Muscle interstitial glucose and lactate levels during dynamic exercise in humans determined by microdialysis

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MacLean, Dave A., Jens Bangsbo, and Bengt Saltin. Muscle interstitial glucose and lactate levels during dynamic exercise in humans determined by microdialysis. J. Appl. Physiol. 87(4): 1483–1490, 1999.—The purpose of the present study was to use the microdialysis technique to determine skeletal muscle interstitial glucose and lactate concentrations during dynamic incremental exercise in humans. Microdialysis probes were inserted into the vastus lateralis muscle, and subjects performed knee extensor exercise at workloads of 10, 20, 30, 40, and 50 W. The in vivo probe recoveries determined at rest by the internal reference method for glucose and lactate were 28.7 ± 2.5 and 32.0 ± 2.7%, respectively. As exercise intensity increased, probe recovery also increased, and at the highest workload probe recovery for glucose (61.0 ± 3.9%) and lactate (66.3 ± 3.6%) had more than doubled. At rest the interstitial glucose concentration (3.5 ± 0.2 mM) was lower than both the arterial (5.6 ± 0.2 mM) and venous (5.3 ± 0.3 mM) plasma water glucose levels. The interstitial glucose levels remained lower (P < 0.05) than the arterial and venous plasma water glucose concentrations during exercise at all intensities and at 10, 20, 30, and 50 W, respectively. At rest the interstitial lactate concentration (2.5 ± 0.2 mM) was higher (P < 0.05) than both the arterial (0.9 ± 0.2 mM) and venous (1.1 ± 0.2 mM) plasma water lactate levels. This relationship was maintained (P < 0.05) during exercise at workloads of 10, 20, and 30 W. These data suggest that interstitial glucose delivery at rest is flow limited and that during exercise changes in the interstitial concentrations of glucose and lactate mirror the changes observed in the venous plasma water compartments. Furthermore, skeletal muscle contraction results in an increase in the diffusion coefficient of glucose and lactate within the interstitial space as reflected by an elevation in probe recovery during exercise.

metabolism; recovery; perfusate; dialysate

A RELATIVELY NEW APPROACH used in an effort to gain a better understanding of tissue metabolism is the measurement and quantification of compounds in the interstitial space. This is accomplished by utilizing the microdialysis technique (6), which is based on the principle of diffusion through a semipermeable membrane (microdialysis probe). This method has been applied to a number of different tissues such as brain (1), adipose (24), and muscle (16) to study the interstitial concentrations of many different compounds, including glucose, lactate, glycerol, amino acids, and hormones. However, most of these studies have been carried out in the resting state, whereas only one study has used the technique during exercise. This was done by Rosdahl et al. (22), who investigated changes in dialysate glucose and lactate levels during intermittent static exercise in humans. On the other hand, the microdialysis technique has never been used during dynamic muscle contractions, and a possible reason for this may be the fragile nature of the microdialysis probes, which may limit their use as a result of movement and the high muscle forces produced during dynamic exercise.

To fully utilize the microdialysis technique, an in vivo calibration of the microdialysis probe needs to be made. This calibration allows the researchers to determine how much of a given compound in the interstitial space is diffusing into the perfusion solution (perfusate) as it passes through the microdialysis probe. The determination of this exchange fraction between the interstitial space and the perfusate, termed “probe recovery,” is of major physiological importance because it is necessary to calculate actual interstitial concentrations. Two current methods used for this determination are 1) the “no net flux” and 2) the “internal reference” methods. Although both methods have yielded similar probe recoveries when simultaneously compared in vivo (9), they differ widely in potential applications. The no net flux method was first introduced by Lönroth et al. (15) and is associated with several assumptions, including 1) probe recovery and interstitial concentrations remain unaltered during the 4- to 5-h calibration period and 2) no change in the predetermined probe recovery during the subsequent experiment. However, it is unknown whether these conditions truly exist, either at rest or during exercise.

In contrast, the internal reference method introduced by Scheller and Kolb (23) allows the determination of probe recovery for each collected sample, permitting the continuous monitoring of probe recovery over time. This method requires the addition of a small amount of radioactive tracer, in the form of the compound being investigated, to be added to the perfusate. It has been suggested that the relative loss of the isotope from the perfusate into the interstitial space represents probe recovery for that compound. This was confirmed in vitro by the study of Kurosawa et al. (12) where the simultaneous measurement of tracer loss and compound recovery proved to be similar. Therefore, this method is well suited for experiments where steady-state conditions change, such as during exercise.

The aims of the present study were to determine the interstitial glucose and lactate concentrations of the vastus lateralis muscle and compare those to the femoral arterial and venous plasma water glucose and...
lactate levels during incremental dynamic knee extensor exercise. To fulfill these aims, a probe was made so that microdialysis could be used continuously during dynamic exercise in humans. Furthermore, the no net flux and internal reference methods were evaluated to determine which method was most appropriate for the in vivo determination of probe recovery during exercise.

METHODS

Subjects. The experimental protocol was approved by the Ethical Committees of the Copenhagen and Frederiksberg communities, and 17 male subjects were informed of the purposes and risks of the study. Each subject was a healthy, physically active student.

Microdialysis probes. The fibers used to construct the microdialysis probes were obtained from an artificial dialysis kidney (GF-E18), which had a molecular cutoff of 3,000 Da. Each end of a single fiber was inserted 1 cm into a hollow nylon tube (0.50 mm ID, 0.63 mm OD) and glued. The actual probe length (distance between the 2 nylon tubes) was 4 cm (0.20 mm ID, 0.22 mm OD). To provide tensile strength to the microdialysis probe so that it could withstand the forces generated by muscle contraction, a 10-cm piece of 5-0 suture (Ethicon) was glued to the nylon tubing. The suture was attached so that 3 cm were glued to the nylon tubing on one side of the probe and 3 cm were glued to the nylon tubing on the other. Thus the suture was not only glued to the nylon tubing but also spanned the distance of the probe. This modification allowed the microdialysis probes to function very well during muscle contractions ranging in intensity from mild to maximum. It was further determined in vitro that the addition of the suture did not affect the diffusion of any of the measured parameters across the microdialysis membrane.

Preexperimental protocol. Before the experiment the subjects were familiarized with the Røhrg ergometer modified for one-legged knee extensor exercise as previously described (2). With this model the external work for knee extension is performed exclusively by the quadriceps femoris muscle. All subjects reported to the laboratory after an overnight fast, and, in the subjects from whom arterial and venous blood samples were to be collected, Teflon catheters were inserted below the inguinal ligament into the femoral artery and vein of their dominant leg. The catheters were advanced proximally so that the tips of the arterial and venous catheters were located ~2 cm proximal and 2 cm distal to the inguinal ligament, respectively. The subjects were moved to the exercise apparatus where they rested supine while the leg was prepared for microdialysis probe insertion.

Microdialysis probe insertion. The microdialysis probes were inserted into the vastus lateralis muscle of the subject’s dominant leg. The skin and subcutaneous tissue where the probes were to enter and exit the leg were anesthetized with a local injection (0.5–1.0 ml) of Xylocaine (20 mg/ml) and epinephrine (12.5 µg/ml). The probes were inserted into the muscle by use of a 14-gauge (Venflon, iv) cannula in a direction parallel to the muscle fiber orientation (i.e., 45° moving proximally and laterally). The distance between the entrance and exit sites of the probes was ~9 cm, and the distance between each probe was ~2–3 cm. After insertion the microdialysis probes were attached to a perfusion pump (model 102, CMA) and perfused at a rate of 5 µl/min with a Ringer-acetate solution. The probes were perfused, and the subjects rested supine for 60 min before the experiment was initiated.

Experimental protocol I (8 subjects, 37 probes). This protocol was designed to evaluate the no net flux method for determining probe recovery during exercise. The physiological importance of probe recovery is that it represents an in vivo calibration of the microdialysis probe in terms of the exchange fraction of compounds between the interstitial space and the perfusate, which subsequently allows actual interstitial concentrations to be calculated. The no net flux calibration is performed by perfusing each probe for 60 min with four different solutions containing varying concentrations of glucose and lactate (15). After this, the point of no net flux is determined for the metabolite (Calculations), and then this probe recovery is used during the remainder of the experiment. However, this is not possible during exercise, because each probe would need to be reperfused with the various solutions again, and this would require another 4–5 h to complete. Alternatively, it may be possible to perfuse a number of different probes in the same muscle with solutions containing varying concentrations of glucose and lactate. The perfusate and dialysate concentrations from the probes would then be used to calculate an “across the leg” probe recovery and subsequently interstitial glucose and lactate concentrations, thus allowing an estimation of probe recovery both at rest and during exercise.

In eight subjects (n = 37 probes) an across the leg estimation of probe recovery was made at rest by perfusing each probe with a different solution containing varying concentrations of glucose (range 3.0–6.7 mM) and lactate (0.5–4.5 mM). In four of these subjects (n = 19 probes) an across the leg estimation of probe recovery was also made during exercise. The exercise protocol consisted of exercising the knee extensors of one leg at workloads of 10, 20, 30, 40, and 50 W, performed in random order for 8 min. It was observed that probe recovery for both glucose and lactate was elevated during muscle contraction and tended to increase as exercise intensity increased (Table 1). These data suggest that the extraction fractions of glucose and lactate are significantly altered with muscle contraction and that thus the no net flux calibration normally obtained under resting conditions cannot be used under exercise conditions.

Experimental protocol II (3 subjects, 13 probes). This protocol was designed to simultaneously compare the no net flux and internal reference methods for determining probe recovery in muscle at rest. In three subjects (n = 13 probes), the no net flux method of calibration was performed as previously described (15). A very small amount of D-[6-3H]glucose and L-[U-14C]lactate (<0.2 µCi/ml) was added to the final perfusion solution as the internal reference marker (23). It was observed that probe recovery for lactate and glucose by using

<table>
<thead>
<tr>
<th>Probe Concentration, mM</th>
<th>Interstitial Glucose</th>
<th>Interstitial Lactate</th>
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<tr>
<td>Probe Recovery, %</td>
<td></td>
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<tr>
<td>Rest</td>
<td>3.7 ± 0.2</td>
<td>27.9 ± 2.7</td>
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<tr>
<td>10 W</td>
<td>5.3 ± 0.5</td>
<td>37.4 ± 1.6</td>
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<tr>
<td>20 W</td>
<td>5.5 ± 0.5</td>
<td>39.3 ± 5.5</td>
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<tr>
<td>30 W</td>
<td>5.7 ± 0.6</td>
<td>39.9 ± 1.6</td>
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<td>40 W</td>
<td>5.3 ± 0.4</td>
<td>43.4 ± 1.2</td>
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<tr>
<td>50 W</td>
<td>5.6 ± 0.5</td>
<td>47.7 ± 2.1</td>
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Values are means ± SE.
the no net flux and internal reference methods was similar (Fig. 1). These data suggest that the internal reference method is as reliable as the no net flux method in determining probe recovery and, because probe recovery can be determined in each probe at each time point, makes it a more suitable tool to use under exercise conditions.

Experimental protocol III (9 subjects, 11–30 probes). Arterial and venous femoral catheters were inserted as described in Preexperimental protocol to facilitate blood sampling at rest and during exercise. The exercise protocol consisted of subjects exercising the knee extensors of one leg at workloads of 10, 20, 30, 40, and 50 W, performed in random order for 8 min. Occasional 10-min rest periods between exercise bouts where given to subjects when requested. Arterial and venous blood samples were taken simultaneously at rest and during the last 30 s of each workload. During blood sampling a blood pressure cuff placed around the exercising leg, just below the knee, was inflated (200 mm Hg) to restrict the return of blood from the lower leg. Meanwhile, probe dialysate was collected in sealed micro centrifuge tubes to reduce evaporation, before and throughout each exercise bout (as was done in Experimental protocol I). In an effort to minimize the possibility of draining the interstitial space (4, 15), the perfusate contained 3.0 mM glucose and 0.5 mM lactate. The perfusate also contained the glucose and lactate internal reference marker to determine probe recovery in each sample as described in Experimental protocol II. These probe recoveries were then used to calculate each subject’s interstitial concentrations during exercise (see Calculations). Furthermore, the dialysate collection tubes were weighed before and after each collection, and the actual collection times for each tube were recorded. These data were used to determine the average probe perfusion rate during each workload. It should be noted that a 1.5-min delay exists between the passage of the perfusate through the probe (and the diffusion of compounds into the perfusate) and the collection of the samples, which was corrected for by appropriate timing the collection periods.

It should be noted that not all the subjects exercised at every workload and that, as some experiments progressed, several probes ceased to function (due to breakage or collapsing of the nylon tubing due to shearing forces of the fascia during exercise). As a result, the number of probes used in generating the data varies between workloads. The number of probes used to determine interstitial glucose were 30, 22, 22, 21, 20, and 11 and for interstitial lactate were 20, 11, 16, 17, 16, and 8 for rest and exercise at 10, 20, 30, 40, and 50 W, respectively.

Analysis. A 2-ml sample of femoral arterial and venous blood was collected in heparinized syringes, and 1.5 ml were transferred to chilled Eppendorf tubes and immediately centrifuged. The plasma was removed and analyzed immediately for glucose and lactate with a Yellow Springs Instrument glucose-lactate analyzer. The collected dialysate was also immediately analyzed for glucose and lactate as described above. Furthermore, 10 µl of dialysate were pipetted into a 5-ml scintillation vial, and 3 ml of scintillation fluid were added for the determination of the activity of D-[6-3H]glucose and L-[U-14C]lactate, respectively.

Calculations. Probe recovery determined by the no net flux method was calculated as the slope of the regression line of the perfusate vs. the dialysate minus perfusate concentration for glucose and lactate (15). The actual interstitial concentration was then calculated as the x-intercept (point of no net flux). Probe recovery based on the internal reference method was calculated as follows

\[
\text{Recovery} = \frac{(P_{\text{dpm}} - D_{\text{dpm}})/P_{\text{dpm}}}{(P_{\text{dpm}} - D_{\text{dpm}})/P_{\text{dpm}}}
\]

where \(P_{\text{dpm}}\) and \(D_{\text{dpm}}\) represent the dpm in the perfusate and dialysate, respectively, for glucose and lactate. The probe recoveries were then used to calculate the actual interstitial concentration of glucose and lactate as follows

\[
\text{Interstitial} = \left(\frac{[D_\text{c} - P_\text{c}]}{\text{recovery} + P_\text{c}}\right)
\]

where \(D_\text{c}\) and \(P_\text{c}\) represent the dialysate and perfusate concentrations of either glucose or lactate, respectively. The arterial and venous plasma concentrations of glucose and lactate were corrected to plasma water by using a factor of 0.94.

Statistics. The in vivo determination of probe recovery using the no net flux and internal reference techniques were compared by using a Student’s paired t-test. The change in probe recovery from rest to exercise was analyzed by using an ANOVA, and, if significance was indicated, a Tukey’s (honest significant difference) post hoc test was used to determine where the significance occurred. Because the choice of workload was random, the comparison of the calculated interstitial concentrations to the measured arterial and venous plasma water concentrations were analyzed with an ANOVA at each workload. If significance was indicated, a Tukey’s post hoc test was used to determine where the significance occurred. Each microdialysis probe was used as an individual data point. All values are expressed as means ± SE. Significance was accepted at \(P < 0.05\).

RESULTS

Change in probe recovery with exercise. The rate at which the microdialysis probes are perfused is inversely related to the magnitude of recovery. Therefore, to accurately compare changes in probe recovery, the probe perfusion rate must be constant and not different among the probes being compared. Therefore, to examine the changes in probe recovery from rest to exercise, only probes that maintained a constant perfusion rate of 5 µl/min were included. The resting probe recovery determined by the internal reference method for glucose and lactate was 28.7 ± 2.5 and 32.0 ± 2.7%, respectively. At the onset of exercise, the probe recovery
for glucose and lactate immediately increased and remained higher (P < 0.05) than rest at each exercise intensity (Fig. 2). Furthermore, there was a clear tendency for probe recovery for both these metabolites to increase as exercise intensity increased (Fig. 2). Probe recovery for glucose and lactate had increased from rest to 47.5 ± 3.2 and 52.1 ± 3.3% at 10 W (P < 0.05) and 61.0 ± 3.9 and 66.3 ± 3.6% at 50 W (P < 0.05), respectively.

Interstitial glucose. At rest the interstitial glucose concentration (3.5 ± 0.2 mM) was substantially lower (P < 0.05) than both the arterial (5.6 ± 0.2 mM) and venous (5.3 ± 0.3 mM) plasma water glucose levels (Fig. 3). Although this pattern was similar when a comparison between subjects was made, there was some variability between probes within the same subject (Table 2). The range in which the interstitial glucose levels varied between probes in the same muscle for the experiment was 0.3–1.5 mM. With the onset of muscle contraction, the interstitial glucose concentration for each probe increased, with the mean increase being ~1 mM. Furthermore, the interstitial glucose levels plateaued at ~4.5 mM and remained relatively constant during exercise at the various work intensities. It also appeared that as exercise intensity increased, the variation in interstitial glucose levels between probes in the same muscle decreased (Table 2).

The interstitial glucose concentrations were lower (P < 0.05) than the arterial plasma water levels at each workload. Similarly, the interstitial glucose concentrations were lower (P < 0.05) than the venous plasma water levels at 10, 20, 30, and 50 W.

Interstitial lactate. At rest the interstitial lactate concentration (2.5 ± 0.2 mM) was higher (P < 0.05) than both the arterial (0.9 ± 0.2 mM) and venous (1.1 ± 0.2 mM) plasma water lactate levels (Fig. 4). The variation between probes in the same muscle for the experiment, in terms of interstitial lactate levels, was in the range of 0.5–1.5 mM (Table 2). The interstitial lactate concentration as well as the arterial and venous plasma water lactate levels only increased slightly during exercise at 10, 20, and 30 W, and the interstitial lactate levels remained higher (P < 0.05) than both the arterial and venous plasma water lactate levels. It
dynamic muscle contractions, probe recovery for both observed in the venous plasma water compartment. Interstitial lactate increased and mirrored the changes lower than venous plasma water glucose, whereas rest. However, during exercise interstitial glucose concentrations at venous plasma water compartment concentrations at rest. The interstitial glucose level was lower was substantially increased during exercise compared with rest to even low intensity exercise, it is apparent that part of the increase reported by Rosdahl et al. could be accounted for by a change in probe recovery and not a change in interstitial concentration. These data illustrate the value of accurately determining glucose and lactate was significantly elevated. Even at low exercise intensities probe recovery was dramatically elevated and tended to increase as exercise intensity increased. This increase in recovery was subsequently reflected by an increase in the dialysate concentration of both glucose and lactate. The significance of these findings only underscores the importance of having a reliable method to determine probe recovery, especially in kinetic experiments where the change in dialysate concentration is used as a physiological indicator. For example, Rosdahl et al. (22) reported an ~1- and 2.5-fold increase in dialysate glucose and lactate concentrations, respectively, during intermittent isometric thigh muscle contractions at 40% of maximal voluntary contraction. On the basis of data from the present study for the change in probe recovery from rest to even low intensity exercise, it is apparent that part of the increase reported by Rosdahl et al. could be accounted for by a change in probe recovery and not a change in interstitial concentration.

**DISCUSSION**

This study represents the first time that interstitial glucose and lactate concentrations have been determined during dynamic exercise in humans. It was observed that interstitial lactate levels decreased (~0.8–0.9 mM). During exercise at 40 and 50 W the interstitial lactate concentrations as well as the arterial and venous plasma water lactate levels were all substantially elevated. At these higher workloads no significant differences were found between the interstitial lactate levels and the corresponding plasma water compartment concentrations. For some subjects, exercising at these higher workloads represented working close to their maximum, whereas for others it was still submaximal, as indicated by the low venous plasma water lactate levels (Table 2).

**Fig. 4.** Muscles interstitial and femoral arterial and venous plasma water lactate levels at rest and during exercise. Interstitial concentrations were calculated on the basis of probe recovery of lactate and concentration difference of lactate between perfusate and dialysate. *Significant difference from arterial plasma lactate levels, P < 0.05. **Significant difference from venous plasma lactate levels, P < 0.05.

The factors suggested to influence probe recovery include 1) perfusion rate, 2) probe length, 3) probe membrane characteristics, and 4) the rate of diffusion in the interstitial space (1, 14, 11). In the present study, factors 1–3 were constant and not different between rest and exercise, and thus, the change in probe recovery most likely was due to a change in the diffusion rate of the molecules within the interstitial space. The interstitial space is a biological medium, and the diffusion of molecules in this complex medium differs from that in a quiescent medium. The two main factors that determine diffusion in the interstitial space are tortuosity and volume fraction (11, 21). Tortuosity refers to the increase in diffusional pathlength of the molecule and is related to the dynamic interaction in vivo between tissue release, uptake, and degradation as well as the existence of structures and macromolecules in the interstitial space. Meanwhile, volume fraction refers to the volume of interstitial fluid related to the whole tissue. Therefore, any change in these variables has a direct impact on the diffusion of molecules in the interstitial space (for a complete description refer toRefs. 11 and 21).

The result of altering one of these variables is best illustrated in relation to Fick’s law for diffusion

\[ J = -D \cdot \Phi \cdot \nabla c \]  

(1)

where \( J \) is the microscopic flux, \( D \) is the diffusion coefficient, \( \Phi \) is the porosity, and \( \nabla c \) is the concentration gradient. In this example, the flux is chiefly determined by how fast the molecule will diffuse (D) and by the fraction of the total volume that is diffusible (\( \Phi \)). The relationship between the diffusion coefficient in a tissue (such as muscle \( D_m \)) and the diffusion coefficient in a liquid (such as the perfusate \( D_p \)) is expressed by the formula (21)

\[ D_m = D_p / \lambda^2 \]  

(2)
where $\lambda$ is the tortuosity factor representing the increase in pathlength of a diffusing particle in a complex medium compared with a quiescent medium. Meanwhile, the volume fraction is expressed as (21)

$$\alpha = \frac{V_o}{\mathcal{V}}$$  \hspace{1cm} (3)

where $V$ is the total tissue volume and $V_o$ is the interstitial volume fraction. Equation 3 can now be rewritten as

$$J = -D_p/\lambda^2 \cdot \nabla \mathcal{V} \cdot \nabla c$$  \hspace{1cm} (4)

From this equation it is evident that either a decrease in the tortuosity or an increase in the interstitial volume fraction results in an increase in microscopic flux.

In the present study the increase in probe recovery was most likely the result of both a decrease in the diffusional pathlength for glucose and lactate and an increase in the interstitial volume fraction during exercise. The former was likely due to the rhythmical pattern of muscle contraction and relaxation, which caused a better “mixing” of the interstitial space and in turn increased the diffusion coefficient and facilitated a greater flux of glucose and lactate into the probe. Meanwhile, it has been demonstrated that exercise increases the extracellular water content of muscle and that this increase is greater from rest to submaximal exercise than from submaximal to maximal exercise (25). Therefore, part of the change in probe recovery, especially during the submaximal workloads, was most likely due in part to an increase in the interstitial volume fraction. However, other factors that may have contributed to the change in probe recovery during exercise, such as an increase in blood flow and an increase in intramuscular pressure, cannot be overlooked. It has been suggested that changes in blood flow do not affect in vivo recovery (23), but only small (severalfold) changes in blood flow have been investigated. In the present experiment blood flow from rest to exercise at 50 W was increased some 20-fold (2) and may have resulted in the greater removal of large molecules from the interstitial space and thus helped to decrease tortuosity. In fact, it may be a combination of the larger muscle forces and greater blood flows produced at the higher workloads that explains why probe recovery tends to increase as exercise intensity increases. However, it should be noted that several limitations surround the measurement of blood flow with reference to the microdialysis technique and that further studies are clearly needed to elucidate the importance of blood flow in determining probe recovery during muscle contraction.

In the present study the interstitial glucose levels at rest were lower (~2 mM) than both the femoral arterial and venous plasma water lactate levels (~1.5 mM). In studies by Hagström-Toft et al. (7) and Müller et al. (20), both reported human skeletal muscle interstitial lactate concentrations of 1.9 mM, which were higher than the venous plasma water lactate concentrations. Similarly, Rosdahl et al. (22) reported that the dialysate lactate concentration at a flow rate of 0.5 µl/min was higher than the fingertip venous plasma lactate value. Although very few values are available, these data are in good agreement with findings in the present study.

It has been proposed that the high interstitial lactate concentration at rest may be due to glycolytic activity in the area around the probe as a result of leakage from damaged tissue (3). In the present study the interstitial lactate levels during exercise at 10 and 20 W were similar to rest. However, muscle blood flow during these exercise bouts would have been substantially increased (>10-fold) compared with rest (2). Subsequently, one would expect that, in conjunction with muscle contraction, much of the possible leakage would have been removed. Similarly, if there was a high amount of glycolytic activity occurring, resulting in high lactate levels, one would also expect correspond...
ingly low glucose levels. In the present study there was no significant correlation between these variables at rest ($r^2 = 0.274$). Last, it has been shown that, after probe insertion, interstitial ATP is transiently increased (3) but that it had dissipated after 30 min. In the present study, following probe insertion, 60 min of perfusion were allowed before collection was started. For the above reasons we are confident that both the interstitial glucose and lactate concentrations represent the actual interstitial concentrations under normal physiological conditions.

During exercise at 40 and 50 W, substantial lactate accumulation was observed in the plasma, and the interstitial lactate levels mirrored the changes in the plasma. However, there were no significant differences between these parameters, and this may be partially explained by the fact that for some subjects exercise at these workloads approached their maximum, while for others it was relatively moderate. As a result, there was a large variation between subjects in lactate production and subsequently the interstitial and plasma lactate concentrations, as reflected by the large error bars for these measures at 40 and 50 W. However, it is evident that the mean interstitial lactate levels change in the same direction and magnitude as did the venous plasma lactate levels during exercise, and this pattern is the same when values for single subjects are analyzed.

In each subject there was some variation between the interstitial glucose and lactate levels for probes in the same muscle, and this variation appeared to be greatest at rest. This variation could be the result of a number of factors, including differences in nutritive blood flow, differences in local metabolism, and possibly the type of muscle fibers surrounding the probe. It is well documented that a mismatch exists between the supply of muscle blood flow and muscle fiber energy turnover, which could lead to local differences in the composition of the interstitial space (17). This has been demonstrated in resting muscle, but, although the mismatch is reduced with contraction, it still remains in exercising muscle (8). In the present study it was observed that interstitial glucose levels increased during exercise, whereas in a few subjects interstitial lactate levels dropped when rest was followed by exercise at 10 W. These data suggest that part of the variation between probes in the interstitial concentrations of glucose and lactate may be explained by differences in nutritive blood flow.

It is also possible that the local metabolism of glucose and lactate may vary between different parts of the muscle as muscle fiber type distribution also varies somewhat in the vastus lateralis (13). Thus the possibility exists that more slow twitch than fast twitch or vice versa surround the microdialysis probes in the same muscle. Subsequently, the combination of differences in glucose uptake and lactate release, in conjunction with differences in fiber type, could easily result in substantial differences in the interstitial concentrations of these metabolites. For example, Karlsson (10) observed in the dog gracilis muscle that intramuscular lactate concentrations differed widely throughout the same muscle. If the above discussion regarding differences in blood flow is applied, then the potential for differences in the interstitial concentrations of glucose or lactate becomes great. It is evident that many of the differences between probes in the interstitial concentrations of glucose and lactate can be explained by physiological factors that determine their extracellular concentration.

It is interesting to consider whether the interstitial space as a whole and the concentration of the studied metabolites play a role beyond providing the concentration gradient needed to facilitate glucose uptake by the muscle or lactate diffusion to the blood. For example, the interstitium contains a rich supply of group III and IV afferents, which, when stimulated, result in elevated sympathetic outflow (18). The lowering of pH is a factor that has been identified as a possible stimulator of these afferents (26), and, because the buffering capacity of the interstitial space is small, minor elevations in lactate/protons could effect sympathetic activation. To that extent one may consider whether the interstitial space and the change in metabolite concentrations in that space are controlled and not the net result of passive transport systems.

In summary, this study demonstrates that probe recovery for lactate and glucose is substantially increased during dynamic exercise. Furthermore, at rest and during various work intensities, interstitial glucose was lower than both the arterial and venous plasma water glucose levels. In contrast, it was observed that interstitial lactate was higher than both the arterial and venous plasma lactate levels but only at the lower workloads. It was also found that considerable variation occurred in the interstitial concentrations of glucose and lactate between probes in the same muscle.

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