Effect of muscle action and metabolic strain on oxidative metabolic responses in human skeletal muscle

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Combs, C. A., A. H. Aletras, and R. S. Balaban. Effect of muscle action and metabolic strain on oxidative metabolic responses in human skeletal muscle. J. Appl. Physiol. 87(5): 1768–1775, 1999.—A recent report suggests that differences in aerobic capacity exist between concentric and eccentric muscle action in human muscle (T. W. Ryschon, M. D. Fowler, R. E. Wysong, A. R. Anthony, and R. S. Balaban. J. Appl. Physiol. 83: 867–874, 1997). This study compared oxidative response, in the form of phosphocreatine (PCr) resynthesis, with matched levels of metabolic strain (i.e., changes in ADP concentration or the free energy of ATP hydrolysis) in tibialis anterior muscle exercised with either muscle action in vivo (n = 7 subjects). Exercise was controlled and metabolic strain measured by a dynamometer and 31P-magnetic resonance spectroscopy, respectively. Metabolic strain was varied to bring cytosolic ADP concentration up to 55 µM or decrease the free energy of ATP hydrolysis to −55 kJ/mol with no change in cytoplasmic pH. PCr resynthesis rates after exercise ranged from 31.9 to 462.5 and from 21.4 to 405.4 µmol PCr/s for concentric and eccentric action, respectively. PCr resynthesis rates as a function of metabolic strain were not significantly different between muscle actions (P > 0.40), suggesting that oxidative capacity is dependent on metabolic strain, not muscle action. Pooled data were found to more closely conform to previous biochemical measurements when a term for increasing oxidative capacity with metabolic strain was added to models of respiratory control.

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DURING MUSCLE CONTRACTION, eccentric movement involves muscle lengthening, whereas concentric movement involves muscle shortening. In addition to differences in the mechanism of movement, eccentric and concentric muscle actions have been shown to be fundamentally different on a number of levels. Mechanically, these modes differ in peak tension generated and activity-related damage (8, 38). Differences also exist in the energy metabolism associated with these muscle actions. Studies have shown that whole body energy costs, as measured by oxygen uptake, are lower for eccentric compared with concentric muscle action at a similar workload (1). Also, mechanochemical efficiency differences have been reported between the two exercise types (31). These findings suggest that differences exist in the coupling between muscle performance and energy production and consumption between exercise modes.

One of the most intriguing potential differences, in terms of the ramifications for studies of aerobic respiratory control, between concentric and eccentric exercise is that differences may exist for oxidative capacity [maximum rate of aerobic ATP production (Qmax)] (31). Ryschon et al. (31) report that estimates of oxidative capacity were higher in concentric vs. eccentric muscle action. However, significantly different metabolic strains between the two muscle actions occurred in this study that could account for the differences in Qmax (31). Metabolic strain is defined in this context as the metabolic changes that occur in response to workload or stress, including the concentrations of Pi ([Pi]), ADP, ATP, creatine phosphate, and creatine, as well as thermodynamic terms such as the free energy of ATP hydrolysis (∆GATP). It is difficult to directly measure Qmax in vivo because of limitations of blood flow and mechanical work at or near maximal workloads (27). Therefore, Qmax is indirectly extrapolated from models of respiratory control and metabolic data at workloads at which aerobic metabolism predominates (well below Qmax). The accuracy and assumptions of the model used directly affect the estimated value of Qmax. In the prior study (31), Qmax was estimated assuming a simple Michaelis-Menten limitation of oxidative metabolism by ADP at a single workload. It is, therefore, unclear whether the apparent increase in Qmax for concentric action was caused by differences in muscle action or by differences in metabolic strain or was a function of the model used to estimate Qmax.

The purpose of this study was to examine the relationship between respiration and metabolic strain resulting from these two types of muscle action and to evaluate different metabolic models in analyzing the data. Toward this goal, 31P-magnetic resonance spectroscopy (31P-MRS) and muscle dynamometry were used as previously described (31). However, metabolic response, in the form of phosphocreatine (PCr) resynthesis rate (V), was examined over a broad range of cellular energetic states within aerobic limits rather than at one workload. This enabled estimation of oxidative capacity from more than one model of respiratory control and enabled a direct comparison of the oxidative response over the full range of workloads and metabolic strains supportable by aerobic metabolism.

Presently, the two most accepted models of the mechanism of respiratory control involve either kinetic limitation of respiration by cytoplasmic ADP (5, 11, 20) or a quasi-linear, thermodynamic dependence of respiration on the cytoplasmic ∆GATP (26). Both of these models enable calculation of oxidative capacity from...
rates of aerobic PCr recovery after exercise but differ in the definition of oxidative capacity and the assumed mechanism of respiratory control (16, 18, 26). The kinetic model assumes a hyperbolic relationship between respiration and cytoplasmic [ADP] and requires empirical knowledge of the slope of respiration vs. oxidative capacity. The thermodynamic model requires empirical knowledge of the slope of respiration with changes in the effective $\Delta G_{ATP}$. Both of these general models were evaluated in this study.

**METHODS**

Design of the study. High-energy phosphate (HEP) levels and pH from the tibialis anterior (TA) muscle of the right leg were measured by $^{31}$P-MRS before, during, and after concentric and eccentric dorsiflexion exercise to compare rates of oxidative metabolism (V) as a function of HEP depletion between exercise types. The TA muscle aids in dorsiflexion of the ankle and is composed of predominantly type 1 fibers (approximately <30% type 2 fibers) (15). Exercise intensity was varied within aerobic tolerances to produce a range of HEP depletion in each individual. To facilitate direct comparisons between exercise types, both eccentric and concentric exercise bouts were conducted in each individual during the same exercise session. Custom-written programs in Interactive Data Language (IDL; Research Systems, Boulder, CO) enabled rapid data analysis after each exercise interval and subsequent matching of exercise intensity to desired HEP depletion level.

Subjects. Seven healthy adults (men, ages 25–38 yr) consented to participate in this study after being informed of the purpose and potential risks of the study according to the guidelines of the Human Subjects Use Committee at the National Institutes of Health.

Control of muscle action and exercise intensity. Exercise type, intensity, and duration were controlled by a custom-built dynamometer (30); the experiments were conducted as described previously (31). Briefly, the dynamometer was calibrated to a known torque before each exercise session. After attachment of the subject to the dynamometer, the peak torque attained in two brief (2–3 s) maximal-effort isometric dorsiflexions was measured and designated to be the maximal voluntary contraction (MVC). A 15-min rest period separated measurement of MVC and the subsequent exercise bouts. Each exercise bout consisted of voluntary and intermittent activation of the TA muscle, either in concentric or eccentric mode (5-s contraction, 5-s rest; 50% duty cycle) for a total of 5 min. For the duration of a given exercise bout, muscle activation was kept at a set level, which was prescribed as a percentage of MVC. Each exercise bout was followed by a 15-min period of rest. During exercise, ankle rotation speed was set at 6% MVC. Torque measurements were conducted at a rate of 10 Hz. The dynamometer was calibrated to a known torque before each exercise session. After attachment of the subject to the dynamometer, the peak torque attained in two brief (2–3 s) maximal-effort isometric dorsiflexions was measured and designated to be the maximal voluntary contraction (MVC). A 15-min rest period separated measurement of MVC and the subsequent exercise bouts. Each exercise bout consisted of voluntary and intermittent activation of the TA muscle, either in concentric or eccentric mode (5-s contraction, 5-s rest; 50% duty cycle) for a total of 5 min. For the duration of a given exercise bout, muscle activation was kept at a set level, which was prescribed as a percentage of MVC. Each exercise bout was followed by a 15-min period of rest. During exercise, ankle rotation speed was set at 6% MVC. Torque measurements were conducted at a rate of 10 Hz. These readings were expressed as the average tension-time integral per stroke and were subsequently converted to power (in W; instantaneous torque times the angular velocity for the last 1 min of exercise for a total of 5 strokes).

$^{31}$P-NMR spectroscopy. $^{31}$P-NMR spectra of the TA were obtained at 4 T with a General Electric/Bruker Omega full-body spectrometer at 69 MHz. Before exercise, a 2.5-cm single-turn surface coil was mounted over the TA muscle, and the region of interest was positioned in the magnet isocenter. Four types of $^{31}$P-NMR spectra were acquired. During each exercise bout (before, during, and after exercise), high-temporal-resolution spectra were collected (Fig. 1C). These were collected with a flip angle (500 W, 40–50 µs) that resulted in the largest PCr signal with a 0.325-s transverse relaxation time (TR), 6-kHz sweep width, 512 points, and four transients per spectrum. Gradients were employed to dephase residual transverse magnetization between radiofrequency pulses (all 3 axes, 0.12 g/cm, 100-ms sine-shaped ramps, 20-ms plateau). Saturation factors for the high-temporal-resolution spectra were calculated from a fully relaxed spectrum (TR = 15 s) acquired at the beginning of the exercise session. In addition, a high signal-to-noise ratio (SNR) spectrum (1,024 transients) was acquired before each exercise bout. This served as a reference spectrum for data analysis (Fig. 1B). The high-SNR spectrum acquisition parameters were identical to the ones used for acquiring the time-course spectra. Time-course and high-SNR spectra were found to have fast decaying components (broad hump in middle of spectra, Fig. 1, B and C) attributed to less mobile phosphorus metabolites of bone that were in the volume of interest. To facilitate quantification of peak integrals to be used for calculating metabolite concentrations, a bone-saturated, fully relaxed spectrum was acquired at the begin-
ceiving of each exercise session (Fig. 1A). This spectrum was collected with a 90° flip angle, 15-s TR, 64 transients, 500-W power, 512 points, and 6-kHz sweep width. Saturation of the bone signal was accomplished with a 15-s-duration low-power radio-frequency pulse 30 parts/million downfield of the carrier (Fig. 1B).

1H volume imaging. TA muscle volume in each subject was measured at 4 T on a separate day. This was accomplished by using a proton birdcage resonator, mounted over the lower leg, with the use of a fast spin echo (2D-FSE) sequence. The subjects exercised to exhaustion, and a 2D-FSE sequence provided T2-weighted images that facilitated accurate measurement of maximum muscle cross-sectional area of the TA (31). Maximum cross-sectional areas were obtained instead of volume measurements for convenience. Reports indicate that maximum cross-sectional area correlates well with power output in this muscle (10). 2D-FSE axial images of the lower leg were obtained with an echo train length of eight, 2-s TR, 102-ms effective echo time, 20 × 15-cm field of view, one transient per view, 32-kHz bandwidth, 6-mm slice thickness, 3-mm interslice spacing, and a 256 × 256 matrix size. All images were collected by using a General Electric Signa 5.x Genesis console.

Data analysis. All spectra were processed after exponential multiplication and 30-Hz line broadening. Time-course metabolite concentrations were calculated by comparing spectra acquired during exercise (time resolution of 5.2 s) to the high-SNR reference spectrum acquired during rest. Calculations were performed in IDL by using regression analysis of natural-line shape (14). Saturation factors were calculated and corrected for by means of natural-line-shape comparisons of fully relaxed to the fast-time-course spectra. Integration of peak areas from the bone-saturated, fully relaxed spectrum obtained before exercise allowed for conversion of regression coefficients to concentration equivalents. Before regression, the data were filtered by using a low-pass filter of 8 Hz to remove high-frequency noise from the fast time-course spectra. [ADP] were calculated from the creatine kinase reaction by assuming an equilibrium constant of 1.66 × 109 and a total creatine constant of 42.5 mM (13). Intracellular pH was calculated from the chemical shift of P1 relative to PCr (2). The free energy of ATP hydrolysis was calculated by assuming a standard free energy of −32 kJ/mol at pH 7.0 and 37°C (35), according to the equation

\[ \Delta G_{A TP} = \Delta G^0 + R + T \ln \frac{[ADP][P_i]}{[ATP]} \]

where R is the gas constant and T is temperature.

The majority of the PCr time-course plots showed poor correlation to exponential fitting. Therefore, calculations of V were conducted from regression estimates of the initial V during the first 21.8 s (5.2-s time resolution, 5 time points) after completion of exercise (r2 > 0.90) (31). The use of the initial rate method to estimate V is justified given that initial product formation during a step increase in an enzymatic reaction is linear (32). Use of the initial rate method is valid only for the time period when product formation is linear (32). All initial rate measurements of PCr recovery presented here had R2 values for the linear fit > 0.95, while the high temporal resolution permitted the use of five time points in this analysis. The initial rate method is the classic method used to extrapolate a steady-state rate from a step perturbation. This is simply due to the fact that, during the initial rate, the experimental conditions are closer to those experienced during the work period than to those during the entire recovery curve. Thus the initial rate is not as influenced by the approach to equilibrium occurring after the cessation of the work and better reflects the rate occurring during the previous working condition. Finally, the initial rate method was used to facilitate direct comparison to values obtained in the earlier study (32). Time-course data with evidence of muscular hypoxia or ischemia (pH changes or failure to achieve steady-state [ADP] during the final minute of exercise) were discarded.

Estimation of Qmax, from the kinetic model, was calculated both from hyperbolic fits of instantaneous PCr recovery (V) as a function of cytoplasmic [ADP] and from individual pairs of V by [ADP] after exercise according to the equation (32)

\[ Q_{max} = V(1 + K_m/[ADP]) \]

where the K_m for [ADP] is 30 μM (31). This relationship assumes that anaerobic ATP production is negligible during recovery, ADP is kinetically limiting, and resynthesis of PCr accounts for all but a negligible fraction of ATP hydrolyzed during recovery.

Image processing. Axial 1H images of the lower leg were processed by using a program written in IDL for calculating muscle cross-sectional areas from defined regions of interest. Accuracy of this technique was verified by using phantoms of known volume. Coefficients of variation for volume determinations were <1%.

Statistics. All data are reported as means ± SD. Slope comparisons were made by using paired Student’s t-test. Linear and nonlinear regressions were performed by using procedures in IDL and Sigma-Plot graphical software (San Rafael, CA).

RESULTS

Aerobic submaximal concentric and eccentric exercise intensity was varied to produce a wide range of cellular energy states. Table 1 shows the ranges of the various metabolites for the two types of exercise. Repeated integration of peaks from the bone-saturated, fully relaxed spectrum obtained before exercise indicated a 5–10% uncertainty in quantification of areas used to define initial metabolite concentrations. This uncertainty was reduced by 10.2% on April 5, 2017 http://jap.physiology.org/ Downloaded from
did not complicate comparisons between exercise types, given that both exercise types were performed on the same day and used the same spectrum for establishing initial metabolite concentrations. Natural-line shape analysis prevented the compounding of this error when the lower SNR time-course data were analyzed. Despite these considerations, resting levels of [ADP] and [Pi]/[PCr] were close to other reported values (31, 33, 34, 37). As indicated, a fivefold increase in cytosolic [ADP] and [Pi] with a corresponding 8 kJ/mol decrease in ΔG_{ATP} was achieved. As noted by Ryschon et al. (31), concentric exercise produces a much larger decrease in the concentration of HEP than eccentric exercise does at the same workload. To produce the same range of HEP concentration change, eccentric work was varied over a broader range than concentric work (1.6 times the highest concentric workload) (Table 1). Over this range of workloads, pH changes were minimal (<1 SD from resting levels, Table 1). However, work at higher power levels, not used in this analysis, resulted in pH changes indicative of reliance on anaerobic metabolism.

The range of workloads and corresponding metabolic strain produced a 14.5- and 19-fold change in V for eccentric and concentric exercise, respectively (Table 1). Figures 2A, 3A, and 4A show that V values increase with increasing cytoplasmic [ADP], decreasing cytoplasmic phosphorylation potential, and decreasing ΔG_{ATP}, respectively. Figures 2A, 3A, and 4A also show that the metabolic response, V, to decreasing energy state is similar between exercise types, with concentric and eccentric values for V overlapping over the entire range of values tested.

Fitting of the raw values of V to cytoplasmic [ADP] showed poor correlation to the expected hyperbolic function predicted by the kinetic model for both exercise types (R² < 0.53). Further analysis of the data showed that intersubject variations in the magnitude of V and level of metabolic strain at low workloads unnecessarily complicated fitting of the data and necessitated normalization to a common starting point for each individual. These intersubject variations may be attributed to differences in mitochondrial content, short- and long-term muscle conditioning, or normal biological variations among subjects. Therefore, all subsequent analysis was conducted on both raw and normalized data. Normalization to a common starting point was accomplished by subtracting a baseline response (minimum value of V, [ADP], ΔG_{ATP}, and the cytoplasmic phosphorylation potential) from all subsequent responses. Figures 2B, 3B, and 4B show these corrected data.
tions. Intersubject differences were greatest for $V$ values at the lowest workloads, compared with all other parameters, and, therefore, had the most impact on the fitting of the raw data to the models. Minimum values for $V$, last-minute [ADP], last-minute $\Delta G_{\text{ATP}}$, and last-minute cytoplasmic phosphorylation potential at the lowest workloads were $63.7 \pm 32.7 \mu$mol PCr/s, $17.1 \pm 2.7 \mu$M, $-60.6 \pm 0.7 \text{kJ/mol}$, and $15.9 \pm 3.0 \mu$M, respectively.

Hyperbolic fits of $V$ to [ADP], according to the kinetic model, were only slightly better than a linear fit to the same data (Table 2, Fig. 2B). A strictly linear comparison of individual slopes of $V$ by [ADP] indicated that differences between exercise types were not significant (paired $t$-test, $P = 0.51$). Table 2 also shows the fitted parameters of $V$ by [ADP] according to Michaelis-Menten-type hyperbolic fits of the pooled data from all subjects. Estimation of $Q_{\text{max}}$ from the hyperbolic fits of the pooled data (Table 2) were in the range reported for isolated mitochondria, but not for intact cells (Table 2). The low concentration range of [ADP] (Table 1) in relation to the mitochondrial, but not for intact cells (Table 2). The low concentration range of [ADP] (Table 1) in relation to the mitochondria, but not for intact cells (Table 2).

Table 2. Fitted parameters of model analyses applied to time course of end-exercise PCr recovery ($V$) and last-minute metabolite concentrations from submaximal exercise of tibialis anterior muscle after concentric and eccentric exercise

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$^a$Units are (µmol PCr/s)/(µM). $^b$Units are (µmol PCr/s)/(kJ/mol). $^c$Not significantly different (paired comparisons $t$-test of individual slopes, $P > 0.40$). Fits from data presented in $^a$Fig. 2B, $^b$Fig. 3B, $^c$Fig. 4B. $^d$Average combined resting value (Table 1) added to calculated value.

Table 2 presents the fitted parameters of model analyses applied to time course of end-exercise PCr recovery ($V$) and last-minute metabolite concentrations from submaximal exercise of tibialis anterior muscle after concentric and eccentric exercise.

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Fig. 4. Plot of $V$ after exercise as function of average effective free energy of ATP hydrolysis ($\Delta G_{\text{ATP}}$) for last minute of dorsiflexion exercise of tibialis anterior muscle: A: raw data by exercise type. B: plot of pooled data (eccentric and concentric muscle action combined) normalized among individuals by subtracting minimum value of each parameter for each individual. Lines through data are linear and sigmoidal fits. Fitted parameters according to linear and sigmoidal models are presented in Table 2.

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The apparent $K_m$ (Table 2) precluded accurate estimation of maximum PCr recovery rate ($V_{\text{max}}$) and $K_m$ by log-linear methods (Eadie-Hofstee or Hill plots) (32). The reason for this is the low values of [ADP], basically the total range of aerobic capacity of the tissue, relative to the $K_m$ obtained in this study. By not reaching values above the $K_m$, the reaction appears to be first order with infinite $V_{\text{max}}$ and $K_m$ values (32). Therefore, individual comparisons between exercise types for apparent $K_m$ and $V_{\text{max}}$ were not performed. In addition, each individual provided two to three data points for each exercise, which precluded accurate hyperbolic fitting of the data by individual by exercise type. $Q_{\text{max}}$ (single-point analysis based on ADP model assuming hyperbolic ADP dependence of respiration and $K_m$ of 30 µM) (28) was shown to increase with workload and/or metabolic strain over a broad range (Table 1). The increase in $Q_{\text{max}}$ as a function of [ADP] was roughly linear for most individuals ($R^2$ ranged from 0.33 to 0.87, data not shown). Pairwise individual subject comparisons of linear slope of $Q_{\text{max}}$ by [ADP] indicated that differences between exercise types were not significant (paired $t$-test, $P > 0.65$). Calculation of $Q_{\text{max}}$ by this method is evaluated more fully in the DISCUSSION.
DISCUSSION

In this study, the same muscle was voluntarily activated at various workloads to produce a similar range of metabolic strain with the use of eccentric and concentric modes of muscle action. The ATP synthesis rate was estimated from V. As found in previous studies (1, 31), the metabolic strain associated with a given workload was higher in concentric than eccentric muscle action. However, comparing the rate of ATP synthesis as a function of metabolic strain, plotted as either [ADP], [ADP][Pi]/[ATP], or $\Delta G_{\text{ATP}}$, resulted in a complete overlap of the concentric and eccentric data. All statistical tests, as expected from this distribution, failed to find significant differences of ATP synthesis rate among those parameters between muscle actions. This lack of differences also suggests that any extrapolation of $Q_{\text{max}}$ from these data would result in similar values for eccentric and concentric muscle action. These results suggest that metabolic strain and not muscle action determines the ATP synthesis rate and is the main finding of this study. Secondarily, limitations in present models of respiratory control in skeletal muscle may be apparent from the relationships of V to these parameters.

Because no statistical difference could be found between muscle actions, only the fits to the combined data are presented in Figs. 2B, 3B, and 4B. Figures 2B and 4B and Table 2 show that V can be reasonably fit as a hyperbolic function of ADP (kinetic model) or as a sigmoidal fit of $\Delta G_{\text{ATP}}$ (thermodynamic model). These results are not surprising given that ADP, PCr, Pi, and ATP are covariant with exercise in vitro (6) and associated with the metabolic strain induced in the tissue by the workload. Figures 2B, 3B, and 4B and Table 2 also show that other models fit the data with nearly equal statistical rigor. In total, these results show that no model was statistically superior in describing these data. These results are likely due to the poor discriminatory power of the various models in interpreting in vivo data, although SNR considerations, even at 69 mHz for $^3$P, may also influence this conclusion.

Two aspects of the kinetic fit suggest that this simple model is not adequate to describe these data. First, the $K_m$ value approached 90 µM (Table 2), which is much higher than that found in isolated mitochondria. Higher $K_m$ values have been found in some permeabilized cell preparations (28, 36); however, the complexity of these intact cell measures may contribute to the reported high $K_m$ values. Second, using the single-point and full-fit methods to determine $Q_{\text{max}}$ should provide similar results if the model is correct. However, the calculated $Q_{\text{max}}$ increased with metabolic strain independent of the $K_m$ value when extrapolated from the single-point method by using either the isolated mitochondria $K_m$ of 30 µM (Table 2) or the 90 µM found from the curve fit of the data. These two problems with the simple kinetic fit suggest that other processes, or more complex interactions with ADP, are influencing the metabolic rate as has been suggested by other researchers (7, 17).

A primary limitation of the thermodynamic model is a lack of a molecular mechanism as a basis for the model; thus phenomenological constants are used to fit the data. In addition, the shape or behavior of these thermodynamic models with regard to metabolic parameters is not unique, as shown in a comparison of Figs. 2-5. This lack of specificity will be further evaluated below.

One potential explanation for the problems associated with the interpretation of the data from this study and from the previous study (31) is that $Q_{\text{max}}$ does change as a function of workload. Both the kinetic and thermodynamic models assume that the oxidative capacity of the tissue is fixed as a function of workload. On the basis of the evidence of metabolic and temperature responses to increased work in skeletal muscle, this is an unreasonable assumption. The maximum rate of respiration has been shown to be dependent on the delivery of reducing equivalents to the cytochrome chain (27, 29). For many years it has been known that activation of the rate-limiting substrate oxidation enzymes of intermediary metabolism is increased with
increases in work or metabolic strain (for reviews see Ref. 3, 23, 24). Calcium has been implicated as having some role in this process; however, other modulators might include hormones and changes in mitochondrial matrix volume (12, 22). Temperature may also influence this process profoundly. A 10°C increase doubles mitochondrial ATP production (4, 27). A less peripheral muscle, the vastus lateralis, has been shown to increase by 4° with moderate exercise (9, 21). Thus, due to temperature alone, the maximum velocity of ATP production could increase with exercise by as much as 50%.

The effects of alterations in $Q_{\text{max}}$ were evaluated on both models by including a simple linear term for increasing $Q_{\text{max}}$ with increases in [ADP] or decreasing $\Delta G_{\text{ATP}}$. The kinetic and thermodynamic models were modified as shown below:

**modified thermodynamic model**

$$\dot{V}_O_2 = m(\Delta G_{\text{ATP}})^2 + g_m(\Delta G_{\text{ATP}}) + \dot{V}_O_2 \text{initial}$$

**modified kinetic model**

$$\dot{V}_O_2 = [m([\text{ADP}]) + V_{\text{max}} \text{initial}]/(1 + K_m/[\text{ADP}])$$

where $\dot{V}_O_2$ is oxygen consumption, $m$ is equal to the slope of the linear change in the mitochondrial conductance coefficient for the thermodynamic model and for the slope of the change in $V_{\text{max}}$ for the kinetic model, and $g_m$ is the mitochondrial conductance. Figure 5 shows these modified curves in relation to the data. Note that for all of the models, the alterations in $Q_{\text{max}}$ do not dramatically change the shape of the functions or the quality of the fit, despite the significant change in flux-control mechanisms. The kinetic model is shown in Fig. 5A, with a 60% increase in $Q_{\text{max}}$ over the full range of [ADP] (dashed line). A 60% increase was chosen because it resulted in a good fit with the ADP of [ADP] (dashed line). A 60% increase was chosen with a 60% increase in $Q_{\text{max}}$ over the full range of [ADP], with a 60% increase in $Q_{\text{max}}$ over the full range of [ADP].

In Fig. 5B, the thermodynamic model was fit to the quadratic function above. The fit predicted a 2.8-fold increase in $g_m$ over the range in $\Delta G_{\text{ATP}}$ observed. The fit and shape of the thermodynamic model again were not significantly affected by this major alteration in the model mechanics. Thus, a large increase in $Q_{\text{max}}$ with work could go undetected with the thermodynamic model because of the nature of the mathematics as well as the inherent physiological scatter in the in vivo $^{31}$P-NMR data.

These reasonable model fits with the linear increase in $Q_{\text{max}}$ with work do not prove that an increase in $Q_{\text{max}}$ occurs. This is evident because none of the models evaluated uniquely fit the in vivo $^{31}$P-NMR data. This is due to the similarity of the models’ behavior with metabolic strain over the range studied, the number of undetermined variables in the models, and the real as well as “physiological” noise in the $^{31}$P-NMR data. On the other hand, an increase in $Q_{\text{max}}$ with work cannot be eliminated based on these models. On the basis of the physical and biochemical changes associated with increases in workload in skeletal muscle, we believe that models that incorporate a metabolic adaptation to workload are more realistic to the physiological conditions. In addition, this analysis suggests that the models used to fit these metabolic strain data are not unique and cannot be used to definitively prove a mechanistic model.

In summary, we have shown that the oxidative metabolic response to metabolic strain does not differ between concentric and eccentric muscle action in skeletal muscle. We conclude that previous reports of differences in oxidative capacity with muscle action were due to incorrect assumptions concerning the relationship of oxidative metabolism and cytoplasmic [ADP]. In addition, the idea is developed that change in $Q_{\text{max}}$ with metabolic strain and associated work may be a neglected element in the present models of respiratory control in vivo.

We thank Dr. David Wiesler for help in this project and Dr. Han Wen for many useful discussions.

Received 29 March 1999; accepted in final form 15 July 1999.

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