Limitations of Lactate Production as an Index of Myocardial Ischemia

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SUMMARY The relationship between myocardial lactate production and the severity and duration of ischemia was studied in globally ischemic, isolated rat and rabbit hearts. In both species, the rate of lactate production was not constant, despite a constant degree of ischemia; the coronary venous lactate concentration reached a peak value 10–15 minutes after the onset of ischemia and then decreased by 40–50% during 15–60 minutes of subsequent ischemia. The rate of lactate production in moles/min (concentration × flow rate) was decreased during more severe degrees of ischemia, despite an increase in venous lactate concentration. Maximum lactate production occurred with mild-to-moderate ischemia; during severe ischemia, lactate production was reduced 88% in the rat and 71% in the rabbit myocardium.

A model of regional ischemia was constructed using the rates of lactate production determined in the globally ischemic, isolated hearts. Even under ideal conditions of a "steady-state" degree of ischemia and optimal placement of the coronary sinus sampling catheter, calculated changes in the coronary sinus lactate level did not show a constant or directionally similar relationship to modeled changes in the ischemic condition. Our results indicate that indices of lactate metabolism may not reliably measure sequential changes in the amount or degree of ischemia.

MYOCARDIAL LACTATE METABOLISM is widely used to assess the adequacy of tissue oxygenation. The aerobic myocardium extracts lactate from the arterial blood; myocardial lactate production is evidence of myocardial hypoxia.1,2 Recently, the use of lactate metabolism as an index of ischemia has expanded and the amount of myocardial lactate production has been used as a quantitative estimate of the relative severity of ischemia. Changes in lactate production have been used to assess treatment of angina and coronary artery disease,3–10 myocardial infarction,11,12 cardiogenic shock,13,14 coronary artery surgery15–17 and physiologic maneuvers in patients and animals with myocardial ischemia.18,19

Although net myocardial lactate production indicates the qualitative presence of tissue hypoxia, a quantitative relationship between the relative severity of ischemia, and/or the size of an ischemic region of a ventricle, and the amount of lactate production, has not been defined. During experimental ischemia, glycolysis was inhibited by the increase in tissue lactate that occurred,20,21 suggesting an inverse relationship between the severity of ischemia and the amount of myocardial lactate production. However, previous clinical studies of myocardial lactate metabolism have assumed a direct relationship, i.e., that increasing amounts of lactate production implied an increase in the severity of ischemia and vice versa.

Two additional considerations are important when clinical myocardial ischemia is assessed by the amount of lactate production. Most clinical studies are based on sequential measurements in the same patient, e.g., before and after treatment of a patient in cardiogenic shock. However, the natural time-course of the rate of lactate production during a constant degree of ischemia has not been defined; with constant hypoxemia in isolated heart preparations, the rate of lactate production progressively decreased over time.22 Thus, repeated measurements of myocardial lactate production in a patient with ischemic heart disease might be expected to change with time, despite a constant degree of myocardial ischemia. Second, myocardial lactate production in man is usually assessed by comparison of the coronary sinus and arterial concentrations. However, the coronary sinus level represents a mixed venous sample that results from the combined drainage from the ischemic and normally perfused regions of the ventricle. The lactate level in the coronary sinus sample is determined by the amount of lactate extraction in the normal region, the amount of production in the ischemic region, and the relative flow contributions of the ischemic and normal regions to the mixed coronary sinus sample. These limitations - a changing time-course and regional venous mixing — are generally recognized as possible sources of error in interpreting the pattern of myocardial lactate metabolism; however, the magnitude of the error that may result has not been quantified. Direct evaluation of these factors in man is obviously difficult, because it is virtually impossible to study the metabolic behavior of ischemic human myocardium over a range...
of constant, quantifiable degrees of ischemia of different durations. Accordingly, in the current study, we addressed this problem experimentally by maintaining heart muscle at a constant degree of ischemia and measuring the time-course of the rate of lactate production, and by measuring the changes in lactate production that occurred when the degree of ischemia was changed.

Methods

Isolated heart muscle was subjected to 30–75 minutes of graded global ischemia that varied in degree between groups, but was held constant in each heart; during the ischemic period, the amount of lactate production was measured. Groups of isolated rat and rabbit hearts were perfused with oxygenated Krebs-Henseleit buffer at 37°C using techniques and methods previously published; the buffer contained 5.5 mM glucose and 1.0 mM lactate as substrate. Basically, in this system, a variable flow pump provided coronary perfusion via the aortic root. A fluid-filled balloon was placed in the left ventricular cavity; the myocardium thus contracted isovolumically and developed intraventricular pressures in the physiologic range under well-oxygenated conditions. Heart rate was held constant with a right ventricular pacing wire. Myocardial metabolism was assessed by collecting the coronary venous effluent. The isolated hearts were first perfused for a 30-minute control, well-oxygenated period at a coronary arterial flow of 8 ml/min in the rat hearts or 30 ml/min in the rabbit hearts (approximately 15 ml/min/g in each species). Because the perfusate did not contain hemoglobin, these relatively high coronary flow rates were required to provide adequate oxygen delivery to achieve contractile performance in the physiologic range during the control period. After the control period, ischemia was induced by reduction of the coronary perfusion pump flow rate.

During ischemia, we wished to simulate the tissue flow rate that would occur in patients in the central or border zones of a myocardial infarction, and also use a coronary flow rate that would be in the ischemic range for the in vivo rat or rabbit heart. A myocardial perfusion rate of 2.5 ml/min/g was taken as normal for the rat and rabbit hearts. Three groups of rat hearts were each subjected to a different degree of ischemia for 30 minutes: 1) mild ischemia (n = 8), where coronary flow was 1.50 ± 0.03 ml/min/g or 60% of normal; 2) moderate ischemia (n = 8), where coronary flow was 0.70 ± 0.03 ml/min/g or 28% of normal; and 3) severe ischemia (n = 8), where coronary flow was 0.08 ± 0.01 ml/min/g or 3% of normal. In the rabbit hearts, two degrees of ischemia were induced. One group (n = 27) underwent 75 minutes of moderate ischemia at a coronary flow rate of 0.49 ± 0.04 ml/min/g or 20% of normal; a second group (n = 20) underwent 75 minutes of severe ischemia at a coronary flow rate of 0.05 ± 0.004 ml/min/g or 2% of normal.

Arterial and venous perfusate samples were collected and analyzed for their lactate concentration by a specific enzymatic method. Venous effluent samples were mixed with 10% trichloracetic acid solution and refrigerated until analysis.

To extrapolate from the globally ischemic ventricle to the condition of regional ischemia, we constructed a regional flow model and applied to the ischemic region of the ventricle the rate of lactate effluent determined in the isolated hearts subjected to graded, global ischemia. The nonischemic region of the ventricle was assumed to have a rate of lactate extraction in the normal range for man, i.e., 10–60% of the arterial level, and a myocardial blood flow value in the normal range was used (1.0 ml/min/g). Because normal myocardial blood flow in the rat and rabbit is 2.5 ml/min/g, the ischemic coronary flow values used in the isolated hearts were expressed as a percentage reduction from the normal value. For example, the rate of lactate effluent at a coronary flow rate of 1.5 ml/min/g (60% of normal) in the isolated rat heart represented mild global ischemia, and this rate of lactate production was assumed to exist in our model of mild regional ischemia, where regional perfusion was reduced to 60% of normal in man. Despite a constant degree of ischemia in the isolated hearts, the rate of lactate production decreased over the 30-minute period.

Figure 1. Lactate production during mild and moderate ischemia in rat heart groups. The coronary venous effluent lactate concentration is plotted for the mild (coronary flow 1.5 ± 0.03 ml/min/g) and moderate (coronary flow 0.7 ± 0.03 ml/min/g) ischemic rat heart groups. There was no significant difference between the groups at 5 and 30 minutes; between 5 and 25 minutes, the mean differences were significant, as noted. Despite a constant degree of ischemia, the rate of lactate production decreased over the 30-minute period.
lactate efflux was not constant during the ischemia period (see below); therefore, the mean lactate effluent rates during the ischemic period were used to calculate the lactate fluxes in our model of regional ischemia.

Using the mean rate of lactate production in our model obviates an unrealistic manner the practical clinical problem of minute-to-minute changes in the effluent lactate concentration. Our model is constructed to test the relationship between coronary sinus lactate levels and the severity of ischemia under the best of circumstances. If such a relationship cannot be defined under ideal conditions in a model, its clinical usefulness is even more doubtful.

**Results**

During the control, well-oxygenated state, both the rat and rabbit hearts showed net lactate extraction and an "aerobic" pattern of metabolism. Despite the relatively high coronary flow rates during the control period, the rat hearts extracted 5% and the rabbit hearts 12% of the 1.0 mM perfusate lactate in one passage through the myocardium.

During ischemia, all groups of rat and rabbit hearts showed a prompt reversal of the pattern of net lactate extraction to one of lactate production. The time-course of the lactate production is shown in figures 1-4.

**Rat Myocardium**

The group data for the isolated rat hearts is shown in figure 1. In both the mild and moderate ischemia groups, the effluent lactate concentration increased during the first 10–15 minutes and then decreased during the next 20 minutes. The moderate ischemia group reached a significantly higher peak level and subsequently decreased at a more rapid rate than the mild ischemia group. During the first 5 minutes and after 25 minutes of ischemia, there was no significant difference between the two groups; thus, the measurement of the effluent lactate concentration would have distinguished between mild and moderate ischemia only between 10 and 25 minutes of the ischemic period.

The rat hearts generally showed a pattern of a sharply increasing effluent lactate concentration that peaked after 5–20 minutes of ischemia and subsequently decreased rapidly. Because there was some variation in the time at which the peak values occurred, the group data in figure 1 underestimate the constancy of the rate of lactate production in a single heart. Figure 2 shows the time-course of lactate production in six rat hearts. Despite a constant degree of ischemia, the concentration of lactate in the venous

**Figure 2. Lactate production in individual ischemic rat hearts.** The coronary venous effluent lactate concentration in representative experiments is shown for three moderately ischemic rat hearts (top panel) and three mildly ischemic rat hearts (bottom panel). See text for discussion.

**Figure 3. Lactate production during moderate and severe ischemia in rabbit heart groups.** The venous effluent lactate concentration is plotted for the moderate (coronary flow 0.49 ± 0.04 ml/min/g) and severe (coronary flow 0.05 ± 0.004 ml/min/g) ischemic rabbit heart groups. There was no significant difference between the groups during the first 5 minutes of ischemia; after 5 minutes of ischemia, the mean differences were significant (p < 0.001).
effluent was not constant during the 30-minute ischemic period, especially in the moderate ischemia series. Each heart was analyzed by comparing its peak effluent value with subsequent values. In the moderate ischemia group, the effluent lactate concentration decreased by 22 ± 10% \((p = 0.10-0.05)\) 5 minutes after reaching the peak effluent level, by 35 ± 12% \((p < 0.025)\) 10 minutes after the peak value, and by 54 ± 16% \((p < 0.025)\) 15 minutes after the peak value. Likewise, in the mild ischemia group, the effluent lactate concentration decreased by 20 ± 8% \((p < 0.05)\) 5 minutes after reaching the peak value, and by 28 ± 11% \((p < 0.05)\) 10 minutes after the peak value.

The mean effluent lactate concentration during the 30-minute ischemic period was also calculated for each group of rat hearts. The severe ischemia rat heart group did not produce an adequate volume of venous effluent to make timed collections; therefore, the entire 30-minute ischemic collection was analyzed as a single sample to provide a mean value of lactate production and to permit comparison between the three ischemic rat heart groups. The mean effluent arterial-venous \((AV)\) lactate concentration gradients during the ischemic period for the severe, moderate and mild ischemia groups were 3.66 ± 0.98, 2.73 ± 0.15, and 1.78 ± 0.26 mM respectively. The difference between the mild and moderate ischemia groups was significant at \(p < 0.01\), but the difference between the moderate and severe ischemia groups was not statistically significant \((p = 0.2-0.4)\).

As with the rat hearts, the rabbit hearts showed a time-course of lactate production that progressively increased to a relatively short-lived peak value and then progressively declined (fig. 4). In the severe ischemia group, after reaching the peak value, the effluent lactate level decreased by 8 ± 2% \((p < 0.005)\) during the subsequent 10 minutes, by 22 ± 4% \((p < 0.001)\) after 30 minutes, and by 36 ± 6% \((p < 0.001)\) after 50 minutes. In the moderate ischemia group, the effluent lactate concentration decreased from the peak value by 12 ± 5% \((p < 0.025)\) after 5 minutes, by 32 ± 7% \((p < 0.001)\) after 30–35 minutes, and by 42 ± 8% \((p < 0.001)\) after 60–65 minutes. Thus, in both species, the rate of lactate production decreased progressively, despite a constant degree of ischemia.

**Lactate Production and Severity of Ischemia**

The amount of myocardial lactate production \((V-A)\) concentration difference \(\times\) myocardial perfusion rate\) was progressively reduced at more severe degrees of ischemia, despite an increase in the concentration difference across the heart (fig. 5). In the rat myocardium, the amount of lactate production in the severe ischemia group was only 12% of that in the mild ischemia group; likewise, in the rabbit myocardium, the amount of lactate production during severe ischemia was only 29% of that during moderate ischemia. Thus, more severe ischemia resulted in a marked reduction in lactate production in both species.

**Model of Regional Ischemia**

To apply our data to patients with coronary artery disease, we constructed a model of heterogenous myocardial perfusion using the rates of lactate production obtained in the isolated myocardial preparations, and calculated the resultant lactate level in the mixed coronary sinus sample composed of ischemic and non-ischemic drainage. This extrapolation from the global to regional ischemic condition is complicated by two factors. First, because the rate of lactate production was not constant (figs. 1–4), we used the mean rate of lactate production for each degree of ischemia in the isolated hearts. Second, because the normal coronary
perfusion rate per gram of myocardium is approximately 2.5 times greater in the rat and rabbit heart than in man.\textsuperscript{21, 24} We considered various degrees of ischemia in terms of a percentage reduction of the normal coronary arterial flow, and assumed that the rate of ischemic lactate production would be similar for comparable relative degrees of ischemia. Lactate metabolism in the nonischemic region was calculated using lactate extraction coefficients of 10% or 60%, which represent the lower and upper normal limits in man,\textsuperscript{4} a nonischemic regional flow rate of 1.0 ml/min/g, and an arterial lactate concentration of 1.0 mM, because these values are also in the normal range for man.

We reasoned that the degree of regional ischemia could change in one of two ways, by amount or severity. The amount of ischemic tissue could remain a constant fraction of the ventricle, but the severity of the ischemic state could vary; alternatively, the amount of ischemic tissue could also vary. We calculated how the arterial-coronary sinus lactate concentration gradient would be affected 1) when a constant fraction of the ventricle changed in severity of ischemia, and 2) when the percentage of ischemic ventricular tissue increased from 20% to 50% of the ventricular mass while the severity of the ischemic state remained constant.

The results of our analysis are shown in table 1 and figure 6. The data in panel A of table 1 result when 20% of the ventricle is ischemic; in panel B, the data result when 50% of the ventricle is ischemic. Each panel is subdivided to consider a nonischemic rate of lactate use of 10% or 60%. Five degrees of ischemia are tabulated.

**Discussion**

In this study, we investigated the ischemic metabolic behavior of isolated myocardium from rats and rabbits to determine whether the rate of lactate production or the effluent lactate concentration could serve as a reliable index of the degree of ischemia. An isolated, globally ischemic heart preparation was used to permit the myocardial perfusion rate to be precisely controlled, so that different degrees of ischemia could be produced and held constant throughout the experimental period. In experimental models where a coronary occlusion is used to produce ischemia, the ischemic region consists of a mixture of moderately and severely ischemic tissues;\textsuperscript{26} therefore, the local venous drainage from an ischemic region of a ventricle probably represents the average of effluents of areas with different metabolic rates. Further, with regional ischemia, it is impossible to exclude the possibility of a well-oxygenated collateral contribution to the local venous drainage; such collateral flow could “contaminate” the ischemic drainage with nonischemic venous blood and distort any calculations of the metabolic flux in the ischemic tissue.\textsuperscript{26} Our globally ischemic preparation ensured that the venous effluent consisted of a “pure” ischemic sample that accurately reflected the metabolism of the ischemic myocardium.

We made two fundamental observations that bear directly upon the interpretation of myocardial lactate

![Figure 5](http://circ.ahajournals.org) Effluent lactate concentration and rates of lactate production at different degrees of ischemia. The coronary venous – arterial lactate concentration gradient (scale on right) for the isolated globally ischemic rat (o - - - o) and rabbit ( - - - - ) hearts, and for data points calculated from Waters et al.\textsuperscript{4} (△ - - - △) and representing local venous drainage from dog hearts subjected to coronary artery ligation, are plotted for different degrees of ischemia. Rates of lactate production for the rat ( - - - - ), rabbit ( - - - - ) and dog heart ( - - - - ) are plotted according to the scale on the left. Although the lactate concentration gradient progressively increases with more severe ischemia, the rate of lactate production is maximal with mild-to-moderate ischemia and decreases with severe ischemia.
### Table 1. Predicted Coronary Sinus Lactate Levels Under Different Ischemic Conditions

<table>
<thead>
<tr>
<th></th>
<th>A) Ischemia affects 20% of a 200-g ventricle</th>
<th>B) Ischemia affects 50% of a 200-g ventricle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. NIR * = 10% lactate extraction</td>
<td>2. NIR = 60% lactate extraction</td>
</tr>
<tr>
<td>Ischemic region (NIR)</td>
<td>160 g</td>
<td>160 g</td>
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<tr>
<td>Effluent lactate conc (mM)</td>
<td>0.9</td>
<td>0.4</td>
</tr>
<tr>
<td>Regional flow (ml/min)*</td>
<td>160</td>
<td>160</td>
</tr>
<tr>
<td>Regional lactate efflux (μmoles/min)</td>
<td>144</td>
<td>64</td>
</tr>
<tr>
<td>Nonischemic region</td>
<td>40 g</td>
<td>40 g</td>
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1) Mild ischemia (40% decrease in coronary flow)

<table>
<thead>
<tr>
<th></th>
<th>Effluent lactate conc† (mM)</th>
<th>Regional flow (ml/min)</th>
<th>Regional lactate efflux (μmoles/min)</th>
<th>Coronary sinus lactate conc (mM)</th>
<th>Net lactate balance‡</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>2.78</td>
<td>24</td>
<td>66.7</td>
<td>1.15</td>
<td>+15%</td>
</tr>
<tr>
<td></td>
<td>2.78</td>
<td>24</td>
<td>66.7</td>
<td>1.15</td>
<td>-29%</td>
</tr>
</tbody>
</table>

2) Moderate ischemia (72% decrease in coronary flow)

<table>
<thead>
<tr>
<th></th>
<th>Effluent lactate conc† (mM)</th>
<th>Regional flow (ml/min)</th>
<th>Regional lactate efflux (μmoles/min)</th>
<th>Coronary sinus lactate conc (mM)</th>
<th>Net lactate balance‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.74</td>
<td>11.2</td>
<td>41.9</td>
<td>1.09</td>
<td>+9%</td>
</tr>
<tr>
<td></td>
<td>3.74</td>
<td>11.2</td>
<td>41.9</td>
<td>1.09</td>
<td>-38%</td>
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3) Severe ischemia (97% reduction in coronary flow)

<table>
<thead>
<tr>
<th></th>
<th>Effluent lactate conc† (mM)</th>
<th>Regional flow (ml/min)</th>
<th>Regional lactate efflux (μmoles/min)</th>
<th>Coronary sinus lactate conc (mM)</th>
<th>Net lactate balance‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.66</td>
<td>1.2</td>
<td>5.6</td>
<td>0.93</td>
<td>-7%</td>
</tr>
<tr>
<td></td>
<td>4.66</td>
<td>1.2</td>
<td>5.6</td>
<td>0.93</td>
<td>-57%</td>
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4) Moderate ischemia (80% decrease in coronary flow)

<table>
<thead>
<tr>
<th></th>
<th>Effluent lactate conc§ (mM)</th>
<th>Regional flow (ml/min)</th>
<th>Regional lactate efflux (μmoles/min)</th>
<th>Coronary sinus lactate conc (mM)</th>
<th>Net lactate balance‡</th>
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<tbody>
<tr>
<td></td>
<td>3.34</td>
<td>8</td>
<td>26.7</td>
<td>1.02</td>
<td>+2%</td>
</tr>
<tr>
<td></td>
<td>3.34</td>
<td>8</td>
<td>26.7</td>
<td>1.02</td>
<td>-46%</td>
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5) Severe ischemia (98% reduction in coronary flow)

<table>
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<tr>
<th></th>
<th>Effluent lactate conc§ (mM)</th>
<th>Regional flow (ml/min)</th>
<th>Regional lactate efflux (μmoles/min)</th>
<th>Coronary sinus lactate conc (mM)</th>
<th>Net lactate balance‡</th>
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<tbody>
<tr>
<td></td>
<td>7.51</td>
<td>0.80</td>
<td>6.01</td>
<td>0.93</td>
<td>-7%</td>
</tr>
<tr>
<td></td>
<td>7.51</td>
<td>0.80</td>
<td>6.01</td>
<td>0.93</td>
<td>-56%</td>
</tr>
</tbody>
</table>

*The arterial lactate concentration was assumed to be 1.0 mM, and nonischemic regional (NIR) flow to be 1.0 ml/min/g.
†Effluent lactate concentration based on a similar degree of ischemia in isolated rat heart muscle.
‡Net lactate balance = venous − arterial/arterial × 100; net lactate production yields a positive balance.
§Effluent lactate concentration based on a similar degree of ischemia in isolated rabbit heart muscle.
Abbreviations: conc = concentration; NIR = nonischemic region.
production data. First, the rate of ischemic lactate production was not constant under conditions of constant ischemia, but followed a biphasic time course. During the initial 10-15 minutes of ischemia, the effluent lactate concentration progressively increased to a peak value, but with subsequent ischemia it decreased progressively and markedly (figs. 1-4). Second, more severe ischemia resulted in less myocardial lactate production (moles/min), despite an increase in the AV concentration difference.

The inconstant rate of lactate efflux over time significantly complicates the interpretation of clinical data, because it is usually difficult, if not impossible, to know the precise moment of the onset of ischemia and where one stands on the natural time-course of the rate of lactate production when a given coronary venous sample is drawn. Sequential measurements of lactate production in patients should be interpreted with the knowledge that the rate of lactate production can decrease by as much as 50% over a 15-minute period of constant ischemia. Thus, a progressive decrease in myocardial lactate production does not necessarily imply relief of ischemia.

The changing time-course of the rate of lactate production can also obscure differences in the degree of ischemia; a 5-10-minute period of ischemia was required before the effluent lactate concentrations became significantly different, despite different degrees of ischemia (figs. 1 and 3), and after 25 minutes of ischemia, the rate of lactate production had decreased so that two degrees of ischemia no longer produced significantly different effluent lactate concentrations (fig. 1). In clinical studies of lactate metabolism during exercise or pacing-induced ischemia, the ischemic state is usually not maintained for more than 5-10 minutes; the rate of lactate production might not be affected during this time, despite the application of an intervention that altered the degree of ischemia.

The mechanism for the decrease in lactate production with ischemia of progressive duration was not specifically studied, but it was probably due to
progressive acidosis or tissue lactate accumulation that inhibits the glycolytic pathway, \(^{20, 21}\) depletion of myocardial glycogen, \(^{28}\) or the loss of necessary glycolytic co-factors, such as inorganic phosphate \(^{37}\) or adenosine, which leaks out of the ischemic myocardium as inosine and hypoxanthine, \(^{28}\) and is required in the form of adenosine diphosphate for several glycolytic reactions. The restriction of coronary flow itself during ischemia, especially in the severe ischemia experiments where tissue perfusion was markedly reduced, may also have limited the eflux of lactate from the ischemic cell.

Lactate production was decreased during more severe degrees of ischemia. Some mechanisms possibly responsible for the decrease in lactate production at more severe degrees of ischemia have been noted above (i.e., increased tissue acidosis, lactate accumulation or restricted eflux of lactate from the cell due to the low-flow state); regardless of the mechanism, the inverse relationship between lactate production and severity of ischemia profoundly affects the interpretation of coronary venous lactate data.

Our analysis of regional ischemia shows that the coronary sinus lactate level will be lower during more severe degrees of ischemia (table 1 and fig. 6). The inverse relationship between the severity of ischemia and the coronary sinus lactate concentration is the result of two factors. First, the mixed coronary sinus level depends on the net ischemic regional lactate eflux (moles/min), not solely on the ischemic regional concentration. Because the rate of lactate production is markedly reduced at more severe degrees of ischemia (fig. 5), fewer moles of lactate drain from the severely ischemic region. Second, the ischemic regional drainage is diluted in the nonischemic drainage; at more severe degrees of ischemia (i.e., at lesser ischemic perfusion rates), the dilution effect is greater. These two factors are additive in reducing the coronary sinus lactate concentration at more severe degrees of ischemia. Figure 6 and table 1, examples 1–3, show the data for three degrees of ischemia based on lactate metabolism in the rat myocardium. At a constant lactate extraction by the nonischemic region and a constant ischemic fraction of the ventricle (i.e., within each column), the coronary sinus lactate level decreases as the degree of ischemia becomes more severe. A similar pattern occurs in examples 4 and 5, which are based on data from the rabbit myocardium.

Our observation that partial relief of severe ischemia results in an increased rate of lactate production (fig. 5) explains an apparent "paradox" recently reported by Wyatt et al. \(^{19}\) These workers increased the preload in dogs subjected to stenosis of the left anterior descending artery and observed an increase in regional myocardial blood flow, an improvement in regional contractile function and an increase in regional lactate production. They reasoned that the increase in regional lactate production indicated an increase in the relative severity of ischemia and that the increases in regional function and flow were "paradoxes." Our results indicate that no "paradox" exists: The increase in regional lactate production observed by Wyatt et al. \(^{19}\) would be expected with partial relief of a severe degree of ischemia (fig. 5) and is consistent with their observed increase in regional flow and function.

Our model (table 1 and fig. 6) shows that an increase in the size of the ischemic fraction of the ventricle will generally increase the net lactate balance as measured in the coronary sinus; however, for a given ischemic fraction, the change in lactate balance will be inversely related to the severity of ischemia. For example, if a mildly ischemic region increases in size from 20% to 50% of the left ventricle and nonischemic lactate extraction is constant at 10%, our data (table 1 and fig. 5, example 1) predict that the net lactate balance would increase from +15% to +61%, or by 46%. However, if a severely ischemic region increased in size from 20% to 50% of the ventricle (table 1 and fig. 6, example 3) the net lactate balance would increase from −7% to +1%, a change of only 8%. Thus, a given change in lactate balance does not consistently mirror the magnitude of change in ischemic fraction. If both the severity of ischemia and the size of the ischemic fraction changed simultaneously, the net lactate balance could increase, decrease or remain the same.

The rate of lactate use by the nonischemic region of the ventricle is as important, or is more important, in determining the mixed coronary sinus level than is the rate of ischemic lactate production. If the nonischemic region extracts only 10% of the arterial lactate, the coronary sinus lactate level will be abnormal (i.e., <10% extraction of arterial lactate) in all of the examples in table 1 and figure 6. However, if the rate of nonischemic lactate use is at the high end of the normal range (60% extraction), the nonischemic pattern will predominate in the coronary sinus. For example, when 20% of the ventricle is ischemic and the nonischemic region extracts 60% of the arterial level (table 1, panel A, column 2 and fig. 6), the coronary sinus lactate level is well within the normal range for all degrees of ischemia. When 50% of the ventricle is mildly or moderately ischemic (table 1, panel B, column 2, examples 1 and 2), an abnormal coronary sinus lactate level results, but with a more severe degree of ischemia (example 3), even when 50% of the ventricle is ischemic, a nonischemic metabolic pattern is observed in the coronary sinus. Further, changes in lactate extraction by the nonischemic region within the normal range would have a marked effect on the coronary sinus level and could easily change the net lactate balance from abnormal to normal or vice versa, without any change in the degree of ischemia or the size of the ischemic fraction. For example, with mild ischemia and an ischemic fraction of 20% (table 1 and fig. 6, example 1), the net lactate balance would be +15% (abnormal) when the nonischemic region extracted 10% of the arterial lactate and −29%, a value well within the normal range, if the nonischemic region extracted 60% of the arterial level. Likewise, with moderate ischemia and an ischemic fraction of 50% (table 1 and fig. 6, example 4), a 10% extraction rate in the nonischemic region would result in a markedly ab-
normal net lactate balance of + 31%, but a 60% extraction rate in the nonischemic region would result in a normal net balance of −11%, and mask the ischemia affecting half of the ventricle.

Several factors have been shown to influence the rate of lactate extraction and oxidation by normal, well-oxygenated myocardial tissue in both man and experimental studies. In man, the rate of lactate extraction is generally proportional to the arterial lactate level.29 In patients subjected to exercise the lactate extraction ratio (difference in AV lactate concentration/arterial lactate level) did not change significantly,30-32 because the AV lactate difference increased in proportion to the exercise-induced increase in arterial lactate level.30, 31 However, in some patients exercise caused a marked increase (two- to fourfold) in the lactate extraction ratio.30-33 Likewise, atrial pacing did not change the mean lactate extraction ratio in a group of noncoronary disease patients,8 but nonischemic patients have shown 50% increases in their rates of lactate use during a pacing-induced stress;7 during the postspacing recovery period, lactate extraction increased by 30-40% in several nonischemic patients.34, 35 Catecholamine infusion in 15 normal human subjects increased the mean lactate extraction ratio from 26% to 34%, with some patients showing a much more marked response.36 The rate of myocardial lactate extraction and oxidation is also influenced by several biochemical interrelationships. Alkalosis increased lactate extraction and oxidation; a pH shift from 7.1 to 7.7 was associated with a 50% increase in the lactate oxidation rate.37 Lactate oxidation was suppressed 25% by the presence of glucose alone, and completely by the presence of both glucose and insulin.38 The presence of acetate decreased the rate of myocardial lactate metabolism; the effect of fasting is to decrease the rate of lactate oxidation.38-40 Thus, the rate of lactate extraction by nonischemic myocardial tissue is subject to a number of influences, many of which cannot be adequately measured or controlled during clinical studies of myocardial lactate metabolism; nonetheless, the arterial-coronary sinus lactate concentration difference may be influenced more by the metabolic rate of the nonischemic fraction of the heart than by the ischemic fraction.

Our results may warrant a reconsideration of the conclusions of Waters et al.41 regarding the interpretation of changes in myocardial lactate balance. These workers produced progressive stenosis of the anterior descending coronary artery in the dog, observed a progressive increase in the regional AV lactate concentration gradient, and concluded that changes in myocardial lactate balance will generally reflect a parallel change in the degree of ischemia. From the lactate concentration data of Waters et al., we calculated approximate rates of lactate production (assuming an arterial lactate concentration of 1.0 mM and a control coronary flow rate of 1 ml/min/g) and plotted the results (fig. 5). The rate of lactate production in the dog heart, as in the rat and rabbit myocardium, showed a similar relationship to the degree of ischemia, increasing as the coronary flow was reduced from 100% to 20% of normal, but decreasing with further reductions in coronary flow. Thus, the fundamental principle that more severe ischemia results in less lactate production appears to hold in several species, and is probably true in man as well.

Our model of regional ischemia (table 1 and fig. 6) shows that the coronary sinus lactate level depends upon the severity of ischemia, the size of the ischemic fraction of the ventricle, and the rate of lactate use in the nonischemic region. At any given degree of ischemia and nonischemic rate of lactate use, the "critical ischemic fraction" can be derived from our metabolic data; the critical ischemic fraction is the minimal fraction of the ventricle that must be ischemic in order to produce a pattern of net lactate production in the coronary sinus. The calculation of the critical ischemic fraction is presented in detail as an appendix to this paper; the results are shown in figure 7. Comparable estimates of the critical ischemic fraction result from analysis of the data from either the rat or rabbit myocardium.

The critical ischemic fraction is larger when the nonischemic region extracts more lactate, or when the degree of ischemia is more severe (fig. 7). With severe ischemia of more than 95% coronary flow reduction, and a 60% rate of lactate extraction in the nonischemic region, net myocardial lactate production would occur only when more than 85% of the ventricle is ischemic; if the nonischemic region extracted only 10% of the arterial lactate, net lactate production, as measured by coronary sinus sampling, would still re-

![Figure 7](https://example.com/figure7.png)
quire that almost 50% of the ventricle be ischemic. At less severe degrees of ischemia, the critical ischemic fraction is less. At any degree of ischemia, the critical ischemic fraction is markedly increased when there is an increase in the rate of lactate use in the non-ischemic zone, because a greater ischemic mass is required to "compensate" if the coronary sinus level is to exceed the arterial level. This analysis of the critical ischemic fraction offers an explanation for the failure to observe net myocardial lactate production in some patients with coronary artery disease despite clinical and electrocardiographic evidence of ischemia at the time of coronary sinus sampling.5-7, 17, 34, 36

Our analysis of the critical ischemic fraction may also be pertinent to coronary sinus sampling studies of patients with myocardial infarction. Because cardiogenic shock and death occur when more than 35-40% of the left ventricle is severely ischemic,42,43 it is unlikely that a patient could long survive with an ischemic fraction of this size. Consequently, when net myocardial lactate production in a mixed coronary sinus sample is observed in a patient with an infarct, the lactate may be emanating from a region of mild or moderate ischemia, rather than from a severely ischemic region, because in order to yield net lactate production, a severely ischemic region would have to be so large as to be incompatible with life, according to figure 7. Therefore, in a case of myocardial infarction, net lactate production at the coronary sinus level may reflect the metabolic activity of the moderately ischemic border zone rather than the more severely ischemic central zone. These considerations are also consistent with the observation that ischemic metabolic changes in patients who underwent coronary sinus catheterization were more consistently abnormal for subtotal coronary artery occlusions than for total coronary artery occlusions,44 because the latter group might be expected to have a more severe degree of ischemia and a larger critical ischemic fraction.

In this study we used metabolic data obtained from globally ischemic animal hearts to predict ischemic coronary sinus lactate levels in man; such an extrapolation always carries the risk of invalidity due to interspecies differences. However, similar conclusions were reached when we used metabolic data from either isolated rat or rabbit myocardium. Circumstantial evidence supporting the validity of our approach also comes from studies of myocardial metabolism in man. When we used the metabolic data obtained in the globally ischemic rat and rabbit hearts, we calculated a predicted coronary sinus lactate concentration gradient that ranged from negative values to 0.61 mM above the arterial value (table 1). A review of several studies of ischemic myocardial metabolism in man where coronary sinus lactate concentrations were reported during pacing-induced angina45,46 yielded 23 patients in whom lactate production occurred. These patients had coronary sinus lactate levels that were 0.02-1.3 mM above the arterial level, with a mean of 0.34 mM. Thus, these values are consistent with our model, especially considering that we assumed complete mixing in the coronary sinus, whereas, in a given patient, the coronary sinus catheter might selectively sample the ischemic drainage and thereby result in a higher lactate concentration.

In summary, our studies indicate that sequential changes in lactate balance, as measured in the coronary sinus, do not reliably reflect changes in the severity or amount of ischemia. These results may warrant the reevaluation of interventions that were previously judged beneficial or deleterious primarily because of their effect on myocardial lactate metabolism, because the change in lactate balance may have been a misleading measure of any change in the ischemic condition.

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Appendix

Calculation of "Critical Ischemic Fraction"

The critical ischemic fraction was defined as the minimum fraction of the ventricle that must be ischemic if net myocardial lactate production is to occur, i.e., if the coronary sinus level is to exceed the arterial level.

The coronary sinus concentration is determined by

\[ \text{CSC} = \frac{\text{IRE} + \text{NIRE}}{\text{IRF} + \text{NIRF}} \]  

(1)

where CSC is the coronary sinus lactate concentration (µmoles/ml), IRE is the ischemic regional lactate efflux (µmoles/min), NIRE is the nonischemic regional lactate efflux (µmoles/min), IRF is the ischemic regional flow (ml/min), and NIRF is the nonischemic regional flow (ml/min).

The regional lactate effluxes in µmoles/min can be defined in terms of regional flow per gram x regional effluent concentration x grams of tissue in each region. Thus, for the ischemic region, \( \text{IRE} = \text{IRF} \times \text{IG} \times \text{IVC} \), where IRE is the ischemic regional flow rate in ml/min/g, IG is the amount of ischemic tissue (in grams), and IVC is the ischemic venous lactate concentration (µmoles/ml); a similar relation obtains for the nonischemic region, where the NIRE = NIRFR × NIG × NIVC.

For 100 grams of ventricular tissue, the nonischemic tissue will equal 100 grams minus the ischemic tissue (NIG = 100 - IG). Thus, equation 1 can be rewritten:

\[ \text{CSC} = \frac{\left(\text{IRF} \times \text{IG} \times \text{IVC}\right) + \left[\text{NIRF} \times (100 - \text{IG})\right]}{\left(\text{IRF} \times \text{IG}\right) + \left[\text{NIRFR} \times (100 - \text{IG})\right]} \]  

(2)

Assuming a nonischemic regional flow rate (NIRFR) of 1 ml/min/g one can write

\[ \text{CSC} = \frac{\left(\text{IRF} \times \text{IG} \times \text{IVC}\right) + \left[\text{NIRF} \times (100 - \text{IG})\right]}{\left(\text{IRF} \times \text{IG}\right) + \left(100 - \text{IG}\right)} \]  

(3)
Effect of Medical vs Surgical Treatment on Symptoms in Stable Angina Pectoris

The Veterans Administration Cooperative Study of Surgery for Coronary Arterial Occlusive Disease

PETER PEDUZZI, PH.D. AND HERBERT N. HULTGREN, M.D.

SUMMARY The comparative effect of medical vs surgical treatment on symptoms in patients with stable angina has been evaluated in a large-scale randomized study. We obtained systematic information regarding symptoms and medication requirements by questionnaire, and a scoring system was devised to provide an index of severity. Data are available on 384 patients who had an entry questionnaire, 639 with an annual questionnaire and 329 who had both an entry and a 1-year questionnaire. A severe degree of angina and associated symptoms were present at entry. Symptoms were similar in both treatment groups at entry. At 1 year, surgical patients had a significant improvement in symptoms. Approximately 60% had marked improvement or were free of angina, compared with 16% of patients treated medically. Only 14% of surgical patients were unchanged or worse at 1 year, compared with 56% of medical patients. These results are comparable to those reported by other studies that have examined the effect of surgical vs medical treatment of angina. Surgical patients in the Veterans Administration Study took substantially less daily medication at 1 year, while medical patients took moderately more. Relief of symptoms in surgical patients was related to graft patency, and patients who had all grafts patent had the most striking improvement. In 29 patients with all grafts closed, symptoms were significantly less severe at 1 year than in patients who took medical treatment. A placebo effect or an undetermined effect of surgery on pain may explain this phenomenon.

AN IMPORTANT OBJECTIVE of surgery for coronary artery disease is the relief of angina. In most studies, simple, descriptive methods of assessing severity or change in angina have been used. Angina may be described as severe, moderate, mild or absent on the basis of the number of episodes per day and the amount of disability produced. After treatment, angina may be described as absent, improved, unchanged or worse compared with the pretreatment status. Such methods are of limited value in systematic studies, because the frequency and severity of angina may be profoundly altered by the amount of daily physical activity, employment status and the use of prophylactic medications such as long-acting nitrates and β-blocking agents. The New York Heart Association (NYHA) functional classification is often used, but has several limitations, especially in the evaluation of angina. This classification system has recently been revised.3

To assess more systematically the severity of angina and associated symptoms, a physician-administered questionnaire was developed and used in a large-scale prospective randomized study of the effect of medical vs surgical management of stable angina. In this paper we describe the questionnaire used to assess angina and present baseline and 1-year follow-up data on the Veterans Administration (VA) study patients.

Materials and Methods

The VA cooperative study of coronary artery bypass surgery is a controlled clinical trial of medical therapy vs surgical plus medical therapy for patients with coronary artery disease who have stable angina. This study began in 1970 and continued through 1974,
Limitations of lactate production as an index of myocardial ischemia.
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