ABSTRACT

Canine left ventricular wall metabolites (ATP, creatine phosphate, glycogen, glucose, glucose-6-phosphate, and lactate) were assessed in the ischemic region of the wall after 17 minutes of ligation of the left anterior descending coronary artery at its midlevel. Variations in the degree of lactate accumulation were found between different sites in the same ischemic region and between the outer and the inner left ventricular wall at the same site. High levels of lactate were associated with S-T segment elevation in the epicardial electrocardiogram, but no lactate accumulation or only mild lactate accumulation was found at isoelectric sites. Lactate accumulation at isoelectric sites was higher in the outer wall than it was in the inner wall; the opposite tendency was observed at sites of S-T segment elevation. In addition to high lactate levels, sites of S-T segment elevation demonstrated a more pronounced depletion of ATP and creatine phosphate, indicating not only a marked anaerobic glycolysis but also a more pronounced overall anaerobic stress. No relationship was found, however, between the absolute magnitude of S-T segment elevation and the degree of lactate accumulation or ATP depletion at sites of S-T segment elevation within the ischemic region. The data obtained in this study demonstrate that during myocardial ischemia epicardial sites of S-T segment elevation are sites of pronounced subendocardial and epicardial ischemia and of anaerobic metabolism.

KEY WORDS myocardial ischemia myocardial lactate myocardial high-energy phosphates epicardial electrocardiographic mapping left anterior descending coronary artery ligation

Recently Maroko and his associates (1) have demonstrated that a relationship exists between the local epicardial sites of S-T segment elevation and the creatine phosphokinase levels during acute coronary insufficiency. Epicardial sites with the highest S-T segment elevation 10-15 minutes after midlevel left anterior descending coronary artery occlusion are the sites with the lowest creatine phosphokinase levels 24 hours later. However, the precise local myocardial metabolic changes at epicardial sites of S-T segment elevation and at isoelectric sites within the ischemic region of the left ventricle during acute coronary insufficiency have not been previously investigated. If a metabolic relationship for epicardial sites of S-T segment elevation similar to that for creatine phosphokinase depletion exists, then epicardial mapping could potentially be even more widely used to metabolically assess the extent of myocardial ischemia under control and experimental conditions. Therefore, we performed a study using a technique that allowed very small portions of left ventricular tissue (less than 6 mg wet weight) to be biopsied. The objectives of the study were (1) to assess the relationship between the epicardial S-T segment changes during acute myocardial ischemia and the local myocardial metabolite concentrations, (2) to study the influence of local accumulation of anaerobic metabolites on electrical conductivity as reflected by changes in S-T segments during acute coronary insufficiency, and (3) to analyze any differences in the distribution of lactate within the ischemic region of the left ventricle (outer and inner portions of the left ventricular wall).

Methods

Studies were performed on ten mongrel dogs of either sex (15-20 kg) anesthetized with chloralose (30 mg/kg, iv). Respiration was maintained with a
Harvard respirator following endotracheal intubation, and a gas mixture of 95% O₂-5% CO₂ was used. Heart rate was kept constant by atrial pacing. The heart was exposed through a midline sternotomy, and the coronary sinus was cannulated with a large catheter that was subsequently stabilized by suture ligations. This catheter was connected to a loop that communicated distally with the left femoral vein, and a three-way stopcock was inserted in the system so that coronary sinus drainage could be intermittently sampled. Left ventricular pressure and the maximal rate of left ventricular pressure rise were measured through a large-bore steel cannula inserted into the left ventricular apex. Systemic arterial blood pressure was measured through a catheter in the right femoral artery. All catheters were connected to Statham P23Db pressure transducers appropriately calibrated. Pressures were recorded on Electronics-for-Medicine and Sanborn recorders.

Left ventricular ischemia was produced by a reversible ligation placed around the midlevel of the left anterior descending coronary artery. The ligation was maintained for 17 minutes.

Total coronary blood flow was measured by collecting coronary sinus drainage. Systemic arterial and coronary sinus blood samples were analyzed for PO₂, PCO₂, O₂ saturation (spectrophotometry), sodium and potassium concentrations, and osmolality (freezing point determination).

A needle biopsy technique (Vim-Silverman) was used to obtain fresh left ventricular tissue cores of less than 6 mg wet weight. The biopsy specimens were immediately frozen (less than 1.5 seconds) in liquid nitrogen. The frozen specimens were prepared so that two portions were obtained, one corresponding to the outer wall and one to the inner wall, prior to weighing and subsequent analysis. Enzymatic micromethods were used to determine levels of adenosine triphosphate (ATP), creatine phosphate (CP), glycogen, glucose, glucose-6-phosphate (G-6-P), and lactate in the outer and the inner left ventricular wall of each biopsy specimen (2).

The combined epicardial mapping and left ventricular wall metabolite study was undertaken in all ten of these dogs. The epicardial mapping was performed before and 15 minutes after coronary artery ligation according to the method of Maroko et al. (1) with slight modification (3) at locations surrounding the site of the midlevel left anterior descending coronary artery ligation. Sites of definite S-T segment elevation equal to or greater than 1.5 mm (Fig. 1) were then biopsied nearly simultaneously with sites within the ischemic region showing no S-T segment elevation (isoelectric sites); a comparison was made with respect to the depletion of high-energy phosphates and the degree of lactate accumulation. To avoid any possible negative effect of left ventricular wall biopsies on the epicardial electrocardiograms following ischemia, no control specimens were obtained before ligation in these ten hearts. Control data for ATP, CP, glycogen, glucose, G-6-P, and lactate levels for the outer and the inner wall were obtained in a different group of nine dogs randomly biopsied in the left ventricular wall. These control dogs were fed and cared for in the same way as were the experimental dogs.

Results

Table 1 presents the hemodynamic and blood analysis data. The left ventricular end-diastolic pressure tended to increase, but the maximal derivative of left ventricular pressure and the coronary blood flow decreased with left anterior descending coronary artery ligation. The osmolality\(^1\) of the venous effluent tended to increase at the end of the ligation period compared with the control value, indicating water retention, release of osmotically active agents into the venous blood by the heart, or both.

Figure 2 presents the data from the outer and the inner left ventricular wall metabolite determinations from epicardial sites of S-T segment elevation and from isoelectric sites. ATP and CP depletion in both the outer and the inner wall was evident in the specimens obtained from sites of S-T segment elevation compared with the levels in the outer and the inner wall of controls. At sites of S-T segment elevation, ATP concentration averaged 3.4 ± 0.3 (µmol/g wet weight) and 2.9 ± 0.2 µmoles/g wet weight in the outer and the inner wall, respectively. The corresponding control values were 5.4 ± 0.5 and 6.0 ± 0.6 µmoles/g wet weight. Both differences were significant (P < 0.001). CP concentrations at sites of S-T segment elevation averaged 4.9 ± 0.5 and 4.8 ± 0.4 µmoles/g wet weight for the outer and the inner wall, respectively, compared with 7.3 ± 1.1 (P < 0.05) and 6.9 ± 1.3 µmoles/g wet weight (P < 0.05) in controls.

ATP and CP depletion at isoelectric sites was less pronounced compared with control values than was

\(^{1}\)Range of error in the osmolality measurement was ± 3 mosmoles.

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TABLE 1

<table>
<thead>
<tr>
<th>Circulatory Characteristics and Blood Gas, Electrolyte, and Osmolality Data</th>
<th>Control</th>
<th>Ligation</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDP (cm H(_2)O)</td>
<td>4.8 ± 1.0</td>
<td>5.3 ± 0.8</td>
<td>0.5*</td>
</tr>
<tr>
<td>Max LV dP/dt (mm Hg/sec)</td>
<td>2720 ± 60</td>
<td>1900 ± 196</td>
<td>0.01*</td>
</tr>
<tr>
<td>Coronary blood flow (ml/100 g min(^{-1}))</td>
<td>54 ± 5</td>
<td>41 ± 4</td>
<td>0.01*</td>
</tr>
<tr>
<td>PO(_2) (mm Hg)</td>
<td>491 ± 17</td>
<td>461 ± 26</td>
<td>0.001†</td>
</tr>
<tr>
<td>Arterial</td>
<td>23 ± 2</td>
<td>25 ± 1</td>
<td>0.001†</td>
</tr>
<tr>
<td>Venous‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PO(_2) (mm Hg)</td>
<td>23 ± 2</td>
<td>22 ± 2</td>
<td>0.001†</td>
</tr>
<tr>
<td>Arterial</td>
<td>34 ± 2</td>
<td>31 ± 3</td>
<td>0.001†</td>
</tr>
<tr>
<td>Venous‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.5 ± 0.0</td>
<td>7.5 ± 0.0</td>
<td></td>
</tr>
<tr>
<td>Arterial</td>
<td>41 ± 2</td>
<td>37 ± 3</td>
<td>0.001†</td>
</tr>
<tr>
<td>Venous‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O(_2) Saturation (%)</td>
<td>98 ± 0</td>
<td>98 ± 0</td>
<td>0.001†</td>
</tr>
<tr>
<td>Arterial</td>
<td>41 ± 2</td>
<td>37 ± 3</td>
<td>0.001†</td>
</tr>
<tr>
<td>Venous‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium (mEq/liter)</td>
<td>151 ± 2</td>
<td>154 ± 1</td>
<td>0.05*</td>
</tr>
<tr>
<td>Arterial</td>
<td>155 ± 2</td>
<td>154 ± 2</td>
<td>0.05*</td>
</tr>
<tr>
<td>Potassium (mEq/liter)</td>
<td>3.0 ± 0.1</td>
<td>2.8 ± 0.1</td>
<td>0.05*</td>
</tr>
<tr>
<td>Arterial</td>
<td>2.9 ± 0.2</td>
<td>2.6 ± 0.2</td>
<td>0.05*</td>
</tr>
<tr>
<td>Venous‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osmolality (mosmoles/kg)</td>
<td>308 ± 4</td>
<td>309 ± 4</td>
<td>0.05*</td>
</tr>
<tr>
<td>Arterial</td>
<td>310 ± 4</td>
<td>313 ± 4</td>
<td>0.05*</td>
</tr>
<tr>
<td>Venous‡</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± se. LVEDP = left ventricular end-diastolic pressure and Max LV dP/dt = maxima derivative of left ventricular pressure.

*Statistically significant comparing ligation and control values.

†Statistically significant comparing venous and arterial values.

‡Refers to coronary sinus values.

depth at sites of S-T segment elevation. For ATP the levels averaged 4.2 ± 0.5 (P < 0.05) and 5.1 ± 0.7 μmoles/g wet weight (P < 0.5) in the outer and the inner wall, respectively. For CP the corresponding values were 5.6 ± 0.9 (P < 0.5) and 6.5 ± 1.3 μmoles/g wet weight (P < 0.5). Since there was no significant difference between the outer and the inner wall values for ATP or CP at isoelectric sites or at sites of S-T segment elevation, these values were combined to evaluate the difference in ATP and CP depletion between sites of S-T segment elevation and isoelectric sites. Significantly greater ATP and CP depletion occurred at sites of S-T segment elevation (Fig. 2).

Although marked lactate accumulation (P < 0.001) occurred at sites of S-T segment elevation (Fig. 2) in both the outer (12.5 ± 1.9 μmoles/g wet weight) and the inner (14.8 ± 2.5 μmoles/g wet weight) wall compared with control levels (1.6 ± 0.4 and 1.6 ± 0.5 μmoles/g wet weight, respectively), only a slight depletion in glycogen levels occurred. The mean glycogen levels for the outer and the inner

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**SITES OF ST SEGMENT ELEVATION**

![Image of sites of ST segment elevation](image1)

**SITES OF ISOELECTRICITY**

![Image of sites of isoelectricity](image2)

**FIGURE 2**

Left ventricular wall ATP, CP, glycogen (as glucose units), glucose, G-6-P, and lactate levels in the outer and the inner left ventricular wall expressed as μmoles/g wet weight after 17 minutes of ligation of the left anterior descending coronary artery at the midlevel. The P values in the top of the figure refer to differences between metabolites at sites of S-T segment elevation and at isoelectric sites.

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wall were 36 ± 3 (P < 0.05) and 41 ± 3 μmoles glucose units/g wet weight, respectively in experimental dogs. Control levels were 45 ± 3 and 42 ± 3 μmoles glucose units/g wet weight, respectively.

There was an increase in glucose concentration at sites of S-T segment elevation in the outer wall (3.0 ± 0.5 μmoles/g wet weight, P < 0.05) and in the inner wall (3.4 ± 0.3 μmoles/g wet weight, P < 0.001) compared with control concentrations (1.5 ± 0.3 and 1.7 ± 0.2 μmoles/g wet weight, respectively) (Fig. 2). G-6-P levels at sites of S-T segment elevation were, however, unchanged and averaged 1.4 ± 0.2 and 1.6 ± 0.2 μmoles/g wet weight in the outer and the inner wall, respectively, compared with control levels of 1.9 ± 0.2 and 2.2 ± 0.3 μmoles/g wet weight.

At isoelectric sites lactate accumulation was much less pronounced compared with that at sites of S-T segment elevation (Fig. 2) and averaged 4.1 ± 0.9 (P < 0.05 compared with control) and 1.5 ± 0.5 μmoles/g wet weight (P > 0.5) in the outer and the inner wall, respectively. The difference between inner and outer left ventricular wall lactate levels at isoelectric sites was significant (P < 0.05). Glycogen values in the outer and the inner wall at isoelectric sites (42 ± 6 and 39 ± 5 μmoles glucose units/g wet weight, respectively) were similar to control values. Glucose accumulation in the outer and the inner wall tended to be elevated compared with controls and averaged 3.2 ± 0.8 (P < 0.1) and 2.3 ± 0.5 μmoles/g wet weight (P > 0.5); however, G-6-P levels were unchanged (1.1 ± 0.1 and 0.8 ± 0.2 μmoles/g wet weight, respectively).

Lactate accumulation was greater in the outer wall than it was in the inner wall at isoelectric sites but much less at isoelectric sites than it was at sites of S-T segment elevation; moreover, the average lactate accumulation tended to be higher in the inner wall than it was in the outer wall at sites of S-T segment elevation, although this difference was not significant. To further study this relationship, individual pairs of outer and inner wall lactate values were plotted with outer wall data on the x-axis and inner wall data on the y-axis (line-of-identity plotting) (Fig. 3). The orthogonal regression line indicated that when severe lactate accumulation was present the highest values were likely to be found in the inner portion of the wall corresponding to the endocardium and that when mild lactate accumulation was present the highest values were likely to be found in the outer portion of the wall corresponding to the epicardium.

Discussion

Previously Morgan and Parmeggianni (4, 5), Kühler and Spieckermann (6), Williamson (7), and Opie (8) have investigated and reported the metabolic consequences of anoxia and similar conditions on the left ventricle of experimental animals. Their studies have demonstrated that as myocardial Po2 falls a reduction in high-energy phosphates occurs. The depletion in myocardial high-energy phosphates is accompanied by an increase in myocardial lactate concentration.

The present study demonstrated that there were marked local variations in the degree of lactate accumulation in a grossly homogeneously ischemic region of the left ventricular wall after acute left anterior descending coronary artery ligation. The tissue specimens were obtained from within the ischemic region of the left ventricle after epicardial mapping to identify sites of S-T segment elevation and isoelectric sites. A statistically significant difference in lactate accumulation was found between sites with no S-T segment elevation and those with S-T segment elevation: sites with S-T segment elevation had higher lactate concentrations than did sites with an isoelectric electrocardiogram.
This pattern, however, was not consistent in all experiments. The peak level of lactate at isoelectric sites was 6.4 μmoles/g wet weight. At 3 of 20 sites with definite S-T segment elevation equal to or greater than 1.5 mm, the level of lactate accumulation in the outer and the inner portions of the biopsy specimen was equal to or less than 5.0 μmoles/g wet weight. This overlapping seems to exclude the possibility that lactate accumulation per se is a major causal factor in determining the ultimate degree of S-T segment elevation that develops in ischemic myocardium. This conclusion is further supported by the fact that no direct relationship existed between the degree of lactate accumulation at a biopsied site and the magnitude of the S-T segment elevation at the same site (Fig. 4). It might have been surmised that lactate accumulation per se was not the causal factor for S-T segment elevation in this model, since the S-T elevation occurred almost instantaneously after experimental coronary artery ligation and became progressively more severe at least during the initial 10–15 minutes after occlusion. Although lactate accumulation does not occur rapidly enough to explain the earliest S-T segment elevation, its potential contribution to the progressive time-related increase in S-T segment elevation following experimental coronary artery occlusion was previously uncertain. Lactate accumulation in muscle tissue is generally regarded as being synonymous with anaerobic metabolism (2) and as potentially being associated with acute shifts in water and electrolytes in extra- and intracellular compartments (9). The reason for S-T segment elevation might well be related to the former, the latter, or both of these functions. As documented in the present study, S-T segment elevations were related not only to lactate accumulation but also to depletion of high-energy phosphates, although these were not exhausted. The 3 sites with definite S-T segment elevation without marked lactate accumulation did demonstrate the expected pattern of high-energy phosphate reduction. However, as was true for lactate, there was no direct relationship between the magnitude of S-T segment elevation and the severity of ATP depletion at any individual epicardial site.

The relationship between tissue glucose concentrations and G-6-P concentrations in the grossly ischemic region of the left ventricle in this study was not a simple one. Tissue glucose concentrations were elevated at epicardial sites of S-T segment elevation, but there was not a significant difference between G-6-P values at these sites compared with those obtained from control dogs. The tissue glucose levels reflect the balance between rates of intracellular transport, glucose phosphorylation, and glycolysis. Glucose levels might or might not correlate with G-6-P levels, depending on the relative relationship between the cellular accumulation of glucose and the formation or subsequent metabolism (glycolysis) of G-6-P. The increased tissue glucose concentrations at epicardial sites of S-T segment elevation probably reflect a combination of degradation of glycogen to glucose (5), increased intracellular transport of glucose during cellular hypoxia (8), and possibly tissue retention of extracellular fluid. The disparity between the elevated glucose concentrations and the apparently normal G-6-P concentrations might reflect either an...
accelerated rate of glycolysis with a relative block between glucose and G-6-P, a deviation from equilibrium at the phosphoglomutase step, or both. Phosphoglomutase catalyzes the formation of G-6-P from glucose-1-phosphate and during the later stages of myocardial ischemia helps to determine glycolytic flux (5).

It was possible at sites with isoelectric electrocardiograms to distinguish between outer and inner wall lactate levels; higher values occurred in the outer wall. Sites of S-T segment elevation appeared to have higher lactate levels in general; also the levels were slightly but not significantly higher at the inner wall (Fig. 3). Significant S-T segment depressions were not found in any experiments, so biopsy of such sites could not be included in the present study. Previously Griggs and his associates (10) have shown that there is a significant lactate gradient during experimental coronary constriction in dogs which increases from the outer to the inner left ventricular wall and a significant ATP gradient which decreases from the outer to the inner left ventricular wall. Lundsgaard-Hansen et al. (11) have also reported a higher activity for several different glycolytic enzymes in the inner wall of the canine left ventricle.

With the present results as a background, it appears that S-T segment elevation (recorded with an epicardial electrocardiogram) occurring in association with acute midlevel left anterior descending coronary artery ligation metabolically reflects pronounced subendocardial and epicardial ischemia. Isoelectric electrocardiograms obtained from within the grossly ischemic portion of the left ventricle reflect no ischemia or very mild ischemia. In the case of some of the isoelectric sites, the epicardium appeared to be the area metabolically involved by the mild ischemic process. At present it cannot be concluded whether the metabolic stress per se caused the S-T segment elevation or whether secondary effects caused changes in tissue conductivity.

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References

Relationship between Epicardial S-T Segment Changes and Myocardial Metabolism during Acute Coronary Insufficiency

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