flow debt and lasted about three times as long as the period of occlusion. Peak flow during RH was 4.7 times the control value.

When heart temperature was lowered to 30°C, the flow repayment averaged 228% of the debt and lasted 1.6 times the period of occlusion. Peak flow was only 3.1 times the control flow. At 25.6°C, the repayment of flow debt dropped to 143%, with further shortening of the duration of RH. The peak flow averaged 2.5 times the control value.

On rewarming to 36.4°C, there was recovery of the reactive hyperemic response but the percentage repayment was not back to the initial value. This may be due, at least partly, to the augmentation of coronary flow with time, as noted in control experiments (fig. 1). Furthermore, in many experiments it was found that the flow after RH did not readily return to the pre-occlusion values. In such cases, it was not possible to calculate the repayment accurately. The measured RH areas tended to be smaller than the true values.

The coronary blood flow at 25.6°C was not significantly different from that of the control at 36.7°C, despite the fact that blood viscosity increases at low temperatures. This indicates that cooling causes a dilatation of the coronary vessels. In the heart-lung preparation, part of the dilatation may be related to the time factor. On rewarming, the flow increased to about twice the initial value, confirming an observation reported previously. This dilatation may be due partly to the effect of the duration of the preparation.

Discussion

Pappenheimer has reported that RH disappears completely in isolated blood-perfused hindlimbs of cats and dogs after 60 minutes of perfusion. It was, therefore, necessary to know whether or not the perfused myocardium in the HLP exhibited a similar trend. Preliminary studies showed that RH
in the coronary bed of the HLP persisted for the duration of the preparation (two to four hours), with a tendency to decline after 60 minutes of perfusion. The peak flow during RH did not change appreciably with the duration of the preparation, whereas the control coronary flow showed a gradual increase. The latter is a well-known observation in the HLP. Its exact mechanism has not been elucidated. It seems likely that the decline in repayment of blood debt with time is due, at least partly, to the increase of control coronary flow and thereby the greater blood flow debt for a given period of occlusion.

It has been reported that RH in the coronary bed is very marked, even with occlusions as short as five seconds. Presumably this is related to the high metabolic rate of the working myocardium (6 to 10 cc O₂/100 g heart/min). A period of occlusion of ten seconds gave rise to very substantial RH which could be studied quantitatively.

Our results demonstrated that cooling the denervated working heart down to 25°C reduces the magnitude and duration of RH in the coronary bed (fig. 3). Lewis and Grant studied the changes in the volume of the forearm of man during RH at different temperatures of the plethysmograph. They found that RH was much more intense at 40°C than at 15 to 20°C. However, their method did not quantify the blood flow. Freeman obtained quantitative data with venous occlusion plethysmography in the sympathectomized hand of man. He reported that between 23 and 34°C bath temperature, and with occlusions lasting two to twelve minutes, the blood flow (repayment) in reactive hyperemia was equal to the blood flow debt. Subsequent workers have been unable to confirm this finding in other vascular beds. In 1955, Patterson and Whelan reported 50 to 200% repayment of blood flow debt in the resting human forearm with varying periods of occlusion at body temperature.

In the coronary bed of the open-chest dog, Coffman and Gregg reported 190 and 267% repayment of flow debt in two groups of experiments with 10-second occlusions. Our values were higher and averaged 431% under normothermic conditions. These values are in contrast to those of Katz and Lindner who reported an average of 60% repayment in the isolated perfused fibrillating dog ventricles with occlusions that lasted from fifteen seconds to five minutes. The fact that repayment of blood flow debt varies so widely suggests that the vascular response in RH is not adjusted for the repayment of the “blood debt.”

Some investigators have studied the repayment of the “oxygen debt.” Coffman and Gregg found that oxygen repayment showed a deficit of 0.4 cc for 10-second left coronary artery occlusions, an excess of 1 cc in 15-second, and 3.5 cc in 30-second occlusions. These discrepancies are considerable in comparison with the values of the calculated oxygen debts incurred and may be due, at least partly, to certain unavoidable errors in the method of estimating the oxygen debt and its repayment. It was also noted that soon after the release of the artery, the coronary sinus blood was almost completely desaturated for a very short period of time and then saturation rose above the pre-occlusion levels before returning to control
values. This indicates that the extraction of oxygen is the other variable in the repayment of the oxygen debt. From available data it appears that hyperemic response repays neither blood flow debt nor oxygen debt. Possibly it restores the entire "biochemical or metabolic disturbance." This includes not only the debt for oxygen but also the debt for other nutrients from the plasma as well as the removal of excess metabolites from anaerobic metabolism.

It is difficult to explain the effect of hypothermia on RH, because the mechanism of RH is still obscure. It is well-known that hypothermia reduces the oxygen consumption of tissues, including that of the heart. If we accept the concept that RH is caused by the accumulation of vasodilator metabolites during ischemia, it is clear that a decline of metabolic rate, due to cooling, would reduce the accumulation of metabolites and the magnitude of RH. However, other factors may also be involved. The rate of diffusion of metabolites from the ischemic myocardium to the vascular muscle cells is slowed at hypothermic temperatures. This would tend to reduce the degree of vascular dilatation. On the other hand, if the postulated metabolite(s), e.g., adenosine, etc. are inactivated by an enzyme(s), then cooling can reduce the rate of destruction and, hence, augment the action of the vasoactive substance(s). Some authors have suggested the possibility that lack of oxygen per se to the vascular smooth muscle may constitute the stimulus. Our results could be explained equally well by this concept. Finally, the possibility also exists that the response of vascular smooth muscle to a given intensity of stimulus may be altered at low temperatures. Electrolyte studies in cooled cardiac and skeletal muscles have been reported with somewhat contradictory results. It is still unknown whether or not alterations in the concentration of electrolytes occur in vascular smooth muscles during hypothermia and possibly change the response of the tissue to chemical and mechanical stimuli.

Summary

Left coronary artery inflow was recorded in the dog heart-lung preparation by means of a Gregg cannula and a Shipley-Wilson recording rotameter. Reactive hyperemia (RH) was induced by 10-second occlusions. The excess blood flow after release was quantified by planimetry and related to the "blood flow debt" incurred during the period of occlusion. In the normothermic heart, the excess coronary flow was 431% of the flow debt. At heart temperatures of 30 and 25.6°C, it dropped to 228% and 143% respectively. There was shortening of the duration of reactive hyperemia and reduction of peak flow at lower temperatures. These results were discussed in the light of chemical theories of the mechanism of reactive hyperemia and the effect of hypothermia thereon.

References

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