Whole Body Oxygen Uptake and Evoked Torque During Subtetanic Isometric Electrical Stimulation of the Quadriceps Muscles in a Single 30-Minute Session

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Abstract

Objective: To evaluate the time course of fatigue in torque output and oxygen uptake during isometric subtetanic neuromuscular electrical stimulation (NMES) to facilitate the design of NMES-based rehabilitation protocols that can accumulate a defined aerobic exercise volume within a given time period.

Design: Single-arm intervention study with within-subject comparisons.

Setting: University research laboratory.

Participants: Volunteer sample of healthy men (N = 11; mean age, 34.2 ± 11.5 y; range, 19 - 53 y; body mass, 79.1 ± 11.7 kg; range, 58 - 100 kg).

Intervention: A single 30-minute session of continuous bilateral isometric quadriceps NMES at 4 Hz evoking a mean twitch amplitude of 12% of the maximum voluntary contraction.

Main Outcome Measures: Whole body oxygen consumption rate (VO2), and evoked torque were measured simultaneously throughout.

Results: Mean increment in VO2 was 596 ± 238 mL/min, and average exercise intensity during the session was 3.47 metabolic equivalents. The VO2 and torque declined slowly at a rate of 0.54% ± 0.31% and 0.47% ± 0.57% per minute, respectively.

Conclusions: Despite having a higher incremental VO2, the observed fatigue rate was considerably less than that previously reported during intermittent isometric tetanic stimulation, suggesting that subtetanic isometric NMES is more sustainable for exercise interventions aimed at accumulating a therapeutic aerobic exercise volume.

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There is increasing interest in the use of isometric neuromuscular electrical stimulation (NMES) as part of cardiopulmonary rehabilitation for patients with limited capacity for movement or volitional exercise. Recent intervention studies with NMES have reported improved aerobic capacity in patients with heart failure, chronic obstructive pulmonary disease, and spinal cord injury. Because of rapid fatigue during NMES-induced muscle activity, it can be difficult to sustain therapeutically significant exercise intensities for long enough to accumulate a meaningful exercise volume. In healthy neurologically intact subjects, exercise intensities in the range of 3 to 5.9 metabolic equivalents (METs), accumulating to 10 METs h wk⁻¹, are associated with reduced cardiovascular disease and reduced premature mortality. Patients with abnormally low functional capacity may benefit from lower exercise loads. The relation between incremental volume of oxygen uptake per minute (VO2) and pulse frequency in the range of 1 to 12 Hz during bilateral quadriceps stimulation has recently been investigated; however, the duration of stimulation at each frequency was limited to 4 minutes, which precluded any conclusion about fatigue. Continuous low-frequency (4 – 5 Hz) NMES, designed to elicit a train of unfused twitches of the quadriceps, hamstring, and gluteal muscles, has recently been demonstrated to achieve exercise intensities of 4.6 METs in healthy subjects and may provide a less fatiguing alternative to conventional tetanic stimulation for evoking sustained aerobic exercise in sedentary or patient populations. This exercise intensity corresponded to a mean oxygen uptake of 19.1 mL min⁻¹ kg⁻¹, which is equivalent to light to moderate

Disclosures: Minogue is an employee of Biomedical Research Ltd, who produces the stimulator used in the study; however, the reported results could be obtained with any stimulator capable of producing the pulse train specified. The other authors have nothing to disclose.
exercise. However, the decline in oxygen uptake during sustained evoked activity at these frequencies has not yet been quantified. Intervention studies with this form of NMES have reported increased aerobic capacity in patients with spinal cord injury and chronic heart failure. The metabolic cost of contraction has been proposed as a primary factor in fatigue. Consistent with this, exercise patterns, whether volitional or electrically stimulated, giving the greatest metabolic changes have been shown to result in the greatest fatigue. Substantial attention has been paid in the past to the rapid decline in muscle force output, which occurs in response to repeated electrical stimulation. So rapid is the reduction in force output that most studies consider only a few minutes of stimulated muscle activity. As a typical example, a reduction in force output of 40% was observed within 2 minutes using repeated 0.3-second bursts of 20-Hz stimulation that evoked contractions at 20% of the maximum voluntary contraction (MVC) in the quadriceps muscles. The rate of fatigue has been shown to increase with stimulus pulse frequency but not with pulse duration or pulse amplitude, a finding attributed to the higher metabolic cost per active muscle area at higher stimulation frequencies. The rate of fatigue during intermittent stimulation also depends on the duty cycle of the contraction relaxation sequence. The peak force response to NMES has been shown to be a more important factor in predicting fatigue than the force time integral, which has been attributed to the higher metabolic cost of force development than force maintenance.

The short time scales of most studies of fatigue during isometric NMES are insufficient to characterize the contribution of the aerobic energy production system. Few studies report energy rate and force output over prolonged periods that are representative of the duration of a typical exercise session. Hultman and Spriet examined muscle biopsy samples during 45 minutes of intermittent (1.6s on/1.6s off) 20-Hz stimulation at a level initially producing 26% of the MVC. Output force decreased rapidly, reaching 25% of the initial value by 20 minutes, and the corresponding adenosine triphosphate rates reduced by more than half. However, whole body oxygen consumption was not measured. Hamada et al observed an 18% decline in incremental whole body oxygen uptake after 20 minutes of intermittent 20-Hz stimulation; however, initial VO2 was less than twice resting levels, which may not be therapeutically significant.

The use of continuous subtetanic isometric stimulation appears to evoke higher VO2 responses than intermittent tetanic isometric stimulation, and there is evidence that the elevated oxygen uptake is sustainable for longer. However, in the studies to date using subtetanic stimulation, stimulus intensity was adjusted to compensate for fatigue; therefore, the reduction in VO2 during fatigue could not be determined directly. Furthermore, these studies did not measure the evoked torque to assess the oxygen cost of isometric force production or the extent of force fatigue. An understanding of the fatigue response of the muscle during sustained electrically elicited contractions as necessary to design effective stimulation protocols, which can accumulate a defined aerobic exercise volume within a given time period.

The aim of this study was therefore to measure oxygen uptake and evoked torque during 30-minute sessions of bilateral continuous subtetanic isometric NMES of the quadriceps muscles to determine the rate of decrease of both variables over a time scale relevant to the delivery of an aerobic exercise dose. It was hypothesized that both force output and oxygen uptake would decline slowly, reflecting a less stressful metabolic profile compared with conventional intermittent tetanic NMES.

**Methods**

**Participants**

Eleven healthy men took part in the study (mean age, 34.2±11.5y; range, 19–53y; body mass, 79.1±11.7kg; range, 58–100kg). The exercise background of the group was mixed, ranging from moderately to highly active. All subjects had previous experience of electrical stimulation at high intensities. The study and experimental protocols were approved by the Human Research Ethics committee of University College, Dublin. All subjects gave written informed consent to participate in the study.

**Experimental setup**

Subjects were seated in a dynamometer (Cybex) that was configured for measurement of isometric knee extensor torque of the right leg at 60° knee flexion (fig 1). The left leg was also restrained isometrically at the same angle. The torque signal from the dynamometer was continuously recorded using a data acquisition system (Biopac) at a sampling rate of 200Hz. Two large (12×16cm) hydrogel stimulation electrodes (Axelgaard) were applied to the quadriceps of each leg. One was positioned just proximal to the patella and covering the lower quadriceps, including the vastus medialis obliquus, and the other was positioned just distal and parallel to the inguinal fold. The electrodes were connected to a research stimulator (NT2010), which was programmed to produce a constant current, symmetric biphasic, square wave pulse train in each leg at up to a 200-mA peak, with a phase duration of 600μs and an interphase interval of 100μs.

Energy usage during the stimulation session was estimated by indirect calorimetry. The subject was fitted with a face mask connected to a Quarkc pulmonary gas analysis system, which was calibrated prior to each subject. In addition to the breathing rate (R) the following gas exchange responses were collected: VO2, expired volume per unit time (Vt), respiratory exchange ratio (RER), and ventilatory equivalent for oxygen (Ve/VO2).

**Experimental protocol**

Subjects began by performing 3 maximum voluntary isometric knee extensions of the right leg. Each was approximately 5-seconds duration and separated by 60 seconds. The highest value was estimated to be their MVC. Using a continuous 4-Hz pulse sequence, the stimulus intensity was increased slowly until the subject indicated the highest level they could readily tolerate indefinitely. This level was noted and used for the subsequent session. The stimulation frequency of 4Hz was selected after...
preparatory testing, which indicated that all subjects could readily tolerate high-pulse phase charges at this rate; some subjects experienced significant discomfort at 6Hz with the same intensity.

The protocol started with a rest period of at least 4 minutes to establish the subject’s resting VO2. The 30-minute sequence began after the stimulation intensity was set to the subject’s previously determined tolerable level.

Data analysis

For each subject, the 30-minute torque record was divided into 180 ten-second intervals. Peak torque, torque time integral (TTI), and SD of the torque were estimated for each interval. The latter provides an estimate of the average torque fluctuation about the mean level and therefore is an indirect indication of the degree of twitch fusion over time. The respiratory variables were available on an asynchronous breath-by-breath basis. These were linearly interpolated with respect to time and resampled at the same 10-second intervals as the torque. Resting VO2 was subtracted from the measured VO2 to provide an estimate of the incremental VO2 evoked because of the NMES.

The time to peak (tp) and half relaxation time (t50) of the evoked torque twitch were estimated after 1, 15, and 29 minutes of NMES. For each subject, the spike-triggered average twitch torque (10 successive twitches) was estimated at each of the 3 time points, and the time to peak and half relaxation time were calculated.

Statistical analysis

Descriptive statistics of the response variables of torque, TTI, SD of torque, VO2, RER, breathing rate (R), Ve, and Ve/VO2, consisting of the mean and SD, were compiled for the group at each 10-second interval during the experimental session. To estimate the rate of fatigue for each subject during the session, a linear regression model, with time as the independent variable, was fitted to the VO2, torque, and TTI responses. Because the maximum VO2 was not reached until about 5 to 8 minutes into the session, the slope of the decay phase was estimated by omitting the first 500 seconds of the VO2 data. The group mean and SD of the slope and intercept were then calculated. The slope was normalized with respect to the intercept value and expressed as a
percent change per minute. The relation between the \( VO_2 \) and TTI responses during the post–500-second phase was examined using a scatterplot generated for all subjects and fitted with a linear regression model. The torque twitch timing parameters \( t_p \) and \( t_{50} \) at the beginning, middle, and end of the session were compared using a 1-way analysis of variance. Statistical analysis was done using Minitab.

Results

The mean MVC for the group was 275.6±61.6Nm (range, 163–379Nm), whereas the mean resting \( VO_2 \) was 282±47.5mL/min (range, 193–370mL/min). The mean stimulus intensity was 91.0±11.4mA, which gave rise to a mean twitch amplitude of 12.1±4.2% of the MVC at 1 minute.

Figure 2A presents the torque output, whereas figures 2B through E show the pulmonary gas exchange variables for a representative subject, with an inset (fig 2F) showing the evoked twitch torque at 4Hz. Twitch fusion was not evident at any stage during the session. The oxygen uptake in this subject reached a plateau after approximately 8 minutes and declined slowly for the remainder of the session (see fig 2B). The RER exceeded unity for a period at the start of the session before declining to approximately 0.9 (see fig 2C). The \( VE \) and \( VE/VO_2 \) exhibited no evidence of hyperventilation (see fig 2D and E).

The group mean incremental \( VO_2 \) ± SD during the exercise session, together with the peak torque TTI, and SD of the torque waveform, are presented in figures 3A through D. The group mean ± SD of the RER, breathing rate \( R_b \), \( VE \), and \( VE/VO_2 \) are presented in figures 4A through D, respectively.

After an initial transient, \( VO_2 \) (see fig 3A), peak torque amplitude (see fig 3B), and TTI (see fig 3C) declined slowly and progressively. The mean slope and intercept ± SD are presented in table 1, together with the mean normalized slope, expressed as percent change per minute. Within the limited available statistical power, there was no significant difference between the rate of decrease for each of these 3 variables \( (P=.18) \). Similarly, there was no significant difference in timing parameters \( t_p \) and \( t_{50} \) during the course of the session (table 2). The relation between oxygen uptake and TTI is shown in figure 5 along with a linear regression fitted to the data \( (R^2=.72) \).

Discussion

The principal finding of the study was that the observed rates of decline of both output torque and incremental \( VO_2 \) were found to be substantially lower than has been reported for intermittent isometric tetanic stimulation, despite the higher oxygen uptake and energy rates.

There is an underlying assumption that the pulmonary oxygen uptake observed here was consumed by the stimulated muscles and not in other physiological compartments. The breathing rate did not increase excessively (see fig 4B), which otherwise might have suggested a sympathetic response to discomfort or anxiety. There was no muscle work evident in other parts of the body—for example, because of bracing or altered posture. The oxygen uptake because of respiratory muscles is also insignificant in the context of the incremental whole body oxygen uptake.

The mean reduction in peak torque amounted to 14.5% over 25 minutes, from a mean initial torque of 32Nm (12% of the MVC) (see fig 3B, table 1). By contrast, Russ et al explored a range of stimulation frequencies from 20 to 80Hz based around a stimulus intensity, which generated 10% MVC at 100Hz, and observed a reduction in torque output ranging from 43% to 68% in approximately 3 minutes. Similar rates of fatigue have been reported in other studies.

In spite of the low stimulation frequency used and relatively low evoked torque, the mean incremental \( VO_2 \) reached a maximum of 596mL/min (see fig 3A) resulting in an exercise intensity of approximately 3 times the resting levels. The mean exercise...
intensity for the 30-minute session amounted to 3 METs. Comparable studies using intermittent isometric tetanic stimulation have reported VO₂ rates of approximately twice the resting levels. This difference may in part be explained by the intermittent nature of the stimulation used in those studies; however, continuous, rather than intermittent, tetanic contraction would be unlikely to yield higher overall VO₂ rates because of reduced perfusion and rapid fatigue. It has been suggested that the slower rate of muscle fatigue during low-frequency stimulation is caused by a lower ATP consumption when compared with stimulation at higher frequencies. It has been suggested that the slower rate of muscle fatigue during low-frequency stimulation is caused by a lower ATP consumption when compared with stimulation at higher frequencies. However, in the present study using prolonged stimulation, incremental VO₂ was approximately double that reported for intermittent tetanic stimulation over similar timescales; however, the rate of decay of the output torque was considerably less.

In addition to a higher level of evoked VO₂, the results indicate that the rate of decline of oxidative energy conversion during continuous subtetanic stimulation is less than that for intermittent tetanic stimulation. In the present study, the mean incremental VO₂ rate declined by approximately 10% during the last 20 minutes of the session (see fig 3A, table 1). Although Hamada et al reported a decline in incremental VO₂ amounting to 18% after 20 minutes of intermittent 20-Hz stimulation, the peak exercise VO₂ achieved was less than twice the resting levels. Peak torque output declined by 50% during the same period. Theurel et al maintained a constant VO₂, at twice the resting levels, during 17 minutes of intermittent quadriceps stimulation at 85Hz, but this required a 2-fold increase in stimulation intensity to compensate for fatigue.

The relatively slow decline in VO₂ and output torque observed in the results suggests that the oxidative metabolic process was substantially able to meet the prolonged energy demand. This form of low-frequency stimulation may facilitate aerobic energy conversion, which results in less metabolic stress compared with the predominantly anaerobic response observed with intermittent tetanic stimulation. NMES is known to recruit superficial fibers more readily; in the quadriceps these tend to be predominantly type II. The lower frequency used here may simply allow these faster fibers more time to recover between twitches, resulting in reduced metabolic stress, and also avoid fatigue from the transmission process, which has been suggested to occur at higher rates. Gorgey et al argued that higher stimulation frequency leads to accelerated fatigue of force output because it produces more force per activated area of muscle; therefore, the metabolic...
demand from the cross-bridge activity to produce that force is concentrated on the activated area. It may be that the metabolic demand associated with high-intensity, low-frequency stimulation is dispersed over a larger number of motor units, a greater proportion of which will operate within their aerobic capacity because of the very low stimulation frequency used. Also, twitch-like activation may allow better perfusion of the contractile tissue than can be achieved with tetanic stimulation. Hultman and Spiert observed that sustained tetanic contractions >30% MVC can reduce perfusion to the muscle, effectively rendering it ischemic for the period of the contraction. If the motor unit pool,

Table 1  Group mean coefficients ± SD (slope and intercept) for the linear regression model for each of the responses for torque, TTI, and incremental VO₂ with respect to time during the session

<table>
<thead>
<tr>
<th>Response</th>
<th>Slope (°/s)</th>
<th>Intercept</th>
<th>Fatigue Rate (%/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torque (Nm)</td>
<td>-.002±.0010</td>
<td>30.8±12.7</td>
<td>-.54±.31</td>
</tr>
<tr>
<td>TTI (Nm s)</td>
<td>-.012±.0074</td>
<td>86.9±35.7</td>
<td>-.82±.57</td>
</tr>
<tr>
<td>Incremental VO₂</td>
<td>.048±.0599</td>
<td>621.2±238.1</td>
<td>-.47±.41</td>
</tr>
<tr>
<td>(mL/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Incremental VO₂ excludes the first 500 seconds. The fatigue rate, calculated as the slope normalized to the intercept value, is also shown and expressed in percent per minute.

Table 2  Twitch timing parameters (tp and t50) at the beginning, middle, and end of the 30-minute NMES session with corresponding F and P values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Beginning</th>
<th>Middle</th>
<th>End</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>tp millisecond</td>
<td>39±5</td>
<td>40±11</td>
<td>38±11</td>
<td>.11</td>
<td>.90</td>
</tr>
<tr>
<td>t50 millisecond</td>
<td>42±44</td>
<td>38±34</td>
<td>38±32</td>
<td>.04</td>
<td>.96</td>
</tr>
</tbody>
</table>

NOTE. Values are group mean ms ± SD.
or a fraction of it, remains in tetanic contraction for extended periods, perfusion may be composed, and the exaggerated metabolic response observed by Ratkevicius and Quistorff will rapidly become established. The intermittent tetanic stimulation is initially more costly in terms of ATP usage than equivalent volitional exercise; moreover, the resulting metabolic stress is higher, implying a predominantly glycolytic source of energy. In contrast, subtetanic stimulation permits a greater oxidative energetic contribution, which may explain its lower rate of fatigue.

The higher oxygen uptake rate observed here, compared with intermittent tetanic stimulation reported in the literature, arose despite considerably lower evoked peak forces and force time integrals (1542N.s/min compared with 5386N.s/min in Theurel et al), implying a higher oxygen cost of force production. Nonetheless, the TTI was found to be a significant determinant of VO2 (see fig 5). This may simply reflect that more motor units were involved. Greater energy is required to develop muscle force than to maintain it; consequently, a stimulation frequency lying below at which force fusion occurs and which maximizes the total force excursion per unit time may be expected to maximize this effect. Allowing that there was insufficient statistical power to exclude a small change in the twitch timing parameters, there was no apparent substantial difference between twitch timing parameters at the start and end of the stimulation session (see table 2), indicating little change in the twitch fusion properties.

The RER observed in this study (see fig 4A) is consistent with reports from other studies involving prolonged NMES. The RER approaches, or exceeds, unity for a period at the start of the NMES session and declines steadily thereafter, albeit at generally higher values than that which would be expected for the equivalent intensity of volitional exercise. Such a response could occur because of hyperventilation, but in the present study there was no evidence of this in either the VE or VE/VO2 responses (see figs 4B–D). It is therefore more likely to indicate anaerobic metabolism and aerobic utilization of the predominantly carbohydrate substrate.

Although the absolute increment in VO2 reported in the present study is low, corresponding to light aerobic volitional exercise, this increase arose from stimulation of the quadriceps muscles alone. Additional stimulation of the hamstring and gluteal muscle groups in a healthy population can, readily increase this to 50% of maximum aerobic capacity. The low peak torque produced is an advantage in rehabilitation or critical care settings because it avoids the requirement for limb restraint and reduces stress on bones and connective tissue, which may have disease-related weakness.

**Study limitations**

The statistical power of this study was low, largely because of the small sample size, which precludes definitive conclusions. The focus was on evoked oxygen uptake and torque response during low-frequency stimulation in healthy men with quite a diverse range of physical activity profiles. As such, it does not readily permit generalization to any particular clinical population. However, the results provide some insight into how this might beneficially translate to patient populations. Conditions (eg, chronic obstructive pulmonary disease, heart failure, spinal cord injury) can lead to a shift toward type II fibers resulting in a reduced oxidative capacity and altered fatigue response. Further studies are required to examine whether this form of stimulation can beneficially overload the remaining oxidative capacity in such patient groups to achieve an enhanced training effect. This offers the possibility of a therapeutic intervention aimed at retarding or reversing some of these changes and may help to explain the improvement in oxidative capacity and aerobic endurance observed in recent studies.
Conclusions

Oxygen uptake and evoked torque were observed to decrease slowly, with similar rates of decline, during a 30-minute session of subtetanic NMES of the quadriceps muscles. Incremental VO2 was higher, and the rates of fatigue of both evoked torque and VO2 were considerably slower than has been reported for intertetanic NMES, despite the higher oxygen uptake. There was insufficient statistical power in this study to generalize these observations to a wider population. The combined effect of a relatively high VO2 with a low rate of fatigue potentially permits the accumulation of a therapeutic exercise volume within an exercise session. This may provide a novel means of providing an enhanced aerobic exercise intensity to patient populations while avoiding the fatigue and reduction in VO2, which is typical of conventional tetanic stimulation.

Suppliers

a. Cybex, 10 Trotter Dr, Medway, MA 02053.
b. Biopac, 42 Aero Camino, Goleta, CA 93117.
e. Cosmed, Via dei Piani di Monte Savello, 37, Rome 00041, Italy.
f. Minitab, Quality Plaza, 1829 Pine Hall Rd, State College, PA 16801-3008.

Keywords

Electric stimulation; Fatigue; Oxygen consumption; Rehabilitation

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References