Efficiency of human skeletal muscle in vivo: comparison of isometric, concentric, and eccentric muscle action

T. W. RYSCHON, M. D. FOWLER, R. E. WYSONG, A.-R. ANTHONY, AND R. S. BALABAN
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Ryschon, T. W., Fowler, R. E. Wysong, A.-R. Anthony, and R. S. Balaban. Efficiency of human skeletal muscle in vivo: comparison of isometric, concentric, and eccentric muscle action. J. Appl. Physiol. 83(3): 867–874, 1997.—The purpose of this study was to estimate the efficiency of ATP utilization for concentric, eccentric, and isometric muscle action in the human tibialis anterior and extensor digitorum longus in vivo. A dynamometer was used to quantitate muscle work, or tension, while simultaneous 31P-nuclear magnetic resonance data were collected to monitor ATP, phosphocreatine, inorganic phosphate, and pH. The relative efficiency of the actions was estimated in two ways: steady-state effects on high-energy phosphates and a direct comparison of ATP synthesis rates with work. In the steady state, the cytosolic free energy dropped to the lowest value with concentric activity, followed by eccentric and isometric action for comparative muscle tensions. Estimates of ATP synthesis rates revealed a mechanochemical efficiency [i.e., ATP production rate/work (both in J/s)] of 15.0 ± 1.3% in concentric and 34.7 ± 6.1% in eccentric activity. The estimated maximum ATP production rate was highest in concentric action, suggesting an activation of energy metabolism under these conditions. By using direct measures of metabolic strain and ATP turnover, these data demonstrate a decreasing metabolic efficiency in human muscle action from isometric, to eccentric, to concentric action.

LOCOMOTOR ACTIVITY depends on variable contributions from isometric, concentric, and eccentric muscle actions. Activities that predominantly use a single mode of action can be cited. For example, tension development during muscle shortening (concentric action; see Ref. 6) enables the thigh muscles to elevate body mass during stair ascent. Eccentric muscle action, involving tension development during muscle lengthening (6), occurs in the same thigh muscle during step descent, providing a method of decelerating body mass. Isometric muscle actions involve tension development but no change in muscle length (6) and are the basis of posture maintenance.

In addition to the differential implementation of these muscle actions during locomotion, other prominent differences exist between them. Muscles acting in eccentric mode can produce greater peak tension than in other modes (8, 35, 40, 42). In addition, in humans, eccentric muscle action is associated with estimates of whole body energy cost (oxygen uptake) that are lower than for concentric activity at a similar intensity (1, 2). The classic human study is that of Abbott et al. (1), in which the “positive” working cyclist used much less oxygen than the “resisting” cyclist, despite the fact that both generated the same force on opposing bicycles. The differences in the force-velocity relation of eccentric and concentric muscle action increases the discrepancy in efficiency with increasing contraction velocity (1, 17). The lower energy cost for eccentric action could be explained by recruitment of more efficient fibers or by an alteration in the efficiency of converting high-energy phosphate bonds into measurable work [so-called mechanochemical efficiency (24)].

Alterations in the mechanochemical efficiency are of particular interest to muscle biochemists in their understanding of muscle contraction. However, these explanations have important clinical implications as well. In particular, eccentric action of muscle is associated with activity-related damage to muscle involving delayed onset muscle soreness (38), appearance of muscle cytosolic enzymes in the blood plasma (5, 30), and temporary impairment of tension production (14, 18, 32, 38). To date, the role of mechanical and metabolic influences on these observations remains unclear.

The purpose of this study was to determine the metabolic response and estimate the mechanochemical efficiency of human skeletal muscle to isometric, concentric, and eccentric action. Toward this goal, two noninvasive 31P-nuclear magnetic resonance (NMR) spectroscopy methods and dynamometry were used to assess mechanochemical efficiency. In the first method, mechanochemical efficiency was calculated directly from the ratio of mechanical power output to ATP synthesis rate during steady-state concentric and eccentric action. ATP synthesis rate was inferred from the initial rate of phosphocreatine (PCr) resynthesis immediately after exercise (20, 21), as measured by 31P-NMR. Mechanical power was measured directly with a dynamometer. After correcting for the free energy in ATP, both the ATP synthesis rate and work could be expressed in the same units (J/s).

The second approach provided a qualitative confirmation of the direct method, along with an estimate of the efficiency of isometric action. This method relied on the measurement of tension, or work, and the available free energy for contraction in the phosphorylation potential of the muscle in the steady state. This is analogous to measuring the voltage of a battery as a function of the load resistance (28). During muscle action of submaximal intensity, energy metabolism is the “battery” providing energy through a source resistance of metabolic pathways. The load resistance represents the hydrolysis of ATP by myosin during work or tension development. As power output increases, ATP hydrolysis rate increases, reducing the load resistance
and decreasing the battery voltage [i.e., the free energy of ATP hydrolysis ($\Delta G_{\text{ATP}}$)]. In this paradigm, $\Delta G_{\text{ATP}}$ reflects the efficiency of the ATP utilization as long as the battery and source resistance (i.e., ATP synthesis pathways) are similar under the conditions examined.

It is hypothesized that for a given mechanical power output, relatively efficient action would result in a slower ATP resynthesis rate (resulting in a higher calculated mechanochemical efficiency) and less of a reduction in $\Delta G_{\text{ATP}}$.

**METHODS**

Subjects. Twelve healthy adults (9 men, 3 women; ages $36 \pm 4$ yr) consented to participate in this study after being informed of its purpose and risks according to the guidelines of the Human Subjects Use Committee at the National Institutes of Health.

Control of muscle action and power output. In this study, the influence of contraction mode on muscle efficiency was studied in the primary muscles of foot dorsiflexion, the tibialis anterior (TA) and extensor digitorum longus (EDL). A custom dynamometer, described previously (33), was used to control the mode and intensity of activity in these muscles. Before each study, the dynamometer was calibrated by using a known torque, as described previously (33). No drift in the instrument calibration was detectable over the 2-h time period of a study. The coefficient of variation determined from sequential torque readings during application of a known torque was $<2\%$.

Each subject was familiar with the instrument from previous experiments or was given a training period well before the study to prevent any additive effects of the training period. After the subject was attached to the dynamometer, the peak torque achieved during 3–5 min of maximal-effort isometric dorsiflexions (1- to 3-s duration, foot at 95° relative to lower leg axis) was measured and designated as maximal voluntary contraction (MVC). After 15 min of passive rest, the TA and EDL were voluntarily and intermittently activated (5 s on, 5 s off; duty cycle 50%) to 30% of MVC for a total of 5 min with the sequential use of isometric, concentric, and eccentric actions. Each mode was separated from the next by a 10-min period of passive rest. During the test of the isometric mode, the foot was positioned at 95° relative to the axis of the lower leg. During dynamic actions (concentric and eccentric), ankle rotation speed was 6°/s (0.105 rad/s). External sampling of pedal velocity by an optical encoder at 20 Hz indicated that the pedal reached this velocity after direction changes in 50 ms. During trials, torque was sampled at 10 Hz and expressed as the average tension-time integral per stroke ($\text{TTI}$). The use of the initial rate of PCr resynthesis to estimate $\Delta G_{\text{ATP}}$ of the sequence in terms of contrast/noise per unit time. All data were collected by using a General Electric Signa Console modified to operate at 4 T.

Data analysis. TTI was calculated by using a custom-written subroutine in Interactive Data Language (Research Systems, Boulder, CO) that integrated the torque area for each effort stroke over the selected time period (1 min). The area of each peak in the $^{31}$P-NMR spectra was determined by sequential torque readings during application of a known torque was $<2\%$.

For efficiency calculations, the ATP production rate equivalent of mechanical power output was calculated from Eq. 1 for each condition (see Table 1).

![Mechanical and metabolic responses during final minute of isometric, concentric, and eccentric foot dorsiflexion in vivo](image-url)

<table>
<thead>
<tr>
<th>Mode</th>
<th>TTI, N·m</th>
<th>$\Delta G_{\text{ATP}}$, kJ/mol</th>
<th>ADP, µM</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isometric</td>
<td>54.1 + 4.3</td>
<td>44.6 ± 0.6</td>
<td>10.4 ± 1.4</td>
<td>7.06 ± 0.02</td>
</tr>
<tr>
<td>Concentric</td>
<td>52.9 ± 5.0</td>
<td>39.7 ± 0.71</td>
<td>25.8 ± 3.2</td>
<td>6.97 ± 0.03</td>
</tr>
<tr>
<td>Eccentric</td>
<td>55.7 ± 5.3</td>
<td>42.6 ± 0.6</td>
<td>15.2 ± 2.0</td>
<td>7.04 ± 0.02</td>
</tr>
</tbody>
</table>

Values are means ± SE; no. of experiments for each mode = 8. TTI, tension-time integral; $\Delta G_{\text{ATP}}$, free energy of ATP hydrolysis; *$P < 0.05$ vs. isometric, concentric, and eccentric actions; †$P < 0.05$ vs. rest, isometric, and eccentric actions; ‡$P < 0.05$ vs. concentric and eccentric.
ATP synthesis rate during steady-state exercise is valid as long as ischemia or hypoxia was not induced. This appears to be the case for these studies, because pH was not different between modes and all subjects felt capable of continuing the more intense, concentric trial beyond the prescribed 5-min duration.

The maximal rate of ATP synthesis \( [Q_{\text{max}} \text{ (in µmol ATP/s)}] \), ignoring the contribution of \( P_i \), was calculated from the following equation (20)

\[
Q_{\text{max}} = Q \left(1 - \frac{K_m}{[ADP]}\right)
\]

where \( Q \) is the initial rate of PCr resynthesis in the first 26 s of recovery, and \( K_m \) is the binding constant for ADP (26 µM (29)). This approach assumes that [ADP] is kinetically limiting the rate of ATP synthesis (i.e., measured PCr resynthesis) under these conditions and follows simple Michaelis-Menton kinetics. Further limitations of this approach are presented in the DISCUSSION.

Regions of interest were evaluated in the proton MRI images to determine the changes in signal intensity observed with exercise. Regions of interest values were determined by using in-plane voxel dimensions of \( \sim 0.5 \text{ cm}^2 \) with the use of software resident in the Signa console.

Repeated-measures analysis of variance was used to test for mode effects on normally distributed variables with follow-up Student-Newman-Keuls analysis for multiple comparisons. The Mann-Whitney rank sum test was used for variables with nonnormal distribution or unequal variance. A \( P \) value of \( < 0.05 \) was considered significant, and all values are presented as means \( \pm \) SE.

RESULTS

The torque values obtained at MVC in this study (women, 28.1 \( \pm \) 2.9 N·m; men, 44 \( \pm \) 2.5 N·m) are comparable to published values (12). Torque measurements from the final five strokes of isometric, concentric, and eccentric action are shown for a representative subject in Fig. 1. Overshoot of target torque occurred more often with dynamic modes than with isometric action. Nonetheless, TTI was comparable between modes (Table 1), and mechanical power output was not different between concentric (1.1 \( \pm \) 0.1 W) and eccentric modes (1.2 \( \pm \) 0.1 W; \( P = 0.739 \)).

\( ^1\text{H} \) MRI images were collected to confirm the localization of the surface coil by using the dual-tuned surface coil as well as to evaluate muscle recruitment by using the larger birdcage coil. Muscle recruitment was evaluated by imaging the lower leg immediately after exhaustive exercise. In the course of these studies, it was noted that at maximum exertion, it took roughly twice as long for each subject to reach exhaustion during the eccentric action. Figure 2 shows two series of multislice data from the same subject before and after concentric or eccentric activity on two different days. Note the selective enhancement of the anterior compartment of the leg. No significant changes in signal intensity were observed in the other muscle groups when normalized to fat-signal intensity in the bone marrow. These data suggest that the large majority of muscle activation was occurring in the anterior compartment in these studies. These studies were randomized and conducted on separate days to minimize any effects of the previous study. This was confirmed by the control image collected just before each trial.

\( ^3\text{P} \)-NMR spectra, accumulated to 1-min resolution, from each mode of action are shown in Fig. 3. Isometric and eccentric muscle actions reduced [PCr] and \( \Delta G_{\text{ATP}} \) less than concentric action (Figs. 3 and 4; Table 1). In five separate studies, the order of the muscle action in the study was reversed, with no statistical difference (\( P = 0.69 \)) in TTI or steady state [PCr] or \( \Delta G_{\text{ATP}} \). These studies suggest that the larger decrease in [PCr] in the concentric action is independent of the order of the trials. The replicate studies were not included in the summary data. These data suggested that isometric activity, followed by eccentric and concentric action, was the most efficient in generating TTI.

Determinations of the kinetics of [PCr] at the onset and end of muscle action were made by using spectra that were accumulated to 13-s resolution (Fig. 5) to...
evaluate whether a metabolic steady state was established during exercise. As noted above, the drop in [PCr] with concentric action exceeded that found in isometric and eccentric modes. Thus concentric action induced the greatest metabolic strain of the three modes and was least likely to result in a metabolic steady state during exercise. In all studies, [PCr] decreases to a steady-state level for the last 2–3 min of the exercise period. To illustrate this point, [PCr] is plotted for all of the subjects over the concentric exercise period (Fig. 5). [PCr] decreased in the first 2 min of muscle action, reaching a steady state that was maintained for the remainder of the trial. Thus the steady-state requirement of the study design was satisfied.

At the termination of exercise, [PCr] increased, with the first ~30 s of the response being essentially linear (linear regression analysis, \( r > 0.9 \); Fig. 6). This initial linear period was assumed to provide adequate temporal resolution to determine the initial rates of PCr resynthesis. The linearity of the data over this time course for eccentric or concentric activity was not significantly different. The initial rate of PCr resynthesis showed that the concentric rate (190 ± 16 \( \mu \text{mol/s} \)) was significantly higher than either isometric (62 ± 10 \( \mu \text{mol/s} \); \( P < 0.05 \)) or eccentric (98 ± 20 \( \mu \text{mol/s} \); \( P < 0.05 \)), while the rates for isometric and eccentric action were not significantly different. The corresponding mechanochemical efficiency was 34.7 ± 6.1\% for eccentric action and 15.0 ± 1.3\% for concentric action (\( P = 0.017 \)). Because no external shortening is measurable...
with isometric action, efficiency cannot be directly calculated.

To ensure that changes in spin-lattice relaxation times were not contributing to the initial rates, the pulse width was reduced by a factor of three from the optimal pulse width in three subjects. This effectively alters the Ernst angle relationship, resulting in less T1 weighting of the NMR data. Despite a decrease in the signal-to-noise ratio of the PCr resonance, no difference was observed in the initial rates of recovery from eccentric or concentric action as a function pulse width (i.e., magnetization flip angle).

The estimated $Q_{\text{max}}$ in concentric action ($391 \pm 22 \mu\text{M/s}$) was significantly higher than either isometric ($235 \pm 43 \mu\text{M/s}$) or eccentric action ($271 \pm 44 \mu\text{M/s}$; $P < 0.05$). The $Q_{\text{max}}$ was not statistically different between isometric and eccentric modes. These data suggest that the predicted higher metabolic rate of concentric action is associated with an activation of aerobic metabolism. It should also be pointed out that the assumptions that [ADP] is the sole kinetically limiting factor under these conditions could also result in a systematic error.

**DISCUSSION**

In this study, the same muscle mass was voluntarily activated to similar submaximal levels of torque output, at a fixed duty cycle, using isometric, concentric, and eccentric modes of muscle action. Under these comparable mechanical conditions, significant differences were found for several metabolic variables between the different modes of action. These metabolic changes are consistent with an increasing metabolic strain for a given TTI, going from isometric to eccentric action.

The higher rate of ATP hydrolysis associated with the changes in muscle length (24) likely explains the lower $\Delta G_{\text{ATP}}$ for concentric and eccentric action compared with isometric action. However, between eccentric and concentric action, the muscle is changing the same length in the same time (i.e., same velocity), resulting in comparable power output. If the mecanochemical efficiency of cross-bridge formation were identical for both modes, the metabolic requirements should be identical. However, the metabolic strain, or drop in $\Delta G_{\text{ATP}}$, was greater with concentric action, consistent with a lower mecanochemical efficiency. This conclusion was confirmed by the direct calculation of mecanochemical efficiency (i.e., ATP production rate/work) from the [PCr] resynthesis rates where the eccentric action was found to be $-35\%$ more than twice as efficient as the $-15\%$ observed for concentric activity. It is interesting to note that the concentric and eccentric efficiency values found in these studies are well below the 55–60% values reported for isolated amphibian muscle at low temperatures ($\sim 1.5^\circ\text{C}$) (10, 24).

The observed differences in mecanochemical efficiency between eccentric and concentric action may be attributable to altered energetics in the working muscle fibers. This implies that the coupling between ATP demand and power output is adjustable within the working fibers, assuming the same population of fibers was activated. The same observations could occur if a population of more efficient fibers were activated. In this regard, electromyography (EMG) suggests that eccentric action activates fewer fibers for a given tension output than concentric action, according to some (2, 4, 36, 40) but not all studies (22, 23, 36). In studies showing lower EMG activity during eccentric action, the EMG-to-torque ratio is approximately twofold higher.
in concentric action (40), indicating a 100% increase in eccentric efficiency. This is consistent with our estimates of mecanochemical efficiency for these muscle actions. However, if fewer fibers are recruited during eccentric compared with concentric action, then each activated fiber must produce a greater fraction of the work and a higher associated metabolic strain.

Two lines of evidence suggest that this did not occur. First, if a selective pool of fibers were maintaining the workload in the steady-state during eccentric action with the same overall mecanochemical efficiency as during concentric action, then the calculated rate of ATP resynthesis should be the same for the two modes, because this measure is independent of pool size. In contrast, eccentric action had a lower calculated ATP synthesis rate, inconsistent with the compartmentation hypothesis but consistent with the notion that total ATP requirements are lower in eccentric action.

Second, no significant change in intracellular pH or splitting of the Pi peak was observed in any of these submaximal workload studies. This is also inconsistent with a small, highly activated fiber population. A highly active fiber population would potentially dominate the overall muscle Pi resonance because of a high concentration of Pi in these fibers. These data are inconsistent with the notion that a small, efficient fiber population is recruited in eccentric action. On a larger scale, 1H images suggest that only the anterior compartment was significantly involved in the work performed at maximal workloads. However, recruitment below the T2 threshold of this study or outside of the field of view (i.e., upper leg) cannot be completely discounted, nor can these data be used to estimate the percentage of fiber activation in these muscles. It was interesting to note that the eccentric action required roughly twice as much time to reach exhaustion as concentric activity in the present study. This result is consistent with the notion of higher metabolic efficiency in the eccentric action.

These results suggest that the higher mecanochemical efficiency of eccentric compared with concentric action is due to an alteration of the actino-myosin-ATP stoichiometry. We speculate that some component of eccentric muscle action (the direction of length change or energy added to the muscle through the lengthening process) lowers the requirement of ATP per second per watt of mechanical power. Studies of single fibers during shortening have demonstrated a larger sliding distance between actin and myosin than expected from the ratio of ATP hydrolyzed (16). This could represent multiple power strokes per molecule of ATP hydrolysis (27) or a longer power stroke (>5–10 nm) than predicted from in vitro studies (16). The preferential occurrence of either of these phenomena during eccentric action could explain the higher efficiency. An alternative explanation may be that in the eccentric mode the muscle is actually dissipating a potential energy rather than generating it, as in the other modes. Under these conditions, the external load applied to the muscle could overcome weakly bound actin-myosin states or other passive elements, resulting in a resistance to the motion with little ATP hydrolysis. This latter model, where the tension is generated by stretching or destroying passive elements, may explain the higher potential for muscle damage in eccentric action, as discussed above. In any event, the higher efficiency of the eccentric action may contribute to the lower eccentric EMG activity seen in some studies, because less muscle activation is required to provide a given level of work.

The estimated mecanochemical efficiency found in this study for concentric action was much lower than observed in human exercise protocols (13), which are limited by potential errors in the measurement of both metabolic energy cost and mechanical power output (37). In general, studies on humans are difficult because local metabolic rates and muscle power are difficult to determine noninvasively, muscle group recruitment is hard to control, and subject compliance is mixed.

In the present study, we have attempted to minimize many of these problems, although a perfectly controlled study is always extremely challenging in humans. The local metabolic rate in the muscle of interest was directly assessed by using 31P-NMR. Care was taken in the positioning and coaching of subjects to isolate the anterior compartment in these studies. MRI confirmed that the anterior compartment was the dominant group recruited. However, complete exclusion of other muscle groups contributing to the generated force cannot be assured. Subject compliance, outside of positioning, was not as critical in these studies, because muscle power was directly measured, and each individual value was used in the efficiency calculations. This study thus reduces many of the limitations of prior studies by using 31P-NMR in combination with a quantitative dynamometer.

The estimated Qmax was highest in concentric muscle action. This metabolic recruitment could be a response to the larger metabolic strain associated with this relatively inefficient muscle action. Increases in Qmax with the larger metabolic strain associated with concentric action could be mediated by increases in dehydrogenase activity, induced by increases in cytosolic Ca2+ or ADP levels, with subsequent increases in NADH delivery (3). Consistent with this notion is the activation of dehydrogenase activity observed with near-maximum work in human skeletal muscle (31). Another activation site may include the F1–F0 adenosinetriphosphatase directly (9, 34). This type of metabolic activation with work may cause the PCr/Pi “overshoot” observed with recovery after heavy exercise (7) if the metabolic activation persists longer than the exercise period. The increased metabolic capacity persisting after heavy exercise may result in a higher set point for the cytosolic ΔGATP, resulting in the overshoot.

It is unclear whether the apparent larger metabolic activation with concentric action was specifically caused by the muscle action or by the larger metabolic strain compared with eccentric activity. Studies with matched metabolic strain between eccentric and concentric ac-
tion, rather than workload as performed in the present study, may resolve this issue.

The Qmax is estimated by assuming that [ADP] alone is rate limiting for oxidative phosphorylation (20). In the present study, however, significant changes in Pi were also observed in proportion to the decreases in PCR. Pi could also be rate limiting for oxidative phosphorylation with a K_m of \(-1\) mM (3). In the present study, it was estimated that Pi increased to almost 12 mM with concentric activity, from a starting concentration of \(-1\) mM. Thus changes in Pi could be contributing to the differences in observed in Qmax. To test this hypothesis, we used a bireactant model for ADP and Pi control of respiration (19). By using this model, the Qmax equation becomes

$$Q_{\text{max}} = \frac{1 + \frac{[ADP]}{K_{\text{ADP}}} + \frac{[Pi]}{K_{\text{Pi}}} + \frac{[ADP][Pi]}{K_{\text{ADP}}K_{\text{Pi}}}}{[ADP][Pi]}$$

where \(K_{\text{Pi}}\) is the K_m for Pi (1 mM). All other parameters are as described in Eq. 2. By using this approach, the Qmax for concentric action was 410 and 304 \(\mu\)M/s for eccentric action. These results are consistent with the simple [ADP] model presented earlier and support the notion that the calculated maximum rate of respiration is greater with the concentric metabolic strain.

In the present study, the change in Qmax affects the steady-state measurements, because the metabolically ATP production capacity, or the battery and source resistance in the electrical analog model, is not constant with different muscle actions. However, Qmax was highest in concentric action, which would predictably result in a smaller decrease in \(\Delta G_{\text{ATP}}\) with work, not the larger drop observed in this study. Thus the relative efficiency differences between eccentric and concentric action are most likely underestimated by using the steady-state approach because of the apparent increase in metabolic recruitment occurring in concentric muscle action (i.e., higher Qmax).

Several limitations to using the PCR resynthesis rate as a measure of ATP production are critical for the quantitation of the efficiency and estimation of Qmax. An accurate initial rate must be determined with adequate temporal resolution. On the basis of the linearity of the time-course data, the 13-s time resolution seemed to be adequate for these purposes. This measure is aided in skeletal muscle by its relatively low resting metabolic rate compared with active states. The initial rate of PCR resynthesis is useful for these calculations if it is solely dependent on the metabolic production of ATP. Clearly, some contributing factors may include rapid changes in pH, Mg^{2+} concentration ([Mg^{2+}]), spin-lattice relaxation rates, or intra- or intercellular metabolite compartmentation. No significant changes in intracellular pH occurred at these workloads. Changes in intracellular [Mg^{2+}] can be determined from the relative positions of the ATP resonances due to Mg^{2+} binding by using difference spectroscopy (25). No spectral dispersion in the ATP resonance was observed (see Fig. 3) in the different spectra, suggesting that intracellular free [Mg^{2+}] was also constant (i.e., chemical shift of ATP was constant). The potential effects of rapid changes in spin-lattice relaxation rates were evaluated by using variable flip angles, and no significant effect was observed. Severe intra- or intercellular compartmentation of the metabolites could influence these results to some extent; however, as discussed above, these effects would appear to be minor. Finally, these studies were limited to a single workload and contraction velocity. It is possible that different workloads or velocities could result in alterations in the relative metabolic efficiencies observed.

We thank Drs. David Wiesler and Chris Combs for their help in the MRI experiments, the Biomedical Engineering and Instrumentation Program in the National Center for Research Resources for continuing help on the dynamometer, and Dr. Andrew Arai for many useful discussions.

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Received 26 March 1996; accepted in final form 6 May 1997.

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