Glucose Extraction by the Human Myocardium during Pacing Stress

By ALBERT S. MOST, M.D., RICHARD GORLIN, M.D., and J. STUART SOELDNER, M.D.

SUMMARY
Glucose extraction by ischemic human myocardium was investigated at the time of diagnostic cardiac catheterization in 27 subjects who had fasted overnight. Paired arterial and coronary sinus blood samples, obtained before and during coronary sinus pacing, were analyzed for glucose and lactate. Pacing to a rate 50 to 70% greater than control or to the development of chest pain induced no significant change in the arterial level of either substrate. No correlation was noted between arterial level and myocardial extraction of either substrate at rest or during stress.

Three groups of subjects were identified: group I: those with lactate extraction at rest and during pacing (n = 13); group II: those with lactate extraction at rest but production during pacing (n = 7); and group III: those with lactate production at rest with augmented production during pacing (n = 5). Two additional subjects produced lactate at rest but were not paced. Glucose extraction increased significantly with pacing tachycardia in group II (0.09 ± 0.03 mm to 0.26 ± 0.04 mm) and in group III (0.38 ± 0.17 mm to 0.58 ± 0.12 mm). No significant increase was noted in group I. A significant correlation was noted between glucose extraction and lactate production during pacing when groups II and III were combined (r = 0.81; P < 0.001).

Myocardial ischemia in man was associated with augmented glucose extraction. The arterial glucose concentration was not a primary determinant of glucose extraction either before or during induced ischemia.

Additional Indexing Words:
Myocardial ischemia Lactate metabolism Substrate utilization

EXOGENOUS glucose exerts a protective effect on myocardial function during and following myocardial anoxia in a wide variety of experimental conditions. In addition, augmented myocardial glucose uptake occurs during ischemia in dogs. Despite growing interest in the effect of circulating substrates on ischemic human myocardium, little is known about cardiac substrate uptake during myocardial ischemia in man. In this investigation, simultaneous transmyocardial glucose and lactate differences were determined before and during pacing stress in subjects with angina pectoris.

Method

Twenty-seven postabsorptive adult subjects were studied after an overnight fast. This study protocol was carried out at the conclusion of a routine diagnostic cardiac catheterization which included selective coronary cinearteriography. No glucose was administered during the preceding catheterization nor at any time during the stress protocol.

A no. 8 bipolar pacing Goodale-Lubin catheter was placed in the coronary sinus and remained in
a fixed position during the study as ascertained by fluoroscopy. An arterial catheter was left in place following the diagnostic procedure. Simultaneous, paired blood samples were drawn from the artery and coronary sinus, and pacing was then begun from the coronary sinus at a rate 20 to 30% above control. This was increased by 10 beats/min every 2 to 3 min until either angina pectoris developed or a rate 50 to 70% greater than control was achieved. This rate was then continued for 2 to 3 min and paired arterial and coronary sinus blood samples were obtained at the end of the period. Pacing was then discontinued.

Whole-blood glucose was determined by microtechnic on a Technicon autoanalyzer using the ferricyanide method. The coefficient of variation of this method is 1.3%. Each sample was divided into nine aliquots which were analyzed separately. The mean of each set of nine values was used for the blood glucose result. Plasma glucose was determined in triplicate by the glucose oxidase technic in two subjects and these are included without any adjustment for differences in technic (one in group I, one in group III).

Lactate was analyzed in duplicate from a perchloric acid blood extract by an enzymatic method. Duplicate lactate determinations agreed within an average of 0.03 mm.

Lactate extraction was defined as any positive difference in arterial minus coronary sinus (a − cs) lactate concentration. Lactate production was defined as a zero or a negative difference in arterial − coronary sinus (a − cs) lactate concentration and is hereafter interpreted as evidence of myocardial ischemia. Subjects could be subdivided into three groups: I: those with lactate extraction both at rest and during pacing; II: those with lactate extraction at rest and production during pacing stress; and III: those with lactate production both at rest and during pacing stress. Two additional subjects were lactate producers at rest but were not paced. These added to the group III subjects at rest comprise group IIIA.

### Table 1

<table>
<thead>
<tr>
<th>Glucose (mg/100 ml)</th>
<th>Rest</th>
<th>Pace</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 – 89</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>90 – 109</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>110 – 129</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>130 or more</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

### Results

The arterial concentration ranges for glucose and lactate are shown in tables 1 and 2. Glucose is presented in milligrams per 100 milliliters for ease of interpretation. Arterial concentrations of lactate and glucose were remarkably similar from group to group and did not change significantly within any group from the control to the paced state (tables 3 and 4).

No significant first-order relationship was seen between the arterial concentrations of either glucose or lactate and their respective (a − cs) differences under any of the study conditions. Of particular note, no significant relation was seen between the arterial glucose concentration and the (a − cs) glucose difference during pacing stress which resulted in lactate production (groups II and III combined).

A significant increase in lactate production and glucose extraction was observed with pacing in groups II and III. No change was observed in the (a − cs) lactate or glucose differences in group I with pacing stress. A significant (P < 0.001) correlation (r = 0.81) was observed between glucose extraction and lactate production during pacing stress in combined groups II and III (fig. 1).

### Discussion

In this investigation, myocardial ischemia in man was associated with augmented glucose extraction. Stress-induced increases in myocardial lactate production (group III) were associated with augmentation of already high glucose uptakes, raising the question whether exogenous glucose availability could become a significant determinant of myocardial lactate.

### Table 2

<table>
<thead>
<tr>
<th>Lactate (mm)</th>
<th>No. of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.20 – 0.39</td>
<td>2</td>
</tr>
<tr>
<td>0.40 – 0.59</td>
<td>15</td>
</tr>
<tr>
<td>0.60 – 0.79</td>
<td>4</td>
</tr>
<tr>
<td>0.80 or more</td>
<td>4</td>
</tr>
</tbody>
</table>

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Table 3

Arterial and Arterial-Coronary Sinus Lactate Concentrations at Rest and during Pacing Stress

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of subjects</th>
<th>Rest</th>
<th>Pace</th>
<th>p* rest vs. pace</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>13</td>
<td>0.60 ± 0.08†</td>
<td>0.17 ± 0.03</td>
<td>0.62 ± 0.09</td>
</tr>
<tr>
<td>II</td>
<td>7</td>
<td>0.58 ± 0.06</td>
<td>0.16 ± 0.03</td>
<td>0.54 ± 0.06</td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>0.55 ± 0.04</td>
<td>-0.09 ± 0.02</td>
<td>0.55 ± 0.04</td>
</tr>
<tr>
<td>IIIA†</td>
<td>7</td>
<td>0.54 ± 0.04</td>
<td>-0.11 ± 0.03</td>
<td>-</td>
</tr>
<tr>
<td>II &amp; III</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td>0.54 ± 0.04</td>
</tr>
</tbody>
</table>

Abbreviations: a = arterial concentration; cs = coronary sinus concentration; NS = not significant. 
†P values derived from paired t-test.
‡Group III (n = 5) plus two additional subjects who produced lactate at rest but were not paced.

Table 4

Arterial and Arterial-Coronary Sinus Glucose Concentrations at Rest and during Pacing Stress

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of subjects</th>
<th>Rest</th>
<th>Pace</th>
<th>p* rest vs. pace</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>13</td>
<td>5.66 ± 0.20†</td>
<td>0.15 ± 0.04</td>
<td>5.77 ± 0.22</td>
</tr>
<tr>
<td>II</td>
<td>7</td>
<td>5.59 ± 0.26</td>
<td>0.09 ± 0.03</td>
<td>5.80 ± 0.76</td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>5.61 ± 0.31</td>
<td>0.38 ± 0.17</td>
<td>6.02 ± 0.22</td>
</tr>
<tr>
<td>IIIA†</td>
<td>7</td>
<td>5.68 ± 0.24</td>
<td>0.37 ± 0.12</td>
<td>-</td>
</tr>
<tr>
<td>III &amp; III</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td>5.89 ± 0.20</td>
</tr>
</tbody>
</table>

Abbreviations and symbols have same meaning as in table 3.

production. Group III hearts represent chronic ischemia rendered more severe by the imposed stress and may indeed be glycogen depleted and dependent upon exogenous glycolytic substrate as a major precursor for lactate production.

In no instance could a stoichiometric relationship be demonstrated; that is, 2 moles of lactate produced for 1 mole of glucose extracted. As a general rule, more moles of glucose were extracted than moles of lactate produced (1.0 mM glucose extracted for 0.8 mM of lactate released). In group III subjects, however, the increase in lactate production (0.27 mM) was greater than the increase in glucose uptake (0.20 mM). This may reflect a more direct conversion of exogenous glucose into lactate during more prolonged ischemic stress. The absence of a direct 2:1 molar relationship between lactate production and glucose uptake, also reported in the ischemic dog heart,4 can be attributed to (1) heterogeneity of tissue ischemia, (2) continued utilization of endogenous glycogen stores by ischemic tissue, (3) different transmembrane kinetics for glucose (influx) and lactate (efflux) independent of their metabolic interrelationship, and (4) induction of only partial ischemia, permitting hypoxic cells

Figure 1

Correlation between glucose extraction and lactate production during myocardial ischemia in combined groups II and III. All subjects were being paced.

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to continue glucose oxidation. Differing kinetics for lactate and pyruvate have been demonstrated\textsuperscript{12} and a similar disparity may apply to relative movements of lactate and glucose.

Both exogenous glucose and endogenous glycogen are major precursors of lactate production during anoxia.\textsuperscript{2, 13} Using glucose-U\textsuperscript{14C}, Scheuer and Stezoski\textsuperscript{13} have shown that pharmacologic enhancement of myocardial glycogen stores lessens dependence on exogenous glucose as a lactate precursor during myocardial anoxia. Furthermore, physiologic levels of exogenous glucose could not totally substitute for glycogen as a source of anaerobic energy during myocardial anoxia.\textsuperscript{13} It appears that both exogenous glucose and endogenous glycogen simultaneously serve as precursors for lactate production during anoxia, with the former partially sparing the latter.\textsuperscript{2}

These observations, and that of Reeves,\textsuperscript{14} support the premise that exogenous glucose plays an important role as a precursor for lactate production before endogenous glycogen is depleted. It would then seem reasonable to expect that accelerated glucose transport into anoxic myocardial cells\textsuperscript{15, 16} may proceed before labile glycogen reserves are depleted. Given these facts, it is probable that total exhaustion of endogenous glycogen stores following induction of ischemia may be long delayed in vivo where circulating glucose is abundantly available. More prolonged or severe stress may be required before total dependence on exogenous glycogen as a lactate precursor becomes established. The degree and rate of glycogen depletion is unknown for human myocardium, but sufficient species differences are known to exist,\textsuperscript{17} making extrapolation to the human heart unwise.

The focal nature of myocardial ischemia in coronary artery disease\textsuperscript{18} may restrict anaerobic energy production to a very limited portion of muscle at which site it may be sufficient, in spite of proportionately low high-energy phosphate yield, to maintain marginal function.\textsuperscript{2} With coronary sinus sampling, very high glucose uptake in a small zone of ischemia may be totally or partially masked by a simultaneous lower glucose uptake in a larger, well-oxygenated portion of muscle. Similarly, lactate production from a small focus may be masked or minimized by lactate extraction in a larger, better oxygenated zone. These facts make any quantitative analysis of anaerobic energy production, based on available glucose and lactate concentrations, unprofitable. The problem of local venous versus coronary sinus sampling in the metabolic evaluation of myocardial ischemia has been reviewed recently.\textsuperscript{19}

Since coronary blood flow increases with pacing stress\textsuperscript{20} and the arterial substrate concentration was not affected, augmented glucose uptake can be inferred solely from the widened (a – cs) glucose differences. However, the wide variability of (a – cs) glucose differences from subject to subject prohibits use of glucose uptake as an indicator of myocardial ischemia.

Absence of a relationship between myocardial glucose extraction and arterial glucose concentration has been noted previously\textsuperscript{21, 22} but is here expanded to include periods of myocardial ischemia. This raises some doubt that elevating the arterial glucose concentration during ischemia will lead to increased glucose uptake and increased glycolysis. The non-uniformity of myocardial ischemia, however, and the known problems of selective-site coronary venous sampling could well obscure a relationship between concentration and extraction. In this study, no attempt was made to augment glucose availability by either infusing glucose or giving added insulin. It remains to be demonstrated whether such interventions can lead to augmented lactate production under conditions of comparable stress.

References

2. Weissler FA, Krueger FA, Baba N, Scarrelli DG, Leighton RF, Gallimore JK: Role of anaerobic metabolism in the preservation of
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