High Energy Phosphate Stores and Lactate Levels in Different Layers of the Canine Left Ventricle during Reactive Hyperemia

ROBERT B. DUNN, KATHLEEN M. MCDONOUGH, AND DOUGLAS M. GRIGGS, JR.

SUMMARY To study posts ischemic recovery of myocardial energy metabolism in relation to the reactive hyperemic response, the tissue levels of creatine phosphate (CP), adenosine triphosphate (ATP), and lactate were estimated in the outer, middle, and inner layers of the left ventricle before, during, and at several times after a 20-second bilateral coronary arterial occlusion in the open-chest dog. The reactive hyperemic response was characterized by monitoring blood flow in the cannulated coronary sinus in a separate group of dogs. Substantial changes in myocardial CP and lactate, but not ATP, were produced by the occlusion, and reciprocal transmural gradients in CP and lactate occurred such that CP was lowest and lactate was highest in the inner layer. Recovery of high energy phosphate stores (CP + ATP) occurred long before blood flow returned to the preocclusion level, this being achieved in two of the three layers after completion of only 29% of the reactive hyperemic response when the blood flow debt repayment was 151%. Lactate returned to control levels during the response, but recovery times in the different layers were delayed compared to those for the high energy phosphate stores. A transmural lactate gradient was maintained as the regional levels declined, and recovery times were different for each of the three layers, being longest in the inner layer. The results suggest that during the reactive hyperemic response (1) kinetically different processes are involved in the repletion of energy stores and the removal of anaerobically produced metabolites, and (2) metabolic vasodilation of coronary vessels probably is more pronounced and sustained longer in the inner than in the outer ventricular layer.

ALTHOUGH considerable information is available regarding the nature of the reactive hyperemic response in the heart (Olsson, 1975), relatively little is known about the changes in myocardial energy metabolism which accompany this response. One characteristic of the reactive hyperemic response in the heart is overpayment of the blood flow debt incurred during the period of coronary arterial occlusion. Although previous studies (Bache et al., 1974; Eikens and Wilcken, 1974) have provided indirect evidence that the large volume of reactive hyperemic blood flow is in excess of that needed to reverse the changes in myocardial energy metabolism caused by the occlusion, the temporal relationships between reactive hyperemic blood flow and such metabolic events in the myocardium as replenishment of reduced high energy phosphate stores and removal of anaerobically produced lactate have not been established. One purpose of this study was to establish these relationships.

Another characteristic of the reactive hyperemic response in the heart is dependence of its volume and duration on the level of metabolic activity in the myocardium during the occlusion period. This dependence may be related to the production of a vasodilator metabolite in the myocardium. Recent studies indicate that for the left ventricle the level of metabolic activity is greater in the subendocardium than in the subepicardium (Holtz et al., 1977; Weiss et al., 1978), and it has been noted in the totally ischemic left ventricle that the buildup of anaerobically produced lactate is more rapid in the subendocardium (Dunn and Griggs, 1975). These results suggest that metabolic conditions favoring reactive hyperemia may be more pronounced and sustained longer in the subendocardium. Another purpose of the present study was to examine this possibility.

Methods

Studies were performed on 47 male mongrel dogs that had been fasted overnight. The dogs had been screened for microfilaria, medicated against rabies and for intestinal parasites, and maintained on a nourishing diet for at least 30 days. Anesthesia was induced with sodium pentobarbital (30 mg/kg, iv). Additional doses were given as required during the experiment. The trachea was intubated, and respiration was maintained with a Harvard respirator. Supplemental oxygen was added to the inspired air (approximately 10% of the inspired air volume) to...
ensure a normal arterial oxygen tension. Rectal temperature, measured with a Yellow Springs telethermometer, was maintained between 38 and 39°C by the use of a heating pad. Pressure in the arch of the aorta was monitored through a side-hole polyethylene catheter passed retrograde from the femoral artery. A catheter was inserted in a femoral vein for injections and infusions. Left ventricular intracavitary pressure was obtained through a needle (thin wall, no. 17) which was later inserted through the left ventricular wall. Statham pressure transducers (P23Db) and an Electronics-for-Medicine (model DR-8) multichannel oscillograph were used to record pressures.

A right thoracotomy was performed, and the origin of the right coronary artery was exposed sufficiently to pass a ligature around it. The ligature was passed through a length of polyethylene tubing to produce a vessel snare which later was used to occlude the right coronary artery. The sinoatrial node was crushed, and the heart was paced from the right atrial appendage at 150 beats/min. In some dogs a coronary sinus cannula was inserted via a surgical opening in the right atrium and advanced to the coronary sinus ostium. A purse-string suture was placed around the atrial opening to control bleeding and another suture was passed externally around the coronary sinus to secure the tip of the cannula in the coronary sinus ostium. Coronary sinus blood flow was diverted through a short external circuit containing a Biotronex model 612 electromagnetic flowmeter probe and then returned to the right atrium via another surgical opening. The purpose of this procedure was to obtain an estimation of the time course of the reactive hyperemic response following a period of total ischemia of the left ventricle.

A left thoracotomy then was performed, the main left coronary artery was dissected close to its origin on the aorta, and a vessel snare was prepared for this vessel as described earlier for the right coronary artery. The origin of the septal branch distal to the snare was verified at the end of the experiment. A vessel snare also was placed around the descending thoracic aorta for later tightening to attenuate the fall in left ventricular systolic pressure that sometimes occurred during the period of coronary arterial occlusion. This snare was released as myocardial performance improved during the reactive hyperemic response. Heparin was administered (350 units/kg, iv) and a blood sample was drawn anaerobically from the aortic catheter for the estimation of arterial pH, carbon dioxide tension (PCO₂), oxygen tension (PO₂), and hematocrit. Blood samples were read immediately on an Instrumentation Laboratory blood gas analyzer (model 113-S1). If required, ventilation and oxygen administration were adjusted to maintain an arterial PCO₂ between 30 and 40 mm Hg and a PO₂ between 90 and 110 mm Hg. A final arterial blood sample was taken for gas analysis immediately prior to the experimental period. An arterial blood sample also was drawn and precipitated with cold 6% perchloric acid for subsequent determination of lactate (Hohorst, 1963).

**Experimental Protocols**

Two types of experiments, termed “hemodynamic” and “metabolic,” were performed on different groups of animals as follows.

**Hemodynamic Experiments**

In four dogs prepared with the coronary sinus cannula and external circuit containing the electromagnetic flow probe, the reactive hyperemic response to a 20-second bilateral coronary arterial occlusion was measured. Under steady state conditions, right coronary arterial occlusion was followed by left coronary arterial occlusion within 10 seconds, and this was followed by release of the left coronary arterial occlusion after 20 seconds of bilateral occlusion. Bilateral occlusion was used to assure complete ischemia of the left ventricle in all dogs for the 20-second period. Coronary sinus blood flow was recorded continuously during the reactive hyperemic response until a new steady state was achieved. Only the reactive hyperemic response following the first occlusion was used in each dog for quantitative analysis, because hyperemic responses subsequent to the recovery from the first occlusion were found to be slightly attenuated. Although both phasic and electronically meaned flow signals were recorded, quantitative analysis was limited to the meaned signal for convenience. We concur with Olsson (1964) that the flow rate changes during reactive hyperemia, including the rise to peak flow, are slow enough to permit use of the meaned flow signal to characterize the response. We also determined in two additional dogs that the time course of the flow signal change recorded from the cannulated coronary sinus during reactive hyperemia closely matched that recorded from the simultaneously cannulated main left coronary artery. The following quantitative measurements were made as described by others (Coffman and Gregg, 1960). Blood flow debt = (control flow rate) – (total flow during reactive hyperemia) – (control flow rate × duration of reactive hyperemia). Blood flow debt repayment = (reactive hyperemia flow – total flow during reactive hyperemia) – (control flow rate × duration of reactive hyperemia) × 100.

**Metabolic Experiments.**

In 43 dogs a single transmural tissue sample of the anterolateral wall of the left ventricle was obtained at one of five sampling times. The sampling times and number of dogs sampled at each time were as follows: Control period, nine animals; after 20 seconds of bilateral coronary arterial occlusion, eight animals; after 10 seconds of reactive hyperemia, nine animals; after 20 seconds of reactive
hyperemia, nine animals; and after 30 seconds of reactive hyperemia, eight animals. The transmural myocardial tissue sample was obtained with a cylindrical cutting tool mounted on an electric hand drill as previously described (Dunn and Griggs, 1975). The tissue sample was quickly compressed with large metal tongs precooled in liquid nitrogen. The time required for cutting and compressing the sample was less than 2 seconds. The mean weight and thickness of the frozen sample were 1.13 ± 0.02 (SE) g and 2.59 ± 0.03 mm, respectively. The frozen tissue sample was divided into outer, middle, and inner thirds. Each portion was weighed on an electrobalance (Kahn model 7500) and pulverized; the frozen powder was transferred to a chilled Potter-Elvehjem tube and extracted with 0.3 M perchloric acid. Following centrifugation in the cold, the clear supernatant fluid was removed. Samples of the tissue filtrate were analyzed immediately for creatine phosphate (Purchgott and DeGubareff, 1966) and adenosine triphosphate (Adam, 1963). The remaining filtrate was frozen and later analyzed for lactate (Hohorst, 1963). All analyses were performed in duplicate.

Statistical Methods

Because of evidence of non-Gaussian characteristics in tissue metabolite data obtained in a previous study (Griggs et al., 1971), all results were analyzed by nonparametric statistical methods (Hollander and Wolfe, 1973). Within the different groups of dogs in the metabolic experiments, outer, middle, and inner tissue metabolite values were tested with the Friedman two-way analysis of variance by ranks. If a statistically significant value (P < 0.05) was found, individual differences were analyzed by the Wilcoxon matched pairs test. Likewise, control group values and those in the different experimental groups were first compared using the Kruskal-Wallis analysis of variance, and if significant differences were found, control group values were then compared to each experimental group using the Wilcoxon rank sum test. The preceding also was used to compare blood gases, pH, and hematocrit levels among the groups.

Results

Figure 1A illustrates the mean electromagnetic flow signal recorded from the coronary sinus cannula circuit in one dog before, during, and after bilateral coronary arterial occlusion for 20 seconds. After the left coronary arterial occlusion was released, blood flow climbed rapidly to a peak within 10 seconds and then declined in an exponential manner. Similar blood flow curves depicting the time course of the reactive hyperemic response in the left ventricle were obtained in three other dogs. Figure 1B is a plot of mean data obtained from the group of four dogs, showing the ratio of reactive hyperemic blood flow to control blood flow during the first 60 seconds of the reactive hyperemic response. The values obtained for this ratio at various times during the reactive hyperemic response are given in Table 1. Also in Table 1 are the time-related values for two other parameters of the reactive hyperemic response: (1) the cumulative percentage repayment of the blood flow debt incurred during the period of coronary arterial occlusion, and (2) the accrued percentage of the total reactive hyperemic response completed. Because they coincide with the tissue-sampling times of the metabolic experiments, the values obtained after 10, 20, and 30 seconds of reactive hyperemia are of particular interest and are summarized as follows. After 10 seconds, reactive hyperemic flow was 5.8 ± 0.3 (mean ± se) times control flow. This approximately 6-fold increase in flow is within the 3- to 7-fold maximal increase reported by others (Gregg et al., 1972), indicating that maximal coronary vasodilation was achieved in these experiments. The blood flow debt repayment was 151 ± 2%, signifying that a significant overpayment of flow had already occurred. However, only 29 ± 5% of the total reactive hyperemic response had occurred at this time. After 20 seconds, reactive hyperemic flow was 3.9 ± 0.5 times the control flow, indicating partial recovery of coronary vasomotor tone. The blood flow debt repayment was 341 ± 22%, and now approximately one-half (47 ± 8%) of the response had occurred.
CARDIAC ENERGY METABOLISM AND REACTIVE HYPEREMIA/Dunn et al.

Table 1: Mean Data on Reactive Hyperemic Response in Four Dogs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Time after onset of reactive hyperemic response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactive hyperemia flow (ml/min)</td>
<td></td>
</tr>
<tr>
<td>Control flow (ml/min)</td>
<td>10 sec 20 sec 30 sec 50 sec 85 sec</td>
</tr>
<tr>
<td>Cumulative blood flow debt repayment (%)</td>
<td></td>
</tr>
<tr>
<td>Accrued percentage of excess reactive hyperemic flow</td>
<td></td>
</tr>
<tr>
<td>10 sec</td>
<td>5.8 ± 0.3 3.9 ± 0.5 2.6 ± 0.4 1.4 ± 0.4 1.0 ± 0.0</td>
</tr>
<tr>
<td>20 sec</td>
<td>151 ± 2 341 ± 22 442 ± 48 570 ± 121 594 ± 147</td>
</tr>
<tr>
<td>30 sec</td>
<td>29 ± 5 47 ± 8 80 ± 8 97 ± 6 100</td>
</tr>
<tr>
<td>60 sec</td>
<td></td>
</tr>
<tr>
<td>85 sec</td>
<td></td>
</tr>
</tbody>
</table>

All values are means ± SEM

After 30 seconds, reactive hyperemic flow was 2.6 ± 0.4 times control flow, reflecting further recovery of coronary vasomotor tone; the blood flow debt repayment was 442 ± 48%, and more than three-fourths (80 ± 8%) of the response had occurred.

We maintained mean aortic pressure, which averaged 104 ± 5 (SE) mm Hg for the group before coronary arterial occlusion, within 10% of this value during and after the period of coronary arterial occlusion by tightening and then loosening the aortic snare while monitoring phasic aortic pressure on the oscilloscope of the Electronics for Medicine recorder. Although left ventricular systolic pressure was similarly maintained, left ventricular end-diastolic pressure rose during the period of coronary arterial occlusion and then declined after the occlusion was released. The changes in left ventricular end-diastolic pressure related to those maneuvers are most accurately portrayed in the larger body of data on ventricular pressure obtained in the metabolic experiments (Table 2). Analysis of the pressure data obtained immediately before tissue sampling in the different groups of dogs included in the metabolic experiments demonstrated that dogs studied after 20 seconds of coronary arterial occlusion and after 10 seconds of reactive hyperemia had significantly higher left ventricular end-diastolic pressures than did the control dogs. This finding is similar to that reported by others (Olsson and Gregg, 1965) as the result of a 15-second circumflex occlusion in the unanesthetized dog. Left ventricular systolic pressure was essentially the same in all groups.

Analysis of the arterial blood data obtained for the different groups of dogs prepared for the metabolic experiments revealed the following ranges in mean values (±SE): PCO₂, 34 ± 2 to 37 ± 1 mm Hg; PO₂, 99 ± 3 to 113 ± 7 mm Hg; pH, 7.37 ± 0.01 to 7.40 ± 0.01 U; hematocrit, 41.6 ± 1.9 to 44.2 ± 1.4%; lactate, 0.95 ± 0.09 to 1.09 ± 0.11 mM. No significant differences between groups were present for any of the measured variables.

The myocardial tissue metabolite data obtained in the metabolic experiments are presented in Table 3 and illustrated in Figure 2. The significant findings for the different metabolites studied are summarized as follows.

Creatine Phosphate

Under control conditions the inner layer level was below both the outer and middle layer levels. After 20 seconds of coronary arterial occlusion, the levels in all three layers were below the comparable control levels, and a transmural gradient decreasing from the outer to the inner layer was present. After 10 seconds of reactive hyperemia, only the outer layer level was below the comparable control level and there were no interlayer differences. After 20 seconds of reactive hyperemia, the transmural pattern was different from that under control conditions in that there was an interlayer difference between the outer and middle layers. However, as under control conditions, the inner layer level was below both the outer and middle layer levels. After 30 seconds of reactive hyperemia, the findings were the same as under control conditions.
### Table 3  Tissue Metabolite Data

<table>
<thead>
<tr>
<th>Tissue Metabolite</th>
<th>Outer</th>
<th>Middle</th>
<th>Inner</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Creatine phosphate (μmol/g)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n = 9)</td>
<td>9.90 ± 0.36</td>
<td>9.86 ± 0.42</td>
<td>8.74 ± 0.35</td>
<td>O &amp; M &gt; I†</td>
</tr>
<tr>
<td>After 20-sec occl (n = 8)</td>
<td>5.33 ± 0.45</td>
<td>4.84 ± 0.51</td>
<td>3.88 ± 0.34</td>
<td>O &gt; M &gt; I‡</td>
</tr>
<tr>
<td>After 10-sec R.H. (n = 9)</td>
<td>8.72 ± 0.29</td>
<td>9.02 ± 0.27</td>
<td>8.38 ± 0.23</td>
<td>N.S.</td>
</tr>
<tr>
<td>After 20-sec R.H. (n = 9)</td>
<td>9.64 ± 0.58</td>
<td>10.23 ± 0.44</td>
<td>8.38 ± 0.47</td>
<td>M &gt; O &gt; I‡</td>
</tr>
<tr>
<td>After 30-sec R.H. (n = 8)</td>
<td>9.62 ± 0.32</td>
<td>9.66 ± 0.41</td>
<td>9.02 ± 0.45</td>
<td>O &amp; M &gt; I‡</td>
</tr>
<tr>
<td><strong>Adenosine triphosphate (μmol/g)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n = 9)</td>
<td>5.67 ± 0.14</td>
<td>5.77 ± 0.12</td>
<td>5.62 ± 0.11</td>
<td>N.S.</td>
</tr>
<tr>
<td>After 20-sec occl (n = 8)</td>
<td>5.12 ± 0.11</td>
<td>5.45 ± 0.12</td>
<td>5.28 ± 0.08</td>
<td>N.S.</td>
</tr>
<tr>
<td>After 10-sec R.H. (n = 9)</td>
<td>4.92 ± 0.14</td>
<td>5.55 ± 0.15</td>
<td>5.43 ± 0.13</td>
<td>M &amp; I &gt; O†</td>
</tr>
<tr>
<td>After 20-sec R.H. (n = 9)</td>
<td>5.37 ± 0.11</td>
<td>5.52 ± 0.08</td>
<td>5.34 ± 0.11</td>
<td>N.S.</td>
</tr>
<tr>
<td>After 30-sec R.H. (n = 8)</td>
<td>5.27 ± 0.13</td>
<td>5.67 ± 0.12</td>
<td>5.41 ± 0.18</td>
<td>M &gt; O &amp; I‡</td>
</tr>
<tr>
<td><strong>Lactate (μmol/g)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n = 9)</td>
<td>0.304 ± 0.019</td>
<td>0.315 ± 0.019</td>
<td>0.300 ± 0.022</td>
<td>N.S.</td>
</tr>
<tr>
<td>After 20-sec occl (n = 8)</td>
<td>1.006 ± 0.073</td>
<td>1.182 ± 0.112</td>
<td>1.511 ± 0.157</td>
<td>I &gt; M &gt; O†</td>
</tr>
<tr>
<td>After 10-sec R.H. (n = 9)</td>
<td>0.693 ± 0.066</td>
<td>0.861 ± 0.081</td>
<td>1.205 ± 0.14</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>After 20-sec R.H. (n = 9)</td>
<td>0.436 ± 0.063</td>
<td>0.497 ± 0.055</td>
<td>0.618 ± 0.084</td>
<td>I &gt; M &gt; O†</td>
</tr>
<tr>
<td>After 30-sec R.H. (n = 8)</td>
<td>0.434 ± 0.062</td>
<td>0.447 ± 0.077</td>
<td>0.523 ± 0.082</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

All values are means ± SE, N.S. = not significant; occl = occlusion; R.H. = reactive hyperemia.
* Outer (O), middle (M), and inner (I) layer values compared with each other.
† P < 0.01.
‡ P < 0.05.
§ Values compared with the control group.

### Adenosine Triphosphate

Under control conditions there were no interlayer differences. After 20 seconds of coronary arterial occlusion the outer layer level was below the comparable control level. After 10 seconds of reactive hyperemia the outer layer level was below the comparable control level and also below both the middle and inner layer levels in the same tissue. After 20 seconds of reactive hyperemia the findings were the same as under control conditions. After 30 seconds of reactive hyperemia the transmural gradient was different from that under control conditions in that the middle layer level was above the outer and inner layer levels.

### Lactate

Under control conditions there were no interlayer differences. After 20 seconds of coronary arterial occlusion the levels in all three layers were above the comparable control levels, and a transmural gradient increasing from the outer to the inner layer was present. After 10 seconds of reactive hyperemia the levels in all three layers were above the comparable control levels, and a transmural gradient increasing from the outer to the inner layer was present. After 20 seconds of reactive hyperemia the middle and inner layer levels were above the comparable control levels, and a transmural gradient increasing from the outer to the inner layer was present.
Discussion

In the present study, we assessed regional myocardial energy metabolism by estimating the tissue levels of creatine phosphate, adenosine triphosphate, and lactate in different layers of the canine left ventricle. Creatine phosphate and adenosine triphosphate were examined because they are the two high-energy phosphate compounds most intimately associated with myocardial contraction, and lactate was examined because it is produced rapidly when myocardial energy metabolism becomes anaerobic. In the control dogs creatine phosphate was slightly lower in the inner ventricular layer compared to the outer and middle layers, but adenosine triphosphate and lactate were uniform among the three layers. These results, which are consistent with those obtained previously by us (Dunn and Griggs, 1975) and by Bassenge et al. (1968), are at variance with those reported by other investigators (Ichihara and Abiko, 1975; Allison and Holsinger, 1977) who have noted significant transmural gradients in these metabolites consistent with relative subendocardial hypoxia under ostensibly similar experimental conditions. No explanation other than methodological differences can be offered for these conflicting metabolic data in control dogs. The more rapid tissue-sampling and freezing technique used in our laboratory, which requires less than 2 seconds, could be important if significant changes in metabolite levels take place within the first few seconds after disruption of the circulation.

The finding of transmural gradients in creatine phosphate and lactate in the dogs subjected to complete coronary arterial occlusion for 20 seconds was anticipated in light of our earlier study (Dunn and Griggs, 1975) in which gradients for these metabolites were demonstrated under similar experimental conditions. We showed that gradients for these metabolites occurred after briefly stopping coronary blood flow in the rhythmically contracting, pressure-generating ventricle, but not in the fibrillating or empty beating ventricle (Dunn et al., 1975). We postulated that such metabolite gradients were related to a transmural gradient in ventricular wall stress (Wong and Rautaharju, 1968; Mirsky, 1969). The almost complete absence of regional changes in adenosine triphosphate during such a brief period of occlusion is not surprising in view of the relative inaccessibility for immediate utilization of most of the adenosine triphosphate pool because of intracellular compartmentalization (Gudbjarnason et al., 1970).

The myocardial reactive hyperemic response noted in the present study was typical of that obtained in the dog by others, and the average blood flow debt repayment of 594% was in good agreement with that reported in a number of studies, i.e., 500% (Olsson and Gregg, 1965), 485% (Bache et al., 1974), 618% (Eikens and Wilcken, 1974), and 544% (Giles and Wilcken, 1977). In two of these studies (Bache et al., 1974; Eikens and Wilcken, 1974) it was shown that the volume of the reactive hyperemic response could be significantly curtailed without impairing recovery of coronary vasomotor tone. Thus, the large amount of oxygen transported to the myocardium during the reactive hyperemic response did not appear to be essential for restoring coronary vasomotor tone to normal. Although this might be construed as evidence against the theory that reactive hyperemia is linked to a metabolic change induced in the myocardium by the occlusion (Eikens and Wilcken, 1974; Giles and Wilcken, 1977), other findings in the literature make it diffi-
cult to exclude the participation of a metabolic factor in the regulation of reactive hyperemic blood flow, at least in cases in which the occlusion lasts longer than several heart beats. For instance, it has been shown that the size and duration of the reactive hyperemic response are increased when the level of metabolic activity in the myocardium is increased during the occlusion (Bache et al., 1973; Pauly et al., 1973), and that the decline in reactive hyperemic flow following peak flow is closely linked to the disappearance of a potent vasodilator metabolite, adenosine, which accumulates in the myocardium during the occlusion (Olason et al., 1978).

A unifying hypothesis which accommodates both the evidence that the myocardium is oversupplied with oxygen during the reactive hyperemic response and the evidence that the response is linked to a metabolic change induced in the myocardium by the occlusion has been provided by Bache et al. (1974). These investigators have postulated that the response consists of two components, a flow component which is satisfied by a volume of flow approximately equal to the blood flow debt, and a time component which corresponds to the interval required for removal or inactivation of a vasodilator metabolite. This two-component model of the reactive hyperemic response suggests, in effect, that different processes are required for restoring myocardial energy metabolism to normal and for reversing the metabolically induced coronary vasodilation, and that the former event transpires first in an approximate temporal relationship with repayment of the blood flow debt.

The relationships established in this study between reactive hyperemic blood flow and the myocardial tissue levels of creatine phosphate and adenosine triphosphate show that replenishment of the myocardial high energy phosphate stores occurs long before coronary blood flow returns to the preocclusion level. In the middle and inner ventricular layers, where only the creatine phosphate levels were reduced significantly during the occlusion, a return of the high energy phosphate stores to control levels was apparent at the time of peak reactive hyperemic flow, when only about one-fourth of the response had occurred and the blood flow debt repayment was 151%. In the outer layer, where both creatine phosphate and adenosine triphosphate levels were significantly reduced during the occlusion, the high energy phosphate stores were noted to be at control levels at a time when coronary blood flow was still 3.9 times the preocclusion level and only about one-half of the response had occurred. No plausible explanation for the longer recovery time in the outer layer can be offered at this time other than the possibility that energy utilization is relatively greater in this region during the early phase of the reactive hyperemic response.

The relationship established between reactive hyperemic blood flow and the myocardial tissue levels of lactate showed that reversal of the lactate buildup caused by the coronary arterial occlusion also occurred before coronary blood flow returned to the preocclusion level, but the regional recovery times for this metabolite were delayed relative to those for the high energy phosphate metabolites. In the inner layer, where the greatest lactate changes occurred during the occlusion, the lactate level was still significantly above control after 30 seconds of reactive hyperemia, when approximately three-fourths of the response had occurred and the blood flow debt repayment was 44.5%.

The difference in behavior of creatine phosphate and lactate may reflect a difference in the processes used to restore these metabolites to control levels. The rate of rise of the creatine phosphate level most likely was dominated by the rapidly occurring biochemical process, oxidative phosphorylation, whereas the rate of decline of the lactate level most likely was dominated by the slower occurring physical process, solute diffusion. The results support the two-component model of Bache et al. (1974) in suggesting that the reversal of ischemic metabolic changes in the myocardium are accomplished by processes that are either primarily oxygen dependent or time dependent, and that postocclusion recovery of myocardial energy metabolism can be separated from postocclusion recovery of coronary vasomotor tone on this basis.

There is growing evidence that chemical energy utilization in the left ventricle is uneven in the transmural direction. Recent studies (Holtz et al., 1977; Weiss et al., 1978) have indicated that the rate of oxygen consumption is greater in the subendocardium than in the subepicardium, and we have demonstrated previously that the tissue lactate level rises faster in the subendocardium than in the subepicardium after complete stoppage of all coronary arterial inflow to the working left ventricle (Dunn and Griggs, 1975). These findings suggest that a metabolic stimulus for reactive hyperemia would be more pronounced and sustained longer in the subendocardium than in the subepicardium.

The regional lactate data demonstrated that the transmural gradient of this metabolite was well maintained as the tissue levels declined during the reactive hyperemic response, so that the lactate recovery times in each of the three layers were different, being shortest in the outer layer and longest in the inner layer. If a flow-regulating vasodilator metabolite were to experience this same uneven type of build up and decline, the metabolic stimulus for increased flow would be of varying intensity and duration in different layers of the ventricle. The typical reactive hyperemia blood flow curve recorded from a major coronary vessel could be a composite of many regional blood flow curves whose shapes varied as a function of depth within the ventricular wall. However, it must be acknowledged that the transmural distribution of blood flow during reactive hyperemia may be influ-
enced by many factors (Olsson, 1975), not the least of which is the myocardial tissue pressure gradient which increases from epicardium to endocardium (Kirk and Honig, 1964). Further information on regional flow must await the development of suitable techniques for estimating blood flow in different layers of the ventricle during various stages of the reactive hyperemia response.

Acknowledgments

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