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## Literature Review

# Role of Fatigue in Limiting Physical Activities in Humans with Neuromuscular Diseases

**ABSTRACT**

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New methods of examining both central and peripheral fatigue are now available. A broader understanding of the mechanisms of fatigue in healthy human subjects has begun to emerge. The mechanisms of fatigue in patients with various neuromuscular diseases are even more complex than in healthy persons. Examples of both central and peripheral fatigue in various neuromuscular diseases and other disorders are presented, including metabolic myopathy, chronic fatigue syndrome, postpolio syndrome, and amyotrophic lateral sclerosis.

**Key Words:** Magnetic Resonance Spectroscopy, Force, Electromyography

**T**he goal of this review is to acquaint the reader with various applications of the magnetic resonance spectroscopy (MRS) technique and electromyography (EMG) and force measures to the study of human skeletal muscle fatigue, with emphasis on patients who have neuromuscular diseases. In motivated and healthy young subjects, central fatigue is usually not significant; however, in many patients with neuromuscular diseases, central fatigue is an important component of the fatigue process. To assess central fatigue quantitatively, we utilize the measurement of added force in response to a brief tetanic train of stimuli superimposed on a maximum voluntary contraction (MVC). In addition, we examine the relationship between declining MVC force and declining tetanic tension during fatigue, since they should fall in parallel when there is no central fatigue. To quantify peripheral fatigue, we utilize the compound muscle action potential (CMAP) as an indicator of neuromuscular transmission and muscle membrane function, twitch tension and tetanic tension as an index of muscular force generation, and altered metabolites measured by nuclear MRS to evaluate bioenergetic

changes during fatigue. The difficult task of evaluating excitation contraction coupling impairment is estimated by correlating changes in twitch tension with changes in CMAP, speed of force generation and relaxation in the twitch and the tetanus, and changes in the ratio of surface rectified EMG over force. Upper motor neuron dysfunction is quantified by analyzing rapid repetitive movements, the speed of voluntary force generation during a rapid sub-maximal, static (isometric) contraction, and also the added force measurement.

A distinctive type of fatigue develops in normal persons during repeated rapid muscle contractions. We examined movements that were performed at a speed of one per second in the tibialis anterior muscle, at 40% of MVC force, with each contraction performed in as-fast-as-possible fashion.<sup>1</sup> There was a slowing of the speed of tension development accompanied by a prolongation in EMG burst duration within 1 min after starting the exercise. At the same time point, the dynamic properties of the twitch, the tetanus, and the CMAP were unchanged. The results suggest that the fatigue of rapid repetitive movements, which becomes apparent very quickly at a time when intramuscular metabolites have hardly changed, primarily reflects central factors with reduced discharge frequencies and recruitment speed.

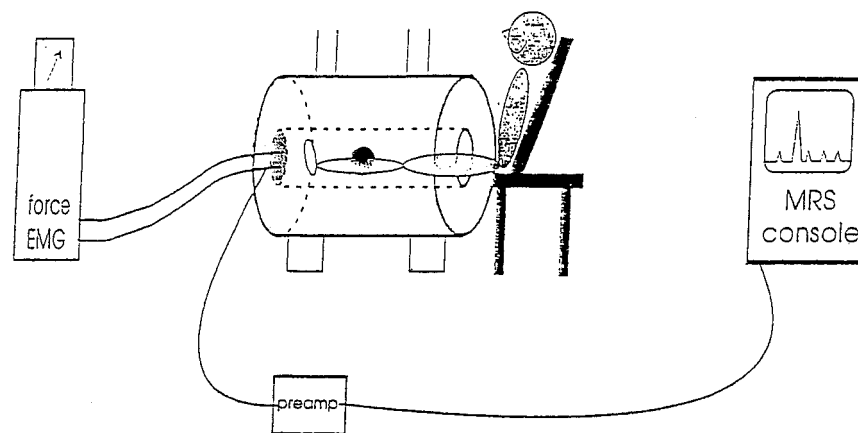
The first in vivo MRS studies of human skeletal muscle were reported in the early 1980s.<sup>2-4</sup> Since that time, access to this technique has broadened. Its use has now expanded into fields as diverse as biochemistry, medicine, and exercise science. The advantages and limitations of this technique have been delineated, and better methods have been developed. My purpose here is to review, in terms of both breadth and significance of contribution, the body of knowledge that has emerged from the application of MRS to the study of exercising human skeletal muscle.

The first part of this review deals with studies of healthy human muscle; the second part concerns the effects associated with various disease states. The increase in the number of studies of human skeletal muscle that use the MRS technique has been exponential; thus, this review will not be all-inclusive. For an expanded review of clinical MRS studies of skeletal muscle, see Kent-Braun et al.<sup>2</sup> To establish a common ground for the discussion of these studies, we will begin with a brief description of the technique of MRS. A full description of the technological development of human MRS is beyond the scope of this review; therefore, publications detailing technique-oriented progress will not be included.

## MRS TECHNIQUE

Studies of human skeletal muscle using MRS require a superconducting magnet, a spectrometer, and nonmagnetic exercise equipment (Fig. 1). Data are obtained with a nonmagnetic coil, the size and shape of which determine the volume of tissue that will be sampled. MRS uses radiofrequency waves transmitted

through the coil in the presence of the static magnetic field to sample the relative concentrations of metabolites containing the nucleus of interest (e.g., phosphorus, carbon, proton). The sensitivity of the MRS measurement varies with the nucleus studied. The quality of the signal depends on the size of the volume studied, the total data acquisition time, and the adequacy of the radiofrequency shielding in use. Figure 2 shows a typical phosphorus-31 (<sup>31</sup>P) MRS spectrum from resting human muscle. The frequency (location on the x axis) of each resonance (peak) relates information regarding the identity of the compound. The area under each peak indicates its relative concentration. In Figure 2, the peaks from inorganic phosphate (Pi), phosphocreatine (PCr), and the three phosphates of adenosine triphosphate (ATP) are all clearly visible. Peak areas can be quantitated using curve-fitting programs designed for this purpose. The data can then be expressed as a simple ratio (e.g., Pi/PCr), or an estimate of metabolite concentrations can be made. During muscular contractions, PCr decreases and Pi increases



**Figure 1:** Typical magnetic resonance spectroscopy exercise system. The surface coil is placed on the tibialis anterior muscle in this case. The coil and volume of interest must be located in the isocenter of the superconducting magnet (dark circle in center). In addition to the metabolic measurements obtained with magnetic resonance spectroscopy, simultaneous force and electromyographic measurements can also be made during exercise. Reprinted with permission from Kent-Braun et al.<sup>26</sup>

es; ATP remains unchanged except during very high-intensity exercise. Adenosine diphosphate (ADP) is present in the muscle in micromolar concentrations and is therefore not visible in the  $^{31}\text{P}$  spectrum. Intracellular pH can be determined from the chemical shift (i.e., the distance) of Pi from PCr. The concentrations of proton ( $\text{H}^+$ ) and monovalent phosphate ( $\text{H}_2\text{P}_4^-$ ) can also be calculated based on Pi and pH. Because MRS is a noninvasive technique, sampling can be continuous. A typical time average for a single spectrum is in the range of 10–60 sec.

The biggest advantage provided by MRS is the capacity to make repeated, noninvasive measurements of muscle energy metabolism. Data can be collected continuously before, during, and after dynamic or isometric exercise. Under the appropriate conditions, comparisons of metabolic capacity can be made between different populations, and in the same persons, before and after an intervention (e.g., exercise training). Of course, there are also disadvantages to this technique, one of which is that the muscle of interest must be located in the isocenter of the magnet. As magnet opening sizes increase, this has become less of a problem. Movement artifact due to muscle contractions can reduce the quality of the MRS signal. Although MRS is useful for measuring relative changes in energy metabolites, absolute quantitation of metabolite concentration is difficult. Likewise, *in vivo* studies of metabolic regulation in humans are complicated by a lack of information regarding muscle fiber composition, activation, and sample volume. However, studies designed to test theories developed *in vitro* under more controlled conditions are valuable for determining the consistency with which a theory fits experimental data.

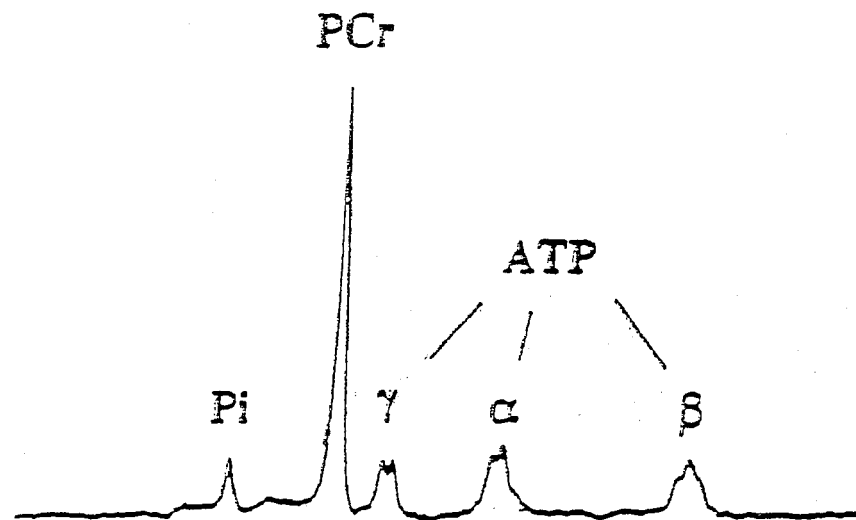
## HEALTHY MUSCLE METABOLISM

### Muscle Energetics

Most of the early applications of  $^{31}\text{P}$  MRS were for the study of intracellular bioenergetics. The metabolites involved in energy production ( $\text{ADP} + \text{PCr} + \text{H}^+$ ,  $\text{ATP} + \text{creatine}$ ) and utilization ( $\text{ATP} - \text{ADP} + \text{Pi} + \text{energy}$ ) are related via the creatine kinase reaction. With certain assumptions, the creatine kinase equilibrium may be used to estimate intracellular ADP concentration. In general, the energy state of the muscle is often represented by the ratio PCr/Pi (or, conversely, Pi/PCr). Because  $^{31}\text{P}$  MRS provides an opportunity to monitor these metabolites continuously and noninvasively, theories previously developed *in vitro* could be tested with the MRS technique.

Intramuscular oxidative metabolism has been studied using progressive exercise during which a meta-

bolic steady state (i.e., substrate and oxygen are not limiting) is achieved at each exercise level. Chance et al.<sup>3</sup> determined that the relationship between work rate and “energy cost” (expressed as Pi/PCr) could be analyzed as a hyperbolic Michaelis-Menten function that represented mitochondrial function. An example of this analysis is presented in Figure 3. The creatine kinase equilibrium can be used to estimate cytosolic ADP concentration from the changes in Pi/PCr. The initial, linear portion of this relationship between work and Pi/PCr (or ADP concentration) was similar to that observed in isolated mitochondrial preparations and thus provided *in vivo* evidence of ADP concentration regulation of skeletal muscle oxidative phosphorylation during relatively low work intensities. This relationship is shown in the *box* in Figure 3. In a subsequent study, it was observed that the slope of work *vs.* Pi/PCr was increased in trained relative to untrained muscle.



**Figure 2:** Representative phosphorus spectrum from the resting tibialis anterior muscle of a healthy human. This spectrum was obtained with a  $3 \times 5$  cm surface coil taped over the belly of the muscle. Total acquisition time was 5 min. Peaks from inorganic phosphate (Pi), phosphocreatine (PCr), and  $\gamma$ -,  $\alpha$ -, and  $\beta$ -adenosine triphosphate (ATP) are clearly resolved. The area under each peak can be estimated using a curve-fitting process, and the relative concentration of each metabolite may then be calculated. Alternatively, the metabolites may be expressed more simply as a ratio (e.g., Pi/PCr). The chemical shift (i.e., distance) between PCr and Pi can be used to calculate intracellular pH. Reprinted with permission from Kent-Braun et al.<sup>26</sup>

In trained muscle, the higher slope of work vs. Pi/PCr reflected an increased capacity for the mitochondria to keep pace with the progressively increasing demands for ATP. The theoretical relationship between work and Pi/PCr was also calculated for conditions in which the metabolic controller is not only ADP, but oxygen, Pi, or nicotinamide adenine dinucleotide).

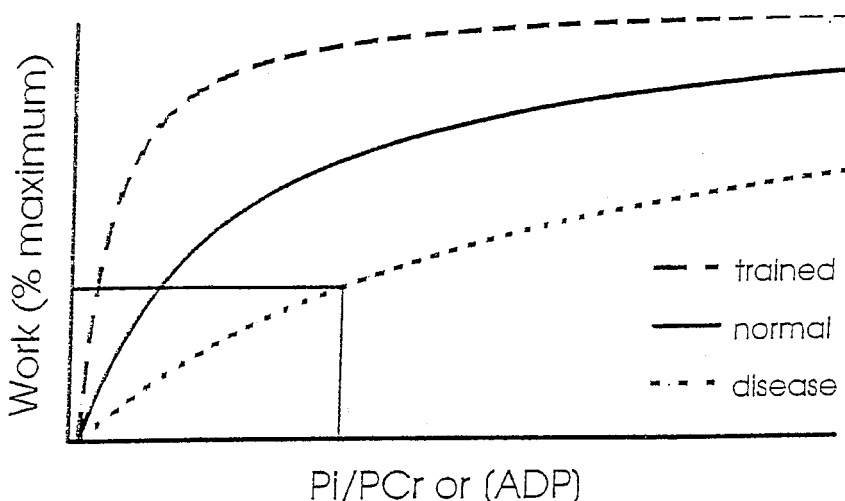
As a result of the early work of Chance et al.,<sup>3</sup> this type of progressive, steady-state exercise protocol has since been used to evaluate muscle performance and oxidative metabolism in healthy subjects and in clinical populations. However, comparisons between different populations, or the same subjects before and after intervention, require adjustments for differences in muscle strength, or aerobic capacity. Comparisons at any given workload require normalization for differences in strength; at the same absolute workload, a person with a smaller muscle will be working at a much higher relative load. Thus, the metabolic demand will be relatively higher. To adjust for differences in muscle mass, changes in force during exercise can be expressed relative to the preexercise force from a MVC. Alternatively, force can be normalized to muscle cross-sectional area (obtained with magnetic resonance imaging). Although these adjustments were not always made in the past, future studies should include them to provide for better interpretation of the results.

In summary, <sup>31</sup>P MRS has proven to be useful for the noninvasive investigation of the relationship between muscle performance and the supply of energy for this performance. By quantitating the temporal alterations of each metabolic parameter, the nature of the relationship between work and the metabolic pathways may be inferred.

**Muscle Fatigue.** Muscle fatigue, generally defined as a decline in force-generating capacity, can arise from a variety of causes. The precise mechanisms of muscle fatigue are not known, although it is now clear that the sources of fatigue depend in part on the type of exercise performed. In 1986, Taylor et al.<sup>4</sup> reported one of the early studies of muscle fatigue using <sup>31</sup>P MRS. The goal of that study was to determine the effect of ATP depletion during fatigue produced by moderate- and high-intensity forearm exercise. High-intensity exercise resulted in a greater change in intramuscular metabolism, PCr depletion exceeded 80%, and intracellular pH fell below 6.2. Depletion of ATP was also observed under these extreme conditions. The recovery of PCr, Pi, and pH was slower after high-intensity exercise compared with moderate exercise, and ATP recovery was much slower than that of the other metab-

olites. These results were interpreted to indicate that intense, fatiguing exercise could lead to severe metabolic depletion associated with slowed recovery.

The relationship between muscle fatigue and metabolism has since been studied during various exercise protocols. Wilson et al.<sup>5</sup> observed a strong linear relationship between fatigue and the increase of monovalent phosphate ( $H_2PO_4^-$ ) during maximum contractions of the wrist flexor muscles in healthy volunteers. Their use of several different exercise protocols provided evidence that the relationship between  $H_2PO_4^-$  and fatigue was stronger and more consistent than was the relationship between pH and fatigue. In a different study, intermittent isometric exercise of the adductor pollicis resulted in more gradual changes in metabolites and force compared with sustained exercise.<sup>6</sup> However, during



**Figure 3:** Schematic of the general relationship between power or force and inorganic phosphate/phosphocreatine (*Pi/PCr*, or adenosine diphosphate [*ADP*] concentration) during progressive exercise. As the workload increases, there is a concomitant increase in *Pi/PCr* as the muscle responds to the increased energy demand. The initial, linear portion of this curve (workload of <40% maximum) can be used to estimate the oxidative potential of the muscle (box). In trained compared with untrained subjects, there is less of an increase in *Pi/PCr* at any given relative workload, thus indicating an improved ability to keep pace with energy needs by means of oxidative phosphorylation. In contrast, in persons with disease that impairs muscle metabolism (either directly or indirectly), the initial slope of work vs. *Pi/PCr* is decreased, indicating a poor capacity for oxidative metabolism. Reprinted with permission from Kent-Braun et al.<sup>26</sup>

both intermittent and sustained exercise, force was more strongly related to proton  $H^+$  and  $H_2PO_4^-$  concentrations than to either PCr or Pi concentrations. Therefore, the authors concluded that  $H^+$  and  $H_2PO_4^-$  play important roles in the development of muscle fatigue. Similar results were later reported for the less fatigable tibialis anterior muscle. An examination of the recovery of force and metabolites after fatiguing exercise indicated that  $H_2PO_4^-$  was most clearly related to maximal force-generating capacity during recovery from fatigue.<sup>7</sup>

In summary, a series of MRS studies of muscle fatigue suggest a role for metabolic inhibition of the contractile process in the development of fatigue during some types of exercise. In general, it seems that fatigue during high-intensity exercise is most likely to be associated with changes in metabolites, whereas fatigue during submaximal exercise also arises from nonmetabolic sources such as impairment of muscular activation (see below).

**Combining MRS and EMG to Study Fatigue.** It is possible to make simultaneous measurements of metabolism and the electromyographic response to exercise.<sup>8</sup> Combining MRS with surface EMG ultimately will provide a more thorough understanding of the complex events that occur during the development of human muscle fatigue. In 1987, Miller et al.<sup>9</sup> reported the time course of change in force, pH, PCr; the CMAP (elicited with a twitch stimulus); and the rectified integrated EMG (RIEMG) in the adductor pollicis muscle of healthy subjects. During maximal isometric contraction for 4 min to produce fatigue, force fell by 90%, pH decreased to 6.4, and PCr was nearly depleted. Both neuromuscular efficiency (force/RIEMG) and the CMAP also decreased during fatigue. There were three phases of recovery after exercise, which suggested three compo-

nents to fatigue. First, changes in the CMAP indicated a rapidly recovering alteration of muscle membrane excitation and impulse propagation; second, recovery of PCr and pH suggested a more slowly recovering alteration in the metabolic state of the muscle; and third, the slow recovery of neuromuscular efficiency was consistent with a long-duration impairment of excitation-contraction coupling. The observation of impaired excitation-contraction coupling was further investigated during low-intensity exercise in the adductor pollicis and tibialis anterior muscles.<sup>10</sup> During fatigue, the fall in twitch tension was markedly greater than that of the CMAP, PCr, or pH, and recovery of twitch tension was quite slow. These results were interpreted to indicate that low-intensity exercise is associated with a non-metabolic form of fatigue and that failure of excitation-contraction coupling is possible with this type of exercise.

It has been suggested that changes in the EMG signal during muscle fatigue may be due to feedback from the accumulation of metabolic byproducts within the muscle during fatigue. This question has been examined by combining MRS and EMG. During fatiguing exercise of the tibialis anterior muscle, the root mean square of the surface EMG signal fell precipitously once PCr decreased below 60–70% of resting level, and pH fell below 6.75.<sup>11</sup> The median frequency of the EMG signal fell linearly with pH ( $r = 0.82$ ). These results again demonstrated the technical capacity for these measurements and thus began an exploration of the relationship between fatigue, metabolism, and the electromyogram.

In summary, these studies demonstrate the utility of combining MRS and EMG in studies of muscle performance. Unfortunately, the relative contributions to the development of human muscle fatigue of (1) metabolic inhibition of the contrac-

tile process and (2) activation failure remain unclear. We developed an approach that combines MRS and EMG in an effort to quantitate muscle activation, metabolism, and fatigue during isometric exercise in several clinical populations.<sup>8,12</sup>

## MUSCLE METABOLISM IN DISEASE

### Metabolic Myopathies

**McArdle's Syndrome.** The first MRS study of a metabolic myopathy was of McArdle's syndrome. Phosphorus MRS indicated no intramuscular acidification in a patient with McArdle's syndrome during exercise, which was consistent with the absence of glycogen phosphorylase. During ischemic exercise of the finger flexors, PCr decreased more in McArdle's than in healthy subjects, which suggested an inability of the muscle to produce sufficient energy from nonoxidative sources. The rate of recovery of PCr after exercise was normal, indicating that oxidative re-synthesis of ATP was unimpaired. A subsequent study of three patients with McArdle's syndrome again showed an abnormally low PCr/Pi after exercise, without acidosis.<sup>13</sup>

**Mitochondrial Myopathies.** Twelve patients with mitochondrial myopathies demonstrated metabolic abnormalities using <sup>31</sup>P MRS.<sup>14</sup> For example, resting PCr/Pi was reduced in most of these patients, and exercise-induced changes of PCr/Pi were abnormal in five patients who could perform submaximal static (isometric) exercise of calf muscles. The fall in pH during similar relative exercise was less severe in the myopathic patients than in the control subjects. The rate of PCr/Pi recovery after low-intensity exercise was slow in 11 of the 12 patients. A recent study demonstrated that lactic acidosis is not causally related to exercise intolerance in patients with mitochondrial myopathy.<sup>15</sup> In a double-blind, placebo-

bo-controlled, crossover study of seven patients with mitochondrial myopathy, lactate was lowered with dichloroacetate. Despite the lowered lactate, there was no improvement in maximal workload,  $VO_2$  in cycle exercise, or in indices of muscle oxidative metabolism measured by MRS.<sup>15</sup> These studies demonstrate that  $^{31}P$  MRS of muscle, both at rest and during exercise, can be of practical value in supporting a diagnosis of mitochondrial myopathies.

### Neuromuscular and Neurologic Diseases

In a number of studies of neuromuscular and neurologic disorders, the use of MRS to study muscle metabolism has provided evidence that there are alterations of muscle energy metabolism at rest and during exercise. Some of these changes are nonspecific and may reflect deconditioning and thus are probably not a primary effect of the disease.

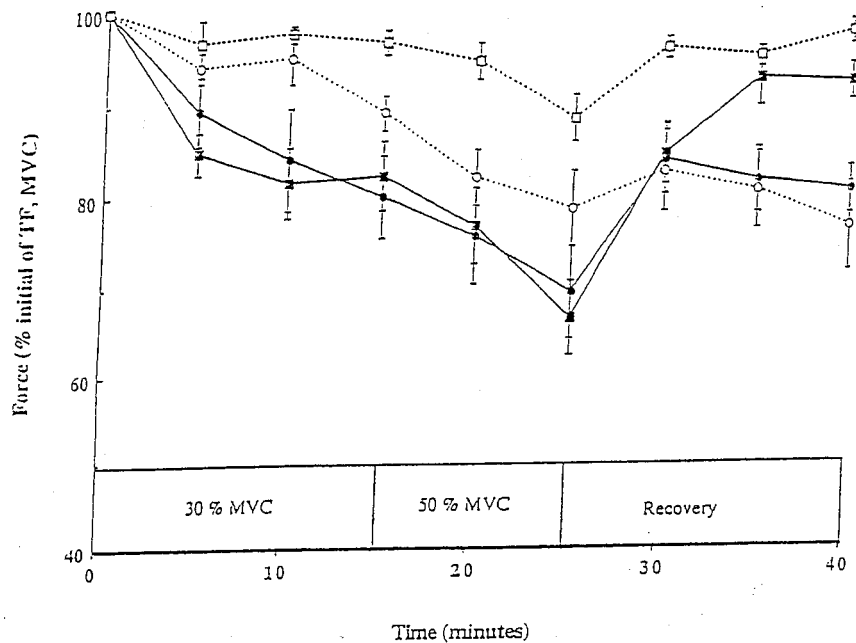
**Muscular Dystrophy.** Phosphorus MRS studies of boys with Duchenne muscular dystrophy demonstrated higher Pi, intracellular pH, and phosphodiester at rest compared with control subjects.<sup>16</sup> In these patients, PCr was reduced, but ATP was not significantly different from control subjects. As the disease progressed, the patients showed further decreases in PCr and PCr/Pi and increases in Pi and phosphodiester; ATP remained unchanged. These results suggested progressive metabolic deterioration in boys with Duchenne muscular dystrophy. A reduction of the total phosphorus signal was the result of muscle fiber loss, and it was concluded that muscle fiber ATP concentration probably was normal.

A recent study of myotonic muscular dystrophy found that resting muscle had normal pH, but Pi/ATP, phosphomonoester/ATP, and phosphodiester/ATP were elevated.<sup>17</sup> In

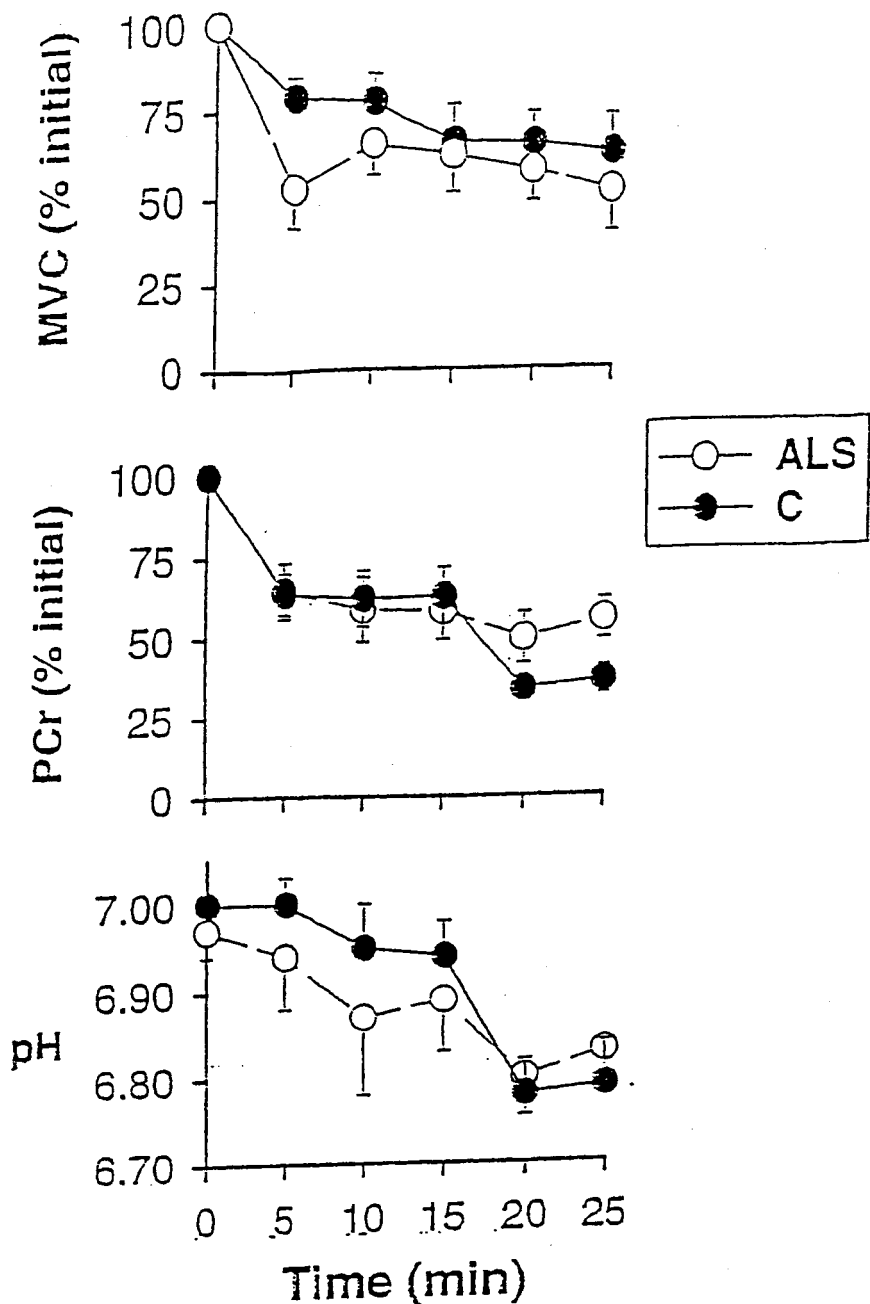
five siblings with autosomal dominant oculopharyngeal muscular dystrophy, PCr/(PCr+Pi) of the forearm flexor muscles was reduced and pH was elevated compared with control subjects.<sup>18</sup> Exercise caused PCr/(PCr + P) and pH to fall rapidly, despite diminished power output. After exercise, PCr/PCr + Pi recovery was normal, but pH recovery was slow. In summary, these reports indicate that there are significant alterations in muscle metabolism at rest and during exercise in various forms of muscular dystrophy.

**Chronic Fatigue Syndrome.** In the chronic fatigue syndrome, there is unexplained persistent fatigue, and no etiology for this syndrome has yet been identified. We examined the mechanisms of fatigue in these patients and found no evidence of any disturbance of nerve or muscle function.<sup>8</sup> We did, however, find impaired central activation before exercise as assessed by the added force measurement during a MVC. During a 4-min sustained MVC of the tibialis anterior, there was a substantial increase in the central component of fatigue in patients, with only a slight increase in healthy control subjects. These results suggest that central fatigue is a major factor for patients who have chronic fatigue syndrome.

**Postpolio Syndrome.** In patients with postpoliomyelitis syndrome, weakness and fatigue are both major complaints. Such patients do have a neuromuscular transmission defect with decremental responses to low-frequency, repetitive nerve stimulation, although the abnormalities are usually modest. We studied patients with postpoliomyelitis syndrome and found little evidence of central fatigue.<sup>12</sup> They did have an excessive decline in force during repetitive exercise compared with controls, but there was little added force in response to superimposed nerve stimulation during a MVC before the exer-



**Figure 4:** Changes in maximum voluntary contraction (MVC) and tetanic force (TF) during intermittent, isometric exercise and recovery in 16 patients with ALS and seven controls (patients' MVC, closed square with solid line; controls' MVC, open square with dotted line; patients' TF, closed circle with solid line; controls' TF, open circle with dotted line). All data are expressed as mean  $\pm$  standard error percentage of initial value. Reprinted with permission from Sharma and Miller.<sup>21</sup>



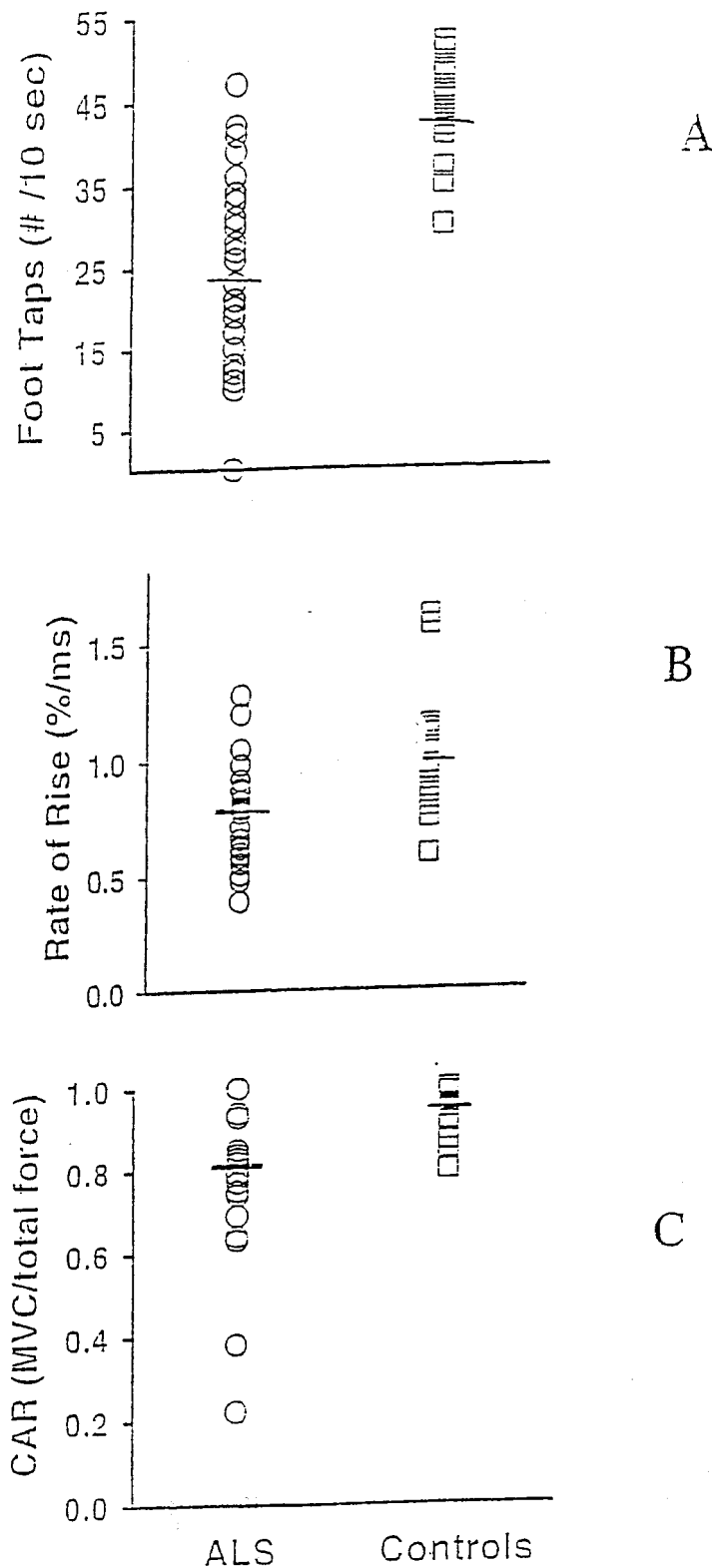
**Figure 5:** Changes during exercise in maximum voluntary contraction (*MVC*, top), phosphocreatine (*PCr*, middle), and pH (bottom) in amyotrophic lateral sclerosis (*ALS*) and control (*C*) subjects (mean  $\pm$  standard error). The first 15 min of exercise consisted of intermittent contractions at 30% *MVC* and the last 10 min was at 50% *MVC*. All subjects completed 15 min of exercise; beyond that, there was attrition due to fatigue (see text for details). Metabolic data are averaged over the last 3 min of each 5-min period. Reprinted with permission from Kent-Braun and Miller.<sup>22</sup>

cise. This, and a comparable decline of voluntary and electrically stimulated force generation from the muscle, suggested that most of the fatigue is peripheral. There was, in fact, reduced muscular activation, as

judged by changes in metabolites, and there are a number of signs that indicate impaired excitation contraction coupling in addition to abnormal neuromuscular transmission as a source of the peripheral fatigue in

these patients. Both central and peripheral fatigue were documented in another study, perhaps due to the difference in techniques used to assess central fatigue.<sup>19</sup>

**Amyotrophic Lateral Sclerosis.** In patients with amyotrophic lateral sclerosis (*ALS*), fatigue is often a major problem, as is weakness. We found that during 25 min of intermittent isometric exercise of the tibialis anterior muscle, both maximum voluntary and tetanic force declined more in patients than in controls, indicating greater muscular fatigability in patients with *ALS* (Fig. 4).<sup>20,21</sup> The similar decline of voluntary and tetanic force suggested that much of the fatigue was peripheral. Evoked *CMAP* amplitudes were preserved during exercise in both groups, indicating no failure of neuromuscular transmission. This suggests that the source of fatigue was not at the neuromuscular junction or within the muscle membrane. Despite greater fatigability, changes during exercise and energy metabolites and proton signal intensity tended to be less in *ALS* subjects compared with controls, which suggest impaired muscular activation (Fig. 5).<sup>22</sup> These data suggest that the greater muscle fatigue in *ALS* patients results from activation impairment, due in part to alterations distal to the muscle membrane and possibly involving excitation contraction coupling. The situation is more complex in patients with *ALS* because of the simultaneous upper motor neuron and lower motor neuron component. We studied three indicators of upper motor neuron function in these patients: (1) number of rapid foot taps in 10 sec, a clinical measure that requires both smooth recruitment and discharge frequency modulation; (2) maximum rate of rise of voluntary force during a rapid submaximal (40% *MVC*) isometric contraction, which depends on the ability to mount high discharge frequencies; and (3) central activation ratio ( $MVC / (MVC + \text{tetanic force})$ ), which indicates the degree of incomplete muscle acti-



**Figure 6:** Individual values for the (A) speed of rapid foot taps (number in 10 sec), (B) rate of rise of voluntary force (normalized to stimulated rate of force development), and (C) central activation ratio (CAR) for amyotrophic lateral sclerosis (ALS, left) and control (right) groups. Group means are indicated by the horizontal bars. The ALS group demonstrated significant impairment in upper motor neuron function compared to control for the speed of rapid foot taps and the rate of rise of voluntary force. Reprinted with permission from Kent-Braun et al.<sup>24</sup>

vation due to an upper motor neuron lesion (Fig. 6).<sup>23,24</sup> In ALS patients, all measures of upper motor neuron function were impaired: (1) number of rapid foot taps:  $43.2 \pm 5.9$  (mean  $\pm$  standard deviation) in control *vs.*  $23.9 \pm 12.6$  in ALS patients,  $P < 0.001$ ; (2) rate of rise of voluntary force:  $0.99 \pm 0.29\%$  msec in controls *vs.*  $0.77 \pm 0.23\%$  msec in ALS patients,  $P = 0.01$ ; and (3) central activation ratio:  $0.95 \pm 0.07$  in controls *vs.*  $0.82 \pm 0.30$  in ALS patients,  $P = 0.02$ . Thus, these data indicate that upper motor neuron function is impaired in the ALS patient group, and the impairment can be quantified. This combination of clinical testing in neurophysiologic measurements may provide a more thorough understanding of the extent of upper motor neuron dysfunction in such patients and may be useful in monitoring the effects of therapeutic intervention in ALS.

**Friedreich's Ataxia.** Friedreich's ataxia is the most common form of autosomal recessive spinocerebellar ataxia. The disease results from an expanded intronic repeat and results in deficiency of a mitochondrial protein called frataxin. Experimental evidence suggests that this deficiency leads to a severe defect of mitochondrial respiration and excessive build-up of free radicals. In a recent study, MRS was used to evaluate the effect of 6 mo of antioxidant treatment with coenzymeQ<sub>10</sub> (400 mg/day) and vitamin E (2100 units/day) on calf muscle energy metabolism in ten patients.<sup>25</sup> After 3 mo of treatment, the cardiac PCr/ATP ratio increased by a mean of 178% ( $P = 0.003$ ), and the maximum rate of skeletal muscle mitochondrial ATP production ( $V_{max}$ ) increased to 139% of baseline values ( $P = 0.01$ ). Improvements were sustained after 6 mo of therapy, although neurologic evaluation detected no beneficial impact. The coenzymeQ<sub>10</sub> and vitamin E administration were well tolerated by all patients, with no side effects. In skeletal muscle, the increase in the  $V_{max}$  corre-

lated positively with the number of repeats, an index of disease severity. This very interesting study suggests that skeletal muscle bioenergetics in patients with some neuromuscular diseases might be improved by antioxidant therapy.<sup>25</sup> Larger randomized trials focusing on not only muscle bioenergetics but also clinical impact will be needed to clarify the role of antioxidants as therapy for this and other neuromuscular diseases.

In conclusion, fatigue is a complex phenomenon, and simultaneous measurement of both central and peripheral factors is necessary to begin to understand its pathophysiology. The use of force, EMG, and MRS measures should be helpful in future studies.

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