Neuromuscular Regulation and Metabolism during Exercise

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This article reviews current evidence regarding neuromuscular regulation and metabolism during exercise. Particular emphases are given on the relationship between motor unit (MU) activity, including single MU analysis results and spinal α-motoneuron excitability, and cardio-respiratory response and blood lactate during dynamic exercise. In addition, a close physiological link between muscle energy metabolism and excitation-contraction processes (failure of one will affect the extent of the other) is summarized in the light of recent nuclear magnetic resonance (NMR) studies and results of neuromuscular disorder patients.

Key words: Motor units, Motoneuron excitability, Cardio-respiratory Response, Blood Lactate

This brief review paper deals with changes in neuromuscular activity during exercise with special reference to muscle metabolism and will be organized under three main topics, i.e., 1) motor unit activity under different physiological conditions, 2) motor unit activity and cardio-respiratory response, 3) energy metabolism and excitation-contraction processes, and 4) blood lactate and alpha motoneuron excitability.

1) Motor Unit Activity under Different Physiological Conditions.

Since the “size principle” of Henneman et al. (1965) was first proposed based upon results from cat motoneurones, strong evidence has been reported that there is a specific sequence of recruitment in order of increasing motoneuron and motor unit (MU) size during muscular contractions (De Luca et al., 1982; Frueh et al., 1975; Milner-Brown et al., 1973). Goldberg and Derfler (1977) have also shown positive correlations among recruitment order, spike amplitude and twitch tension of single MUs in human masseter muscle. Recent evidence have also demonstrated in humans that, for a muscle group with mainly type I (slow-twitch) fibers (e.g., adductor pollicis), rate coding (MU firing modulation) plays a more prominent role in force regulation (Kukulka and Clamann, 1981; Moritani et al., 1986a). For a muscle group composed of both type I and II (fast-twitch) fibers, MU recruitment becomes the major mechanism for generating extra force above 40 to 50% of maximal voluntary contraction (MVC) (De Luca et al., 1982; Kukulka and Clamann, 1981; Moritani et al., 1986a; Moritani and Muro, 1987).

It is well established that eccentric (lengthening) contraction requires less oxygen and lower amount of ATP than concentric contraction (Davies and Barnes, 1972; Infante et al., 1964). Both surface (Komi and Viitasalo, 1977) and intramuscular EMG studies (Moritani et al., 1988) have demonstrated that MU recruitment patterns are qualitatively similar in both types of contractions, but for a given MU, the force at which MU recruitment occurs is greater in eccentric contractions than in either isometric or concentric (shortening) contractions. Interestingly, muscle soreness that has a delayed onset is a common feature among both athletes and untrained individuals. A number of investigators have demonstrated that the eccentric component of dynamic work plays a critical role in determining the occurrence and severity of exercise-induced muscle soreness (Friden et al., 1983; McCully and...
Faulkner, 1986; Newham et al., 1983). It has been also demonstrated that type II fibers are predominantly affected by this type of muscular contraction (Friden et al., 1973). Based on these findings and the results of EMG studies cited earlier, it is most likely that muscle soreness associated with eccentric component of dynamic exercise might be in part due to high mechanical forces produced by relatively few numbers of active MUs which may in turn result in some degree of disturbance in structural proteins in muscle fibers, particularly those of high recruitment threshold MUs.

During development of muscle fatigue, earlier electromyographic studies (deVries, 1968; Moritani et al., 1982) indicated that amplitude of myoelectric signals from the surface electrodes increased progressively as a function of time during sustained submaximal contractions. It was suggested that additional MUs were progressively recruited to compensate for the loss of contractility due to some degree of impairment of fatigued MUs. However, this increased amplitude of the surface EMG could not be demonstrated during sustained maximal voluntary contractions (MVC) (Bigland-Ritchie et al., 1983b; Bigland-Ritchie et al., 1979; Moritani et al., 1985b). Recent evidence has indicated that there is a progressive reduction in MU firing rates during sustained MVC in the absence of any measurable neuromuscular transmission failure (Bigland-Ritchie et al., 1983a; Moritani et al., 1986b). These findings suggest the existence of different MU recruitment and rate-coding mechanisms during sustained maximal and submaximal voluntary contractions. Recent muscle glycogen study by Volles- tad et al. (1984) indicated that glycogen content of types IIa and IIb was unchanged during the first part of exercise. Later a decrease was observed, first in type IIa and finally in IIb, suggesting a decrease in the recruitment threshold force of these fibers. Our intramuscular EMG studies (Moritani et al., 1986a; 1986b) have provided strong support for this notion.

2) Motor Unit Activity and Cardio-respiratory Response.

The concept of an anaerobic threshold (AT) may rest on the assumption that there is a critical point in time at which the dynamic lactate production/utilization equilibrium unbalances as a result of increased anaerobic glycolysis, leading to a rise in plasma lactate concentration (LT). The resulting acidosis is associated with a fall in plasma bicarbonate concentration, an equivalent increase in CO₂ production, and a subsequent disproportionate increase in ventilation (VT). However, a recent study (Green et al., 1983) has demonstrated that LT and VT are not always coincidental, and that the elevation in muscle glycolysis as evaluated from muscle biopsy samples precedes both LT and VT. This dissociation between the onset of muscle glycolysis and blood lactate accumulation could be at least explained by the fact that exercising skeletal muscle extracts a significant amount of lactate during net lactate release (Stanley et al., 1986). Therefore, gas exchange AT and venous blood lactate threshold may represent the second order of changes subsequent to substantial elevations in muscle anaerobic glycolysis.

In a series of EMG studies, we have demonstrated that an abrupt increase in integrated EMG (iEMG) representing changes in MU recruitment and/or MU firing frequency during incremental exercise significantly correlated (r = 0.973, N = 36) with the onset of gas exchange AT (Moritani, 1980). Two independent studies (Nagata et al., 1981; Viitasalo et al., 1985) have recently confirmed our findings. Figure 1 shows the changes in the iEMG equivalent for VO₂ (iEMG/VO₂) similar to ventilatory equivalents before and after the onset of gas exchange AT. This indicates that the iEMG/VO₂ for this subject increased from 111 to 364 µV to achieve an O₂ uptake of 1 liter after the onset of AT. Gladden et al. (1978) demonstrated that in all cases studied (before and after fatigue, partial neuromuscular block with curare or ischemia), there was
no change in the $O_2$ uptake per unit of tension developed, indicating a constant coupling between $O_2$ consumption and developed tension. Therefore, during exercise at sufficiently high intensities, e.g., above AT, a constant coupling between $O_2$ uptake and developed tension can still be maintained, but may require a considerably greater iEMG (increase in MU recruitment and firing frequency) to achieve this constancy so as to compensate for a deficit in the developed tension due to the effects of lowered intracellular pH on the excitation-contraction coupling (Fuchs et al., 1970; Gevers and Dowdle, 1963).

Our subsequent study (Moritani et al., 1981) also demonstrated a sharp and well defined rise in the previously stable iEMG and ventilation ($\dot{V}_E$) upon applying an arterial occlusion cuff to the leg while working at a constant levels of power output on the bicycle ergometer (see Fig. 2). In line with these results, Tibes (1977) and more recently Busse et al. (1989) have shown some evidence that skeletal muscle group II and IV afferent nerves connected to the respiratory center could respond to local chemical stimuli including $[K^+]$, $P_{O_2}$, osmolarity, pH, and $P_{CO_2}$. Furthermore, Hagberg et al. (1982) showed that patients with McArdle's disease responded with normal hyperventilation during intense exercise despite having no $H^+$ or lactate release, suggesting nonhumoral stimuli originating in the active muscles or in the brain during heavy exercise. Since the

![Graph](image1)

**Figure. 1** A typical set of data obtained during the analysis of EMG equivalent for $O_2$ (iEMG/ $V_{O_2}$, i.e., slope of regression) before and after anaerobic threshold (Moritani, 1980).

![Graph](image2)

**Figure. 2** Effects of arterial occlusion on iEMG and $V_E$ during exercise at a constant power output (Moritani et al., 1981).
iEMG levels were very constant and showed no sign of fatigue prior to the occlusion, it may be concluded that some shift in the MU recruitment and/or firing frequency take place due to local muscle hypoxia caused by the occlusion.

On the other hand, the observed sharp increase in $V_e$ from its steady state level after the occlusion may be mediated through some neural pathways to the respiratory center as suggested by Kao (1963), Dempsey et al. (1975), and Mahler (1979), since the abrupt occlusion of the circulation to and from the exercising limb would isolate the respiratory center and chemoreceptors from the effects of chemical products of muscle metabolism. If one could assume that the sharp increases in iEMG during the occlusion represent the summation of a progressively increasing MU recruitment and firing frequency due to the compensation of reduced contractility of some fatigued MUs, a progressive increase in the extracellular $K^+$, for example, could be expected as a result of increased MU activities. And by this means, the ventilatory response may be stimulated via a neural pathway in the absence of circulation.

In agreement with these results, recent studies (Busse et al. 1989; Moritani et al. 1987) have shown some evidence that ventilatory and thereby $[H^+]$ regulation and large proportion of variance in the gas exchange parameters can be accounted for by the plasma $K^+$ concentration and mechanophysiological properties of the peripheral muscles, respectively.

3) Energy Metabolism and Excitation-Contraction Processes.

Undoubtedly there is a close link between energy metabolism and excitation processes. Prolongation and reduction in the evoked action potential have been reported during high frequency nerve stimulation (Jones et al., 1979; Moritani et al., 1985a) or during ischemic contractions (Duchateau and Hainault, 1985), indicating a possible dependency on energy supply for membrane function or removal of metabolites and ions. Edwards and Wiles (1985) have shown that patients who are unable to utilize glycogen because of phosphorylase deficiency manifest a rapid decline in the surface recorded evoked action potential amplitude and the failure of recovery during local ischemia following stimulated contractions at 20 Hz, which in normal subjects recovers rapidly. Furthermore, the depletion of extracellular Na$^+$ has been shown to accelerate the rate of force fatigue in the isolated curarized preparation (Jones et al. 1979). This reduction of extracellular [Na$^+$] or accumulation of K$^+$ may reduce the muscle membrane excitability sufficiently during high frequency tetani to account for the excessive loss of force (Jones et al., 1979; Moritani et al., 1985a). In addition, Moritani et al. (1985a) have also demonstrated that the recording of intramuscular evoked potentials showed the gastrocnemius muscle to have greater reductions in the potential amplitude and conduction time as compared to those of the soleus muscle. Thus, energy metabolism clearly plays an important role influencing neural excitation and electrolyte balance within the cell.

There has been some evidence that a decrease in intracellular pH could interfere with muscular contractile function. For example, the increase in $[H^+]$ has been shown to interfere with Ca$^{++}$ binding to troponin by lowering the apparent binding constant (Fuchs et al., 1970). Nakamura and Schwartz (1972) found the affinity of sarcoplasmic reticulum for Ca$^{++}$ being specifically dependent on pH, thus suggesting the possible participation of $[H^+]$ in excitation-contraction coupling with subsequent deficit in the developed tension. The findings of Karlsson et al. (1975) seem to suggest that at tensions of 30 - 50% MVC the increase in lactate could be responsible for fatigue by direct or indirect changes in pH. However, at higher and lower tensions the possibility that lactate is directly implicated in the development of fatigue seems remote, as electrical and metabolic factors may further complicate this phenomenon (Bigland-Ritchie et al., 1983;
Moritani et al., 1985b; 1986b; Nassar-Gentina et al., 1978). For example, when cat gastrocnemius and soleus muscles were experimentally made to contract, the lactate release was the same from both muscles and yet the gastrocnemius muscle fatigued to a much greater extent than the soleus (Hudlicka, 1971). The results of NMR study (Edwards et al., 1982) also demonstrated that PFK-deficient patients showed virtually no change in pH during muscle fatigue. Hence, other possible mechanisms must be considered. Accumulation of inorganic phosphate (Pi) and ammonia (NH₄⁺), for example, have also been shown to occur during muscular activity as possible inhibitory metabolites contributing to fatigue (Hibberd et al., 1985; Mutch and Banister, 1983). It has been suggested that Pi may bind to myosin in such a way so as to increase the forward rate of cross-bridge cycling and thereby to reduce force output (Cooke and Pate, 1985). Other evidence of Pi-induced force reduction is that patients with McArdle's disease demonstrated greater fatiguability than normal individuals and a concomitantly larger increase in Pi accumulation (Lewis et al., 1985). Very little evidence is, however, available on the role of Pi in fatigue during dynamic muscle contraction.

4) Blood Lactate and Motoneuron Excitability.

Spinal reflexes are often viewed as stereotyped motor patterns with limited scope for modification. However, recent evidence suggests that even short-latency, largely monosynaptic reflexes show a high degree of modulation during simple human motor activities such as walking and standing, and that the pattern of modulation can be specifically altered for the different functional requirements of each activity (Capaday and Stein, 1987; Crenna and Frigo, 1987; Moritani et al., 1989; Yamashita and Moritani, 1989). We have recently investigated the relationship between blood lactate and spinal α-motoneuron pool excitability during incremental exercise on a bicycle ergometer. For this purpose, miniature size bipolar surface electrodes were attached over the motor point area of the medial gastrocnemius (MG). We employed the method of Angel and Hofmann (1963) which depends upon the fact that a single electrical stimulation to the posterior tibial nerve elicits two discrete muscle action potentials in the calf muscles. The first evoked action potential referred to as the M-wave, which results from the direct stimulation of motor axons, whereas the second action potential or H-wave results from stimulation of the largest sensory axons (group Ia afferents arising from the muscle spindle) which have a strong monosynaptic connection to α-motoneurons. The H-wave therefore provides a useful means of testing spinal reflex modulation during motor behaviour as the change in H-wave amplitude would reflect the corresponding change in the monosynaptic reflex excitability in the spinal cord (Stein & Capaday, 1988). To determine the H-reflex amplitude during the incremental exercise test, "phase-dependent" averaging technique was employed by a computerized data processing system. Single rectangular pulses of 500 μsec duration were delivered at the peak torque development phases during cycling. A photo-electronic sensor was used to trigger the stimulator. Owing to the difficulty of isolating the H-reflex potentials from the background EMG activities, particularly during the push-off phase, a minimum of 15 signal averaging was necessary to assure an accurate H-reflex amplitude determination. Figure 3 shows a typical set of H-reflex amplitude changes observed during the incremental exercise. As can be readily seen that H-reflex amplitude markedly augmented after the onset of lactate threshold (LT) as compared to the moderate increase seen prior to LT. Group data (means ± SD, N = 5) indicated that both venous lactate and H-amplitude showed no significant difference between LT and one minute prior to LT. However, when these parameters were tested between LT and one minute after LT, significant increases were observed for lactate (from 1.35 ± 0.
23 to 1.78 ± 0.41 mM, P < 0.05) and H-amplitude (from 0.43 ± 0.29 to 0.58 ± 0.33 mV, P < 0.05). The observed almost parallel changes in lactate and H-amplitude during the incremental exercise thus seem to suggest that spinal α-motoneuron pool excitability is not constant, but can be modulated for increased functional and metabolic requirements of the muscles, and that the exponential increase in H-amplitude after the onset of LT might be due to progressive recruitment of high threshold MUs that are innervating types IIa and IIb fibers with concomitant increase in lactate production.

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