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

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Running Head: Active Muscle Mass and Peripheral Fatigue
ABSTRACT

Greater peripheral quadriceps fatigue at the voluntary termination of single-leg knee-extensor exercise (KE), in comparison to whole-body cycling, has been attributed to confining group III and IV skeletal muscle afferent feedback to a small muscle mass, enabling the central nervous system (CNS) to tolerate greater peripheral fatigue. However, as task specificity and vastly differing systemic challenges may have complicated this interpretation, 8 males were studied during constant workload trials to exhaustion at 85% of peak workload during single- and double-leg KE. It was hypothesized that due to the smaller muscle mass engaged during single-leg KE, a greater magnitude of peripheral quadriceps fatigue would be present at exhaustion. Vastus lateralis integrated electromyogram (iEMG) signal relative to the first minute of exercise, pre- to post-exercise maximal voluntary contractions (MVCs) of the quadriceps, and twitch-force evoked by supramaximal magnetic femoral nerve stimulation (Qtw,pot) quantified peripheral quadriceps fatigue. Trials performed with single-leg KE (8.1±1.2 min; 45±4 W) resulted in significantly greater peripheral quadriceps fatigue than double-leg KE (10±1.3 min; 83±7 W), as documented by changes in the iEMG signal (147±24 vs. 85±13%), MVC (-25±3 vs. -12±3%), and Qtw,pot (-44±6 vs. -33±7%), for single- and double-leg KE, respectively. Therefore, avoiding concerns over task specificity and cardiorespiratory limitations, this study reveals that a reduction in muscle mass permits the development of greater peripheral muscle fatigue and supports the concept that the CNS tolerates a greater magnitude of peripheral fatigue when the source of group III/IV afferent feedback is limited to a small muscle mass.

Word Count: 249

Key words: dynamic exercise, locomotor muscle, knee-extensor exercise, central motor drive
INTRODUCTION

The central projection of group III and IV skeletal muscle afferent fibers, responsive to mechanical deformation and the intramuscular metabolic disturbance (2), has been implicated as a determinant of exercise performance, exerting inhibitory feedback on central motor drive to active muscles during dynamic exercise (3, 4). It has been hypothesized that the voluntarily termination of high intensity, constant workload exercise occurs once a sensory tolerance limit (17) is reached, which 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-extensor exercise (KE) and whole-body cycling (38). This approach was employed to achieve large differences in active muscle mass (~2.5 kg for KE compared to ~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 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 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 employed 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 to double-leg KE.
METHODS

Subjects: Eight recreationally active healthy males (27 ± 1 years, 84 ± 3 kg, 178 ± 2 cm) 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 (T_{lim}). On subsequent visits, separated by 48 - 96 hours and in a counter-balanced order, constant workload T_{lim} trials at 85% of peak workload [60 revolutions per minute (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 minutes during preliminary testing. Prior to the T_{lim} trials, two minutes of resting data were collected and subjects were allowed a 3-minute warm-up period (5 W for single leg KE and 10 W for double leg KE). Throughout each trial, minute ventilation (V_E), gas exchange (VO_2 and VCO_2), heart rate (HR), mean arterial pressure (MAP), stroke volume (SV), cardiac output (CO), the electromyogram from the vastus lateralis (EMG), as well as rating of perceived exertion (RPE (11)), were assessed. To quantify peripheral fatigue, neuromuscular function tests were performed before exercise and again two minutes following task failure. The fatigue assessment procedure in both trials was performed on the same leg used for both exercise trials, which was balanced between dominant and non-dominant limbs (31).
**Knee-extensor exercise:** Dynamic KE was performed utilizing a cycle ergometer (Monark, Sweden) modified to allow the performance of KE (33). Briefly, for single-leg KE exercise, this exercise modality recruits the quadriceps muscle group for active leg extension from 90 to ~170 degrees before a lever arm attached to a flywheel passively returns the leg to 90 degrees. For double-leg knee-extensor exercise, a second lever arm was attached to the contralateral crank-arm of the ergometer such that subjects recruited the quadriceps muscle groups of both legs simultaneously to perform KE. Subjects were instructed to maintain a rate of 60 rpm during all KE exercise trials. For the determination of peak workload, subjects performed one-minute stage, incremental exercise tests to exhaustion (10 W + 5 W/min for single- and 20 W + 10 W/min for double-leg KE).

**Pulmonary and cardiovascular responses:** $V_E$ and pulmonary gas exchange were measured at rest and during exercise using an open circuit system (ParvoMedics, Sandy, UT). HR was determined from the R-R interval of a three-lead electrocardiogram (AcqKnowledge; Biopac Systems, Goleta, CA). SV, CO, and MAP were determined with a finometer (Finapres Medical Systems, The Netherlands) placed at heart level. SV was calculated from beat-by-beat pressure waveforms assessed by photoplethysmography using the Modelflow method (Beatscope version 1.1; Finapres Medical Systems), 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 ($Q_{tw, pot}$) assessed before exercise and again two minutes after both $T_{lim}$ 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 semi-
recumbent, with a knee joint angle of 90 degrees, a magnetic stimulator (Magstim 200, The
Magstim Company Ltd, 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 non-compliant strap placed around the subject’s
ankle. A series of 6 MVCs, each followed by a $Q_{tw, pot}$, were performed with 30 seconds between
each MVC, such that the entire procedure lasted 2.5 minutes. 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 $Q_{tw, pot}$ values (25). To ensure supramaximality of stimulation during
magnetic stimulation of the femoral nerve, the plateau in evoked-twitch forces, obtained every
30 seconds, at 70, 80, 85, 90, 95, and 100% of maximal stimulator output, was also evaluated.

Quadriceps EMG was recorded from the vastus lateralis (VL) 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 VL 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, Goleta, CA). 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 analysis of variance 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 or interaction effect was found. Student’s paired $t$ tests were used to compare the effect of exercise modality on end-exercise physiological parameters and the magnitude of peripheral fatigue. Statistical significance was set at $\alpha = 0.05$. Results are expressed as means $\pm$ S.E.M.
RESULTS

**Peak exercise responses:** Double-leg KE engaged a significantly greater quadriceps muscle mass compared to 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-compared to 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 cardio-respiratory limitations during both single- and double-leg cycling.

**T\textsubscript{Lim} trials:** The T\textsubscript{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\textsubscript{Lim} time at these workloads was not 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\textsubscript{Lim} trials are documented in Figure 1, and the cardiovascular responses are documented in Figure 2. These assessments, apart from MAP and VE/VCO\textsubscript{2}, were augmented during double- compared to single-leg KE; the maximal values obtained, however, remained below the previously documented limits of the cardio-respiratory system in all subjects. RPE was higher for single- compared to double-leg KE during the fifth minute of the T\textsubscript{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 pre-
to post-exercise with both exercise modalities, as indicated by unchanged M-wave
characteristics. MVC and $Q_{tw,\text{pot}}$, measured prior to single and double-leg KE was not different
between conditions (MVC: 553±31 vs 530±41 N; $Q_{tw,\text{pot}}$: 219±18 vs 210±19, for single- 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 to double-leg KE (Figure 3). $Q_{tw,\text{pot}}$, measured
after exercise, was significantly reduced from pre-exercise values, with a fall of 44 ± 6% for
single-leg KE and 33 ± 7% for double-leg KE. This fall in $Q_{tw,\text{pot}}$ was significantly greater for
single- compared to double-leg KE (Figure 3), suggesting greater peripheral quadriceps fatigue
after single-leg KE. MVC force was also reduced from pre-exercise values to a greater extent
following single-leg KE (Figure 3). As VA was reduced from pre- to post-exercise to a similar
extent following both exercise modalities (Figure 3), the greater reduction in MVC following
single-leg KE supports greater peripheral quadriceps fatigue in this trial. The other intra-twitch
indices of fatigue (MRFD and MRR) were also significantly reduced from pre to post-exercise in
both trials, and also revealed greater peripheral fatigue following single-leg KE (Figure 3).
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. Based upon 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 to both quadriceps. 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 (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 to whole-body cycling, which was attributed to muscle-mass induced alterations in afferent feedback (38). Indeed, Freund et al (15) utilized the post exercise 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 to 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- 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 increase in iEMG, as well as a greater decrease in $Q_{tw, pot}$, and all measured indices of peripheral fatigue (Figure 3). Thus, in parallel with our previous study revealing greater peripheral fatigue following single-leg KE compared to 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 pre- to post-exercise reduction in $Q_{tw,\text{pot}}$ (3). Although this level varies somewhat between individuals, numerous studies have identified similar average decreases in $Q_{tw,\text{pot}}$ 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 (~33% exercise-induced decrease in $Q_{tw,\text{pot}}$) 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 quadricepses are predominate 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 $Q_{tw,\text{pot}}$ 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 if 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 (Figure 1) and respiratory (Figure 2) responses to the T_{Lim} trials, but, interestingly, resulted in a greater degree of peripheral fatigue (Figure 3). As the metabolic disturbance in the muscle during exercise substantially influences the magnitude of peripheral fatigue measured 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 typically 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) suggests 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 curtailing 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, in comparison to 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 (Figures 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 (Figure 3), was likely due to both a more diffuse
afferent signal arising from the greater active muscle mass involved during exercise, as well as
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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REFERENCES:


Table 1. Subject Characteristics

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Values expressed as mean ± S.E.M. n = 8.
Figure 1. **Gas exchange and ventilatory response to constant load, single- and double-leg knee-extensor exercise (KE) to exhaustion.** Data are represented as mean ± S.E.M. Group mean data are represented for time points 0-5, and the final point represents values reached at task failure. *Significant difference between single- and double-leg KE.

Figure 2. **Cardiovascular responses to constant load, single- and double-leg knee-extensor exercise (KE) to exhaustion.** Data are represented as mean ± S.E.M. Group mean data are represented for time points 0-5, and the final point represents values reached at task failure, n=5. *Significant difference between single- and double-leg KE.

Figure 3. **Change in quadriceps muscle function as a consequence of constant load, double- and single-leg knee-extensor exercise (KE) to exhaustion.** Data are represented as mean ± S.E.M. and values represent the percent change from pre- to post-exercise, except for the integrated electromyogram signal (iEMG) from the vastus lateralis which is a comparison between the first and last minute of exercise. MVC, maximal voluntary contraction; $Q_{tw, pot}$, potentiated twitch force; MRFD, maximal rate of force development; MRR, maximal rate of relaxation. *Significant difference between single- and double-leg KE.