NONINVASIVE MEASURES OF CENTRAL AND PERIPHERAL ACTIVATION IN HUMAN MUSCLE FATIGUE

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Muscle activation may be defined as the process by which the signal to contract is transmitted from the central nervous system to the contractile machinery within the muscle. Muscle fatigue may be defined as a loss of maximum force-generating capacity during exercise, and is often quantitated as the decrease in force observed during a maximum voluntary contraction (MVC). Depending on the type of exercise performed, fatigue may develop due to failure at one or several sites along the pathway of force production, including those sites involved in activation. For example, fatigue may result from impaired activation, metabolic inhibition of the contractile process, or altered calcium kinetics. As shown in the simplified model in Figure 1, the pathway of force production originates in the central nervous system and proceeds to the periphery across the neuromuscular junction (NMJ) and muscle membrane through the excitation-contraction coupling (ECC) process, with energy simultaneously supplied and force subsequently produced. Central activation occurs within the CNS, and peripheral activation involves activation at the level of the neuromuscular junction, muscle membrane and ECC. In this model, ECC is broadly defined to include the intramuscular transmission of the activation signal as well as any factors that may inhibit this transmission or the performance of the contractile machinery. In humans, several of these sites may be evaluated noninvasively using a combination of surface electromyography, motor nerve electrical stimulation and voluntary muscle contractions. Techniques will be described for the indirect quantitation of failure at the level of central motor drive, the neuromuscular junction and muscle membrane, and ECC.

EXPERIMENTAL ARRANGEMENT
The experimental arrangement involves isometric contractions of the dorsiflexor muscles, primarily the tibialis anterior muscle. This arrangement, which has been described in detail elsewhere, allows measurement of the surface electromyogram (EMG) and force output. Briefly, electrode placement consists of a recording electrode on the belly of the tibialis anterior muscle, a reference electrode on the medial malleolus, a pair of stimulating electrodes over the peroneal nerve and a ground plate on the calf. Supramaximal stimulation of the motor nerve is used in order to ensure recruitment of all motor units. A single (0.1 ms) stimulus is given to obtain measures of the compound muscle action potential (CMAP) and twitch force. A train of stimuli (50 Hz, 500 ms) is also given to quantify tetanic force. Following placement of the electrodes, the leg is fixed in the isometric exercise apparatus with the knee straight and the foot tightly strapped to a foot plate. Force is recorded with a transducer mounted under the foot plate. Force and EMG data are acquired and displayed using a personal computer and stored for later analysis.

MEASURING CHANGES IN CENTRAL ACTIVATION
In general, voluntary force production is modulated centrally by changes in motor unit recruitment and discharge rates. Failure of central activation during exercise may result from decreased motor unit recruitment and/or decreased maximum discharge rates. Methods of measuring changes in central activation during exercise include the central activation ratio (CAR) and a comparison of voluntary and electrically-stimulated fatigue.

The CAR measurement evolved from the superimposed twitch technique. This procedure involves application of a supramaximal train of stimuli (50 Hz, 500 ms) during a 3-4 sec MVC. The stimuli are given after voluntary force reaches a plateau. Any increase in force due to the stimulus suggests central activation failure, which is expressed as the CAR. CAR = MVC/total force.
Pathway to force production

CNS

NMJ, muscle membrane

excitation-contraction coupling

energy supply

force

FIGURE 1. A schematic model of the events along the pathway from the central nervous system (CNS) to muscle force production. Changes in activation at the level of the CNS, neuromuscular junction (NMJ) and muscle membrane, and excitation-contraction coupling (ECC) can all be assessed noninvasively during fatiguing exercise in humans. The role of high-energy phosphate supply in the development of fatigue can also be measured. The pathway shows how failure at any site of activation may contribute to fatigue by reducing the maximum force-generating capacity of the muscle.

where total force=MVC+the superimposed tetanus. Thus, CAR=1.0 indicates complete voluntary activation of the muscle, while CAR<1.0 indicates central activation failure. As demonstrated previously, a superimposed tetanic contraction is significantly more sensitive in detecting central activation failure than a superimposed twitch or twitch-pair.

A second method of measuring central activation failure is to compare the fatigue of voluntary and electrically-stimulated contractions (see for example\(^2\)). This approach distinguishes the fatigue of the entire pathway (including the CNS) from the fatigue of the periphery only, allowing the contribution of central activation failure (or central fatigue) to be determined. This method generally involves a comparison of the fall of MVC with the fall of tetanic force. As an example, if at the end of exercise voluntary and tetanic fatigue are similar, then it may be concluded that all of the fatigue developed at a location distal to the point of stimulation. However, if there is a relatively greater fall of MVC compared to tetanic force (for example, MVC falls to 40% of initial while tetanic force only falls to 60% of initial), then the difference suggests the development of some central fatigue during exercise. Because maximal motor unit discharge rates can vary among different muscles and may in some cases exceed 50 Hz, the optimal stimulation frequency used for this method should be determined separately for each experimental arrangement.

The slowing of voluntary force development during rapid, submaximal contractions may also indicate changes in central activation.\(^1\) Contraction of this type require rapid modulation of both motor unit recruitment and discharge rates. Changes in activation may be localized to the CNS by normalizing voluntary force development rates to tetanic force development rates, thereby eliminating the contribution of any peripheral changes to the slowing of force development.

MEASURING CHANGES IN PERIPHERAL ACTIVATION

Two sites of peripheral activation that may be evaluated noninvasively during fatigue include: 1) the NMJ and muscle membrane; and 2) ECC (Fig. 1). Evaluation of the NMJ and muscle membrane is accomplished by comparing the amplitude of the CMAP before and after fatiguing exercise. A decrease in CMAP indicates a decrease in excitability at either the NMJ or muscle membrane. Because stimulation is at the motor nerve, failure at the NMJ cannot be separated from failure of propagation along the muscle membrane. Activation failure at the NMJ or muscle membrane is observed infrequently, but does occur under some exercise conditions (see for example\(^3\)).

Three indirect methods for assessing ECC function are useful in studies of human muscle fatigue. The first method involves comparing the effects of exercise on the amplitude of the CMAP and twitch force. A reduction of twitch force with no decrease in CMAP amplitude suggests that the same signal is entering the muscle but force output is reduced, thus implicating an intramuscular source of fatigue (for example ECC). A second index of ECC failure is the observation of a slowing of electrically-stimulated force development following fatiguing exercise. Thirdly, very slow or incomplete recovery of force following exercise is consistent with impaired ECC function.\(^1,4\)
Table 1. Summary of central and peripheral activation measures.

<table>
<thead>
<tr>
<th>Site</th>
<th>Measure</th>
<th>Description</th>
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<tbody>
<tr>
<td>central nervous system (CNS)</td>
<td>central activation ratio (CAR)</td>
<td>increased force from train of stimuli (50 Hz, 500 ms) superimposed during MVC indicates central fatigue</td>
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<tr>
<td></td>
<td>voluntary vs. stimulated fatigue</td>
<td>greater relative fall of MVC compared to tetanic force indicates central fatigue</td>
</tr>
<tr>
<td>neuromuscular junction (NMJ)</td>
<td>compound muscle action potential (CMAP)</td>
<td>decrease in amplitude indicates decreased excitation at NMJ or muscle membrane</td>
</tr>
<tr>
<td>excitation-contraction coupling (ECC)</td>
<td>compound muscle action potential (CMAP)</td>
<td>fall of twitch force with preserved CMAP amplitude suggests intramuscular (ECC) source of fatigue</td>
</tr>
<tr>
<td></td>
<td>rate of stimulated force development</td>
<td>slowing of tetanic force development suggests ECC failure</td>
</tr>
<tr>
<td></td>
<td>force recovery after fatiguing exercise</td>
<td>prolonged or incomplete force recovery suggests ECC failure</td>
</tr>
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**ACTIVATION AND ENERGY METABOLISM**

As shown in Figure 1, activation is followed by energy utilization and force production. Simultaneous monitoring of activation and energy utilization is made possible by combining the activation measures described above with the technique of magnetic resonance spectroscopy. This combination allows evaluation of the relative contributions of activation failure and metabolic factors to the development of muscle fatigue (see for example[6,10,11]). These techniques may also be combined to investigate the relationships between neural drive (integrated EMG) and the various energy metabolites that have been implicated in the fatigue process.[9,12] In studies of patients with neuromuscular or neurologic disease, activation failure upstream of the site of energy supply was confirmed by the observation of a smaller than expected energy utilization during voluntary exercise.[6,11]

**APPLICATIONS AND LIMITATIONS**

These methods, summarized in Table 1, may readily be applied to the study of muscle fatigue in aging populations. Questions which may be addressed include: 1) is there greater fatiguability with aging, (particularly in the frail elderly); 2) what types of exercise result in activation failure in the elderly; 3) is activation failure related to functional difficulties (for example falls, fatigue in activities of daily living); and 4) is there a difference in activation between different muscle groups and, if so, what are the functional consequences of these differences? Because these measures are non-invasive, they are quite repeatable, making studies of the effects of a therapeutic intervention (for example exercise training) feasible. Additionally, the relative simplicity of these measures makes them suitable for laboratory studies of sufficient size to ensure adequate statistical power (for example n=20 to 100).

These methods are not without their limitations. They are indirect, making interpretation more difficult. The electrically-stimulated contractions can be uncomfortable, and may be contaminated by inadvertent stimulation of the antagonist muscles. The methods described here for the measurement of central activation require the assumption that "central" includes everything proximal to the site of peripheral nerve stimulation. In addition, measuring central activation failure with these methods does not allow one to determine the causes of central failure (for example motor cortex changes, volition, etc.). The ECC measurements are limited in that it is currently not possible to distinguish what the source of the intramuscular failure may be (for example metabolic inhibition, changes in calcium kinetics, slowed cross-bridge cycling, etc.). In spite of their limitations, the use of these noninvasive measures of muscle activation may further elucidate the role of activation failure in human muscle fatigue. Observations made using these methods may then be used to guide more basic studies of skeletal muscle function in the elderly.
REFERENCES

Sarcopenia and Physical Performance in Old Age