The role of active muscle mass in determining the magnitude of peripheral fatigue during dynamic exercise

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1Geriatric Research, Education, and Clinical Center, George E. Whalen VA Medical Center, Salt Lake City, Utah; 2Department of Exercise and Sport Science, University of Utah, Salt Lake City, Utah; 3Department of Internal Medicine, Division of Geriatrics, University of Utah, Salt Lake City, Utah; and 4Department of Biomedical Sciences for Health, University of Milan, Milan, Italy

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Rossman MJ, Garten RS, Venturelli M, Amann M, Richardson RS. The role of active muscle mass in determining the magnitude of peripheral fatigue during dynamic exercise. Am J Physiol Regul Integr Comp Physiol 306: R934–R940, 2014. First published April 16, 2014; doi:10.1152/ajpregu.00043.2014.—Greater peripheral quadriceps fatigue assessed in the quadriceps following exhaustive, dynamic, single-leg knee-extensor exercise (KE) is directly affected by the ensemble group III/IV afferent input from the active muscles (3). Thus, group III/IV afferents, among other factors (17, 29, 30), facilitate central fatigue, defined as a failure or unwillingness of the central nervous system (CNS) to drive the motor neurons, and, thereby, limit the development of peripheral fatigue, defined as a reduction in muscle force output in response to a given neural input. Indeed, consistent with this paradigm, despite differing levels of oxygen availability and differing exercise intensities, both of which alter endurance time, similar end-exercise levels of intramuscular metabolites linked to peripheral fatigue have been documented following exhaustive exercise (12, 18, 39). However, how the magnitude of end-exercise peripheral fatigue is influenced by active muscle mass and, therefore, possibly by the volume of group III/IV afferent feedback is still not well understood.

Recently, our group examined the magnitude of peripheral quadriceps fatigue following exhaustive, dynamic, single-leg knee-extension exercise (KE) and whole body cycling (38). This approach was used to achieve large differences in active muscle mass [~2.5 kg for KE compared with ~15 kg for cycle exercise (33)] and, therefore, locally vary the magnitude of afferent feedback (15, 20). Specifically, this study was designed and interpreted on the premise that during single-leg KE, the source of afferent feedback would be limited to one quadriceps muscle group, and so the sensory tolerance limit associated with task failure with this model would be reached by a strong, local afferent signal mainly from a smaller muscle mass. This would contrast starkly to cycle exercise during which the equal ensemble afferent feedback associated with the sensory tolerance limit, would consist of the sum of weaker and more diffuse signals from a much larger muscle mass (38). As hypothesized, peripheral fatigue assessed in the quadriceps following KE was far greater than during cycle exercise, suggesting that confining group III and IV skeletal muscle afferent feedback to a small muscle mass enables the CNS to tolerate greater peripheral fatigue (38). However, it is important to acknowledge that although the use of cycle exercise and KE resulted in substantial differences in active muscle mass and a similar muscular action (knee extension), such an approach may have been somewhat confounded by other considerable differences associated with the two distinct exercise modalities. For example, the loss of hip extension power (14) and central cardiopulmonary limitations (34) during bicycle exercise, but not during KE were unaccounted for in this prior study. Additional neural factors, such as differences in coordination and the bilateral deficit (19, 21), may also contribute...
to the task-specific complexities and difference in fatigue accompanying alterations in active muscle mass.

The aim of this study was to better elucidate the role of active muscle mass and associated ensemble afferent input to the CNS in determining the magnitude of peripheral fatigue following dynamic quadriceps exercise. Specifically, we used exhaustive single- and double-leg KE to vary active muscle mass and associated neural feedback, while minimizing concerns about task specificity and cardiopulmonary limitations. We tested the hypothesis that the afferent signal constrained to one quadriceps muscle group during single-leg KE would result in a greater magnitude of end-exercise peripheral fatigue at the attainment of the sensory tolerance and task failure than double-leg KE. Thus, quadriceps fatigue would be greater following single-leg KE compared with double-leg KE.

METHODS

Subjects. Eight recreationally active healthy males (27 ± 1 yr, 84 ± 3 kg, 178 ± 2 cm; Table 1) volunteered to participate in this study. Written, informed consent was obtained from participants prior to their inclusion, and the Institutional Review Boards of the University of Utah and the Salt Lake City Veteran’s Administration Medical Center approved the study. Testing was performed in a thermoneutral environment.

Protocol. During two to four initial preliminary visits to the laboratory, subjects were familiarized with both single- and double-leg KE. Subjects then performed maximal incremental exercise tests with both modalities to determine peak workload and practice constant workload trials to the limit of tolerance (Tlim). On subsequent visits, separated by 48–96 h and in a counter-balanced order, constant workload Tlim trials at 85% of peak workload (60 rpm) for both single- and double-leg KE were performed. This 85% of peak workload led to task failure (defined as a fall below 50 rpm for >10 s) in 5–15 min during preliminary testing. Prior to the Tlim trials, 2 min of resting data were collected, and subjects were allowed a 3-min warm-up period (5 W for single-leg KE and 10 W for double-leg KE). Throughout each trial, minute ventilation (VE), gas exchange (V˙O2), heart rate (HR), mean arterial pressure (MAP), stroke volume (SV), cardiac output (CO), and stroke volume (SV) were determined with a finometer (Finapres Medical Systems, Amsterdam, The Netherlands) placed at the heart level. SV was calculated using beat-by-beat pressure waveforms assessed by plethysmography using the Modelflow method (Beatsoftware version 1.1; Finapres Medical Systems, Amsterdam), and CO was calculated as the product of SV and HR.

Neuromuscular function. The magnitude of peripheral quadriceps fatigue was quantified using supramaximal magnetic stimulation of the femoral nerve (6, 24, 32): the exercise-induced reduction in potentiated quadriceps twitch force (Qtw,pot) assessed before exercise and again 2 min after both Tlim trials. This time delay was necessary to transfer the subjects from the KE ergometer to the neuromuscular function assessment apparatus and was, thus, standardized for both exercise modalities. For the neuromuscular function test procedure, subjects lay semirecumbent, with a knee joint angle of 90°, a magnetic stimulator (Magstim 200; Magstim, Carmarthenshire, Wales) connected to a double 70-mm coil was used to stimulate the femoral nerve. The evoked twitch force was obtained from a calibrated load cell (Transducer Techniques, Temecula, CA) connected to a noncompliant strap placed around the subject’s ankle. A series of six maximum voluntary contractions (MVCs), each followed by a Qtw,pot, were performed with 30 s between each MVC, such that the entire procedure lasted 2.5 min. In addition, to determine the percent voluntary muscle activation (VA), a superimposed twitch technique was employed (6, 28). Peak force, maximal rate of force development (MRFD), and maximal relaxation rate (MRR) were analyzed for all Qtw,pot values (25). To ensure supramaximality of stimulation during magnetic stimulation of the femoral nerve, the plateau in evoked twitch forces, obtained every 30 s, at 70, 80, 85, 90, 95, and 100% of maximal stimulator output, was also evaluated.

Quadriiceps EMG was recorded from the vastus lateralis muscle (6) during exercise, as well as the neuromuscular function assessment procedure. The electrodes were placed in a bipolar configuration over the middle of the muscle belly, with the active electrodes placed over the motor point of the muscle and the reference electrode in an electrically neutral site. These electrodes were used to record magnetically evoked compound action potentials (M-waves) to evaluate changes in membrane excitability, as well as the EMG from the vastus lateralis throughout exercise to provide an index of central motor drive. Raw EMG signals were filtered with a bandpass filter (with a low-pass cut-off frequency of 15 Hz and a high-pass cut-off frequency of 650 Hz) and after visual inspection of the filtered signal, a threshold voltage was set to identify the onset of EMG activity (AcqKnowledge; Biopac Systems). For data analysis, the integral of each EMG burst (integrated EMG, iEMG) was calculated to determine a percent increase in iEMG from the first minute of exercise (6).

Statistical analysis. Two-way repeated-measures ANOVA were used to compare the effect of exercise modality on physiological parameters during exercise, with the Tukey’s honestly significant difference test used for post hoc analysis if a significant main effect or interaction effect was found. Student’s paired t-tests were used to compare the effect of exercise modality on end-exercise physiological

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>26 ± 1</td>
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<tr>
<td>Height, cm</td>
<td>178 ± 2</td>
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<tr>
<td>Weight, kg</td>
<td>73 ± 3</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>23 ± 0.4</td>
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<tr>
<td>Quadriceps muscle mass, kg</td>
<td>2.4 ± 0.1</td>
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<tr>
<td>Peak knee extensor work rate, W</td>
<td>53 ± 4</td>
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<tr>
<td>VO2max, ml·kg⁻¹·min⁻¹</td>
<td>47.4 ± 2</td>
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<td>Hemoglobin, g/dl</td>
<td>16.3 ± 0.4</td>
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<tr>
<td>Triglycerides, µg/dl</td>
<td>92 ± 12</td>
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<tr>
<td>Cholesterol, mg/dl</td>
<td>166 ± 8</td>
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<tr>
<td>HDL, mg/dl</td>
<td>50 ± 3</td>
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<tr>
<td>LDL, mg/dl</td>
<td>103 ± 7</td>
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Values are expressed as means ± SE; n = 8. HDL, high-density lipoprotein; LDL, low-density lipoprotein.
parameters and the magnitude of peripheral fatigue. Statistical significance was set at $\alpha = 0.05$. Results are expressed as means ± SE.

RESULTS

Peak exercise responses. Double-leg KE engaged a significantly greater quadriceps muscle mass compared with single-leg KE (4.8 ± 0.2 kg vs. 2.4 ± 0.1 kg, respectively). The maximal workload attained during the incremental exercise tests was significantly greater for double-leg compared with single-leg KE (98 ± 7 W vs. 53 ± 4 W, respectively), eliciting a higher peak pulmonary oxygen uptake (1.96 ± 0.1 vs. 1.52 ± 0.1 l/min). Of note, the peak oxygen consumption value obtained during the double-leg KE test was significantly less than that obtained by the same subjects during maximal incremental cycling in a separate study (1.96 ± 0.1 vs. 3.46 ± 0.2 l/min, respectively), suggesting the absence of cardiorespiratory limitations during both single-leg and double-leg cycling.

$T_{\text{Lim}}$ trials. The $T_{\text{Lim}}$ trials, performed at 85% of peak workload, equated to 45 ± 4 W for the single-leg KE trial and 83 ± 7 W for the double-leg KE trial. $T_{\text{Lim}}$ time at these workloads was not significantly different between conditions (single-leg KE: 8.1 ± 1.2 min, double-leg KE: 10.0 ± 1.3 min). Pulmonary gas exchange and ventilatory responses to the $T_{\text{Lim}}$ trials are documented in Fig. 1, and the cardiovascular responses are documented in Fig. 2. These assessments, apart from MAP and VE/V$\text{CO}_2$, were augmented during double-leg compared with single-leg KE; the maximal values obtained, however, remained below the previously documented limits of the cardiorespiratory system in all subjects. RPE was higher for single-leg compared with double-leg KE during the fifth minute of the $T_{\text{Lim}}$ trials (data not presented), but was not different between conditions at task failure (double-leg KE: 9.8 ± 0.2, single-leg KE: 9.8 ± 0.3).

Neuromuscular function. Supramaximality of stimulation was demonstrated in all subjects by a plateau in twitch force and M-wave amplitudes with increasing stimulus intensity, representing maximal depolarization of the femoral nerve. Membrane excitability was maintained from preexercise to
postexercise with both exercise modalities, as indicated by unchanged M-wave characteristics. MVC and $Q_{tw, pot}$ measured prior to single-leg and double-leg KE was not different between conditions (MVC: 553 ± 31 vs. 530 ± 41 N; $Q_{tw, pot}$: 219 ± 18 vs. 210 ± 19, for single-leg and double-leg KE, respectively).

**Quadriceps fatigue.** The vastus lateralis iEMG signal normalized to the first minute of exercise, an index of the development of peripheral fatigue during exercise, was increased during exercise to a greater extent during single-leg KE compared with double-leg KE (Fig. 3). $Q_{tw, pot}$, measured after exercise, was significantly reduced from preexercise values, with a fall of 44 ± 6% for single-leg KE and 33 ± 7% for double-leg KE. This fall in $Q_{tw, pot}$ was significantly greater for single-leg compared with double-leg KE (Fig. 3), suggesting greater peripheral quadriceps fatigue after single-leg KE compared with double-leg KE. MVC force was also reduced from preexercise to postexercise to a greater extent following single-leg KE (Fig. 3). As VA was reduced from preexercise to postexercise to a similar extent following both exercise modalities (Fig. 3), the greater reduction in MVC following single-leg KE supports greater peripheral quadriceps fatigue in this trial. The other intratwitch indices of fatigue (MRFD and MRR) were also significantly reduced from pre-exercise to postexercise in both trials and also revealed greater peripheral fatigue following single-leg KE (Fig. 3).

**DISCUSSION**

Presumably, as a component of homeostasis, group III/IV muscle afferents appear to play an important role in determining exercise cessation by inhibiting central motor drive to active skeletal muscle and ultimately restricting the development of peripheral fatigue. On the basis of this paradigm, the current study tested the hypothesis that when the source of group III/IV afferent feedback is limited to a small muscle mass, the central nervous system will tolerate a greater degree of peripheral fatigue. Utilizing single- and double-leg KE to vary group III/IV muscle afferent input to the CNS, while minimizing the potential influence of task specificity and cardiopulmonary limitations, we observed a greater degree of end-exercise peripheral quadriceps fatigue when exercise was confined to one compared with both quadriceps muscle groups. This finding suggests that during small muscle mass exercise (single-leg KE), the sensory tolerance limit, which is greatly affected by afferent feedback (17), was likely evoked by a severe metabolic disturbance in the single quadriceps. This is in contrast to the equal sum, but more diffuse, signals from the...
two quadriceps muscle groups (double-leg KE) that were each likely less challenged metabolically. As exercise-induced adaptation is a response to the degree of homeostatic disturbance, these findings have important implications for optimizing exercise training and rehabilitative medicine.

**Muscle mass and peripheral fatigue.** Previous research from our group has documented greater peripheral quadriceps fatigue following single-leg KE compared with whole body cycling, which was attributed to muscle mass-induced alterations in afferent feedback (38). Indeed, Freund et al. (15) utilized the postexercise circulatory occlusion technique with one or two legs following whole body cycle exercise to isolate the contribution of the metabolite-sensitive afferents to elevations in MAP during exercise and documented higher blood pressure when two legs were occluded, revealing that the magnitude of ensemble-afferent feedback is proportional to active muscle mass. Thus, to reach an equal magnitude of ensemble afferent feedback as a consequence of exercise with one quadriceps compared with two at task failure, attaining the same sensory tolerance limit, a strong, local afferent signal from the small muscle mass would be required. This translates to a greater magnitude of peripheral fatigue and likely intramuscular metabolic disturbance as a consequence of small-muscle mass exercise. In line with this paradigm, Matkowski et al. (27) observed a greater degree of contractile dysfunction following unilateral, submaximal isometric knee extension to task failure in contrast to a bilateral contraction.

The current study utilized single-leg and double-leg KE to mitigate concerns about task specificity of fatigue and cardiopulmonary limitations arising from the comparison of cycling with KE in our previous work (38). The current comparison enabled the desired variation in active muscle mass and isolated the contribution of the lower limbs. Greater peripheral quadriceps fatigue following single-leg KE was evidenced by an almost 50% greater decline in quadriceps MVC and an increase in iEMG, as well as a greater decrease in Qtw,pot and in all measured indices of peripheral fatigue (Fig. 3). Thus, in parallel with our previous study revealing greater peripheral fatigue following single-leg KE compared with whole body cycling (38), these data suggest that the CNS tolerates a greater magnitude of peripheral fatigue when the source of the afferent signal is confined to a small muscle mass. Collectively, these studies support the important link between active muscle mass and afferent feedback and document that a greater degree of peripheral fatigue can be achieved utilizing small-muscle mass exercise.

**Cycle exercise and the magnitude of peripheral fatigue.** Following exhaustive whole body cycling, there appears to be a consistent level of peripheral quadriceps fatigue, which is equivalent to approximately a one-third preexercise to postexercise reduction in Qtw,pot (3). Although this level varies somewhat between individuals, numerous studies have identified similar average decreases in Qtw,pot, suggestive of a critical level of peripheral fatigue, which is not typically surpassed under normal circumstances during high-intensity cycling exercise (3, 6, 7, 9, 22, 23, 38). Interestingly, in the current study, the level of peripheral fatigue following double-leg KE was similar (about 33% exercise-induced decrease in Qtw,pot) to that typically observed following whole body cycling. Thus, similar levels of peripheral fatigue are observed following whole body cycling and double-leg KE, despite differing amounts of active muscle mass across modalities. Although somewhat speculative, these data imply that during cycle exercise, which substantially engages the quadriceps muscles of both legs, the afferent signal arising from these muscle groups may be the dominant source of inhibitory afferent feedback.

As the quadriceps muscles are predominantly muscle groups employed during cycle exercise (33), inference about their role in fatigue determination appears reasonable. However, it is important to acknowledge that the decrease in Qtw,pot exhibited by the subjects in the current study following single-leg KE was less (43%) than that previously observed by our group with this modality (53%) (38). Therefore, if the current subjects, as a whole, simply tolerated less peripheral fatigue in all conditions, the recognized similarity between the level of peripheral fatigue during double-leg KE (which might be expected to result in more fatigue than cycle exercise, due to the smaller muscle mass) and the previously published values for cycle exercise could just be coincidental. Further investigations are required to determine whether this hypothesis about the dominant role of the quadriceps in determining cycle exercise-induced fatigue is correct.

**Muscle mass and the potential for exercise-induced adaptation.** Single-leg KE has previously been utilized as a dynamic exercise model that avoids cardiopulmonary limitations (35, 36). Impressive improvements in peripheral skeletal muscle function, such as increased oxidative enzyme capacity, in both health (1, 37) and disease (13, 26), have been achieved with this approach. In the current study, single-leg KE, utilizing ~2.5 kg of muscle in contrast to the ~5 kg of muscle mass during double-leg KE, attenuated the cardiovascular (Fig. 1) and respiratory (Fig. 2) responses to the TLim trials, but, interestingly, resulted in a greater degree of peripheral fatigue (Fig. 3). As the metabolic disturbance in the muscle during exercise substantially influences the magnitude of peripheral fatigue immediately after task failure, the attainment of greater peripheral quadriceps fatigue following single-leg KE suggests a greater intramuscular metabolic disturbance. Thus, in addition to the typical recognized reduction in the cardiopulmonary demand associated with small-muscle mass exercise, these data reveal that reducing active muscle mass facilitates the attainment of greater peripheral fatigue. As exercise training induces an adaptive response to a homeostatic disturbance, a greater magnitude of peripheral fatigue has the potential to be translated into greater skeletal muscle adaptation following small-muscle mass exercise. Thus, the use of small muscle mass exercise, with a reduced cardiopulmonary challenge, which in and of itself likely promotes better exercise adherence, and the now recognized greater level of tolerable peripheral fatigue has important implications for the use of small-muscle mass exercise in rehabilitative medicine.

**Central motor drive and the sensory tolerance limit.** Previous work from our group, as well as the current study, has predominantly emphasized the role of inhibitory skeletal muscle afferent feedback in determining the sensory tolerance limit and the voluntary termination of exercise. Importantly, other neural mechanisms may have contributed to the observed differences in fatigue. For example, a slight bilateral deficit in peak workload, such that the maximal workload for double-leg KE was slightly less than two times the single-leg peak workload, was observed, which has previously been attributed to the integration of neural factors from both peripheral and
central sources (19). In addition, very recent data (10) suggest that the magnitude of central motor drive (or “neural drive”), which is likely higher when greater muscle mass is engaged during exercise (5), may also increase the perception of effort (16). This could contribute to the sensory tolerance limit, which might limit the magnitude of peripheral fatigue tolerated by the CNS. Recently, our group demonstrated significantly less peripheral fatigue following exhaustive, single-leg KE when the exercise bout was preceded by an exhaustive single-leg KE bout of the contralateral limb (10). These observations were hypothesized to be the result of both inhibitory afferent feedback from the previously exercised leg curtailting the exercise performance of the second leg, as well as elevated central motor drive.

In the current study, indirect evidence for a higher central motor drive during double-leg KE, which engaged twice the active muscle mass, is provided by the greater EMG signal from one leg, multiplied by two to estimate central motor drive during double-leg KE, compared with the EMG signal from the same leg during single-leg KE at exhaustion (~0.2 mVs vs. ~0.1 mVs). Further indirect indices of a higher central motor drive are provided by the greater central cardiovascular and respiratory responses during double-leg KE (Figs. 1 and 2), both of which are determined by feedback and feedforward mechanisms (8). In the presence of greater central motor drive, less overall afferent feedback from the exercising limbs would be required to reach the sensory tolerance limit during double-leg KE. Accordingly, the reduced magnitude of peripheral fatigue following double-leg KE (Fig. 3) was likely due to both a more diffuse afferent signal arising from the greater active muscle mass involved during exercise and greater central motor drive. Thus, when muscle mass and central motor drive are elevated, less peripheral fatigue is tolerated to avoid severe exercise-induced damage, which might threaten whole body homeostasis.

Perspectives and Significance

Reducing the amount of active muscle mass during dynamic KE enabled the attainment of a greater degree of peripheral quadriceps fatigue following constant workload exercise to exhaustion. This is likely due to the constraint of the group III/IV afferent signal to one quadriceps during single-leg KE, in contrast to the more diffuse signals from both quadriceps muscle groups, and potentially elevated central motor drive, during double-leg KE. By minimizing differences in systemic challenge and task specificity, these data substantiate the role of active muscle mass in determining the level of tolerable peripheral fatigue. In addition, these findings have important implications for the adoption of small muscle mass exercise in rehabilitative medicine to facilitate the attainment of greater peripheral quadriceps fatigue, and, thus, potentially promote greater skeletal muscle adaptation.

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