Metabolic Cost of a Proposed NMES Spaceflight Countermeasure Compared to Walking in Active Adults

Thomas J. Abitante; Mohammad Mehdi Alemi; Dava J. Newman; Kevin R. Duda

INTRODUCTION: Astronauts exercise to reduce microgravity-induced bone loss, but the resultant skeletal loading may not be sufficient to reduce fracture risk on an extended Mars mission. Adding additional exercise increases the risk of a negative caloric balance. Neuromuscular electrical stimulation (NMES) induces involuntary muscle contractions, which load the skeleton. The metabolic cost of NMES is not fully understood. On Earth, walking is a common source of skeletal loading. If the metabolic cost of NMES were equal to or less than walking, it could offer a low metabolic cost option for increasing skeletal loading.

METHODS: We measured the oxygen consumed and carbon dioxide produced from 10 subjects during 5-min bouts of walking at 2 mph, 3 mph, and 2 mph on a 6° incline, and of NMES to the legs at duty cycles of 1 s on and 5 s, 4 s, or 3 s off. Metabolic cost was calculated using the Brockway equation and the percent increase above resting for each NMES bout was compared to walking.

RESULTS: Metabolic cost increased $64.9 \pm 52.8\%$ from rest in the most intense NMES duty cycle (1 s/3 s) and $120.4 \pm 26.5\%$, $189.3 \pm 59.5\%$, $281.7 \pm 66.8\%$, for the 2 mph, 3 mph, and incline walking, respectively. The metabolic cost did not differ significantly between the three NMES duty cycles.

DISCUSSION: The increase in metabolic cost of the fastest NMES bout was less than that of the slowest walk, indicating that numerous NMES bouts offer a way to increase skeletal loading at a modest metabolic cost. This might allow for more daily skeletal loading cycles, potentially further reducing bone loss.

KEYWORDS: electrical stimulation, spaceflight countermeasures, energy expenditure.

Abitante TJ, Alemi MM, Newman DJ, Duda KR. *Metabolic cost of a proposed NMES spaceflight countermeasure compared to walking in active adults*. Aerosp Med Hum Perform. 2023; 94(7):523–531.

Astronauts in microgravity experience a substantial loss of bone mineral density (BMD), as high as 1–2% per month, in the lower body as a result of long duration microgravity exposure where the skeleton is not subjugated to the constant daily loading one would experience on Earth.[21] A rigorous exercise regimen (2.5 h/d) is currently prescribed as the primary countermeasure to reduce this bone loss, with heavy resistance training and proper nutrition increasing the efficacy.[35] However, despite improvements in the exercise equipment and the addition of pharmaceutical solutions,[34] there is still large variability in bone loss reduction. In the current operational environment aboard the International Space Station, where astronauts will return to Earth after a 6-mo long mission for rehabilitation,[19] this variation is acceptable. However, for a potential 12- to 18-mo-long mission to Mars, where astronauts would be expected to perform labor upon landing, the current rates of bone loss could lead to a substantial risk of fracture[36] and, therefore, critical mission failure. The difficulty in minimizing or preventing BMD and other bone strength metric losses[38] to levels that would be acceptable on a long duration mission to Mars can be attributed to the fact that astronauts experience negligible skeletal loading outside of the exercise block.

From the Massachusetts Institute of Technology and The Charles Stark Draper Laboratory, Inc., Cambridge, MA, USA.

This manuscript was received for review in September 2022. It was accepted for publication in March 2023.

Address correspondence to: Thomas J. Abitante, B.S., Health Sciences and Technology, Massachusetts Institute of Technology, 77 Massachusetts Ave., 37-219, Cambridge, MA 02139-4301, USA; abitante@mit.edu.

DOI: https://doi.org/10.3357/AMHP.6174.2023

The currently accepted theory concerning bone health is that mechanosensors at the cellular level detect mechanical loading in the form of strain.[15] The total accumulation of mechanical loading in a given day is called the daily strain stimulus (DSS) and ultimately drives bone health and maintenance. DSS is determined by the strain magnitude of a loading cycle, the number of loading cycles, and numerous other nonlinear factors. However, there are still numerous unknowns in what thresholds are required to adequately prevent bone loss.[3,29] Despite these unknowns and the rigor of the current space-based exercise regimen, it is likely that astronauts accumulate an insignificant DSS compared to what is experienced on Earth. The high volume of lower strain, non-exercise-based activity that normally occurs throughout a given day is absent, reducing the potential DSS. Additionally, the mechanisms that trigger bone maintenance habituate to repetitive signals, resulting in diminishing returns. As this habituation will recover with time, bone is more responsive to more frequent loading spread throughout a given day,[31] meaning that the consolidated nature of the exercise reduces the exercise regimen's contribution to the cumulative DSS and, therefore, the subsequent effectiveness.

Unfortunately, to increase the total DSS, the solution cannot be simply adding more exercise blocks throughout the day. There are operational constraints, such as crew responsibilities for spacecraft maintenance and safety, and logistical constraints, such as a greater mass and volume requirements for the additional water, food, oxygen, and carbon dioxide removal, that come with exercise.[32] Additionally, a high volume of exercise requirements can affect compliance.[14] More importantly, there are physiological constraints. Due to numerous physiological and psychological reasons, astronauts can struggle to eat enough to maintain weight. Adding more exercise could result in an increased energy expenditure that may be difficult to overcome, creating a negative caloric balance, which could hinder the benefits of the exercise.[20] Therefore, in order to increase the DSS on a long duration mission to Mars and subsequently reduce the bone loss and risk of fracture, nondisruptive, low-metabolic cost methods to load the skeleton are needed.

Neuromuscular electrical stimulation (NMES) is a technique that uses electrical pulses to cause involuntary muscular contractions[7] and has been previously used as a space-based muscle atrophy countermeasure by Roscosmos.[26] Despite unavailable postflight data from Roscosmos and other limitations, such as difficulties activating multiple body segments simultaneously or other atrophy-prone muscles like the back extensors, NMES has had positive results in the thighs and lower legs in ground analog studies and, thus, is still an active area of research.[24] More recently, however, NMES has been investigated as a bone loss countermeasure in spinal cord injury (SCI) patients, who experience disuse-associated bone loss in a similar manner to astronauts, with studies showing that repetitive daily muscular contractions with NMES can attenuate bone loss in the tibia and femur.[12,33] Furthermore, strain models have shown that NMES contractions in the thigh muscles can produce strains at the hip joint similar to that achieved during walking.[1] Walking is commonly seen as an effective supplement to exercise to reduce bone loss on Earth,[25] highlighting that NMES could therefore supplement exercise in space, reintroducing some of the daily nonexercise skeletal loading that is absent in microgravity. Thus, in addition to the previously used muscle countermeasure, NMES presents itself as a potential bone loss countermeasure for the hip and legs.

Although NMES can produce strains similar to walking, how the metabolic cost of repetitive NMES compares to walking is not fully understood. NMES has been commonly used as an exercise aid for SCI patients, as activating the paralyzed muscle in specific patterns can allow individuals to perform movements such as cycling or rowing. This increases the metabolic response and helps prevent many of the comorbidities associated with immobilization such as cardiovascular disease.[17] Studies on healthy subjects have generally shown that NMES will increase the metabolic output and can, therefore, be used as an ancillary tool to supplement exercise. However, the nature of these studies have varied greatly: rapid nonfused contractions,[5] tetanic contractions,[10,18] and NMES used in tandem with exercise.[13,37] Additionally, while these studies have shown an increase in metabolic cost with NMES compared to rest or NMES with exercise compared to exercise alone, none compared the increase with NMES alone to that of other forms of exercise in healthy individuals[16] as a way to determine to what extent NMES can definitively supplement exercise.

The purpose of this study was to determine the metabolic cost of repetitive isometric tetanic contractions to the legs in active individuals at various duty cycles and to compare it to the metabolic cost of walking at various speeds. Walking at low and high intensities can be considered nonexercise activity or light exercise, respectively. As NMES to the lower body can potentially reintroduce the strains similar to walking into an astronaut's day,[1] we needed to determine whether an NMES protocol would incur metabolic costs similar to walking in order to predict whether NMES, when added as supplemental countermeasure, would require only modest energy expenditure. We hypothesize that the metabolic cost of these NMES contractions will increase as the duty cycle becomes more rapid, but that even the fastest duty cycle will have a metabolic cost significantly less than that of slow walking. A low metabolic cost would imply that numerous sets of repetitive NMES contractions could be applied throughout the day, adding a high volume of skeletal loading cycles, reintroducing the more routine, nonexercise-based skeletal loading that is absent in microgravity. This could have the effect of potentially reducing bone loss without a major increase in energy expenditure such as might occur by simply adding additional exercise using the current in-flight techniques (e.g., cycling, treadmill running, resistive exercises).[20]

METHODS

Subjects

A convenience sample size of 10 active adults (6 men; 4 women) was recruited for this study from members in the local community. Their average (± SD) ages, heights, and body weights were 23.8 (± 3.3) yr, 174.5 (± 10) cm, and 69.7 (± 12) kg, respectively. The sample size of this study is comparable to other studies in which significant differences in the metabolic cost between NMES and other activities were obtained.[5,10,16] The experimental procedures were approved by the Institutional Review Board at the Massachusetts Institute of Technology, protocol number 1810570889. Inclusion criteria required that all subjects be physically active, which was defined as engaging in physical activity for at least 30 min, 4 d/wk. All subjects were required to be free of any illness or ongoing knee or lower body muscle injury and provided written informed consent prior to participating in the study.

Equipment

The NMES devices used in this study were custom built, voltage controlled devices developed at the Massachusetts Institute of Technology (MIT) Human Systems Lab (HSL) in collaboration with MIT Portugal.[27] Each device was comprised of two muscle stimulation units (MSU), each of which contained two attachments for cutaneous electrodes, an Arduino Mega microcontroller, and a custom printed circuit board that attached to the Arduino Mega and to the MSUs via RJ11 ports that communicated with the Arduino Mega's serial communication channels. Each MSU delivers a biphasic pulse with four individually customizable parameters: pulse amplitude (V), pulse frequency (Hz), and positive and negative pulse widths (μs), which when combined are referred to jointly as the pulse width or pulse duration. All these parameters, as well as the duty cycle (on stimulation/off stimulation timing), and total duration of the stimulation could be modified and controlled with the Arduino IDE software.

We developed four NMES devices for this study, allotting a total of eight MSUs (channel 1 and 2 per device). The electrodes used in this study were 10 × 5 cm rectangular electrodes or 5 × 5 cm square electrodes (Ultrastim X, Axelgaard Manufactoring Co., Fallbrook, CA, USA). We selected large electrodes to maximize the muscle contraction strength.[4] With the Microsoft Visual Basic Studio Software, we created a graphical user interface (GUI) to facilitate the simultaneous control and setup of the four NMES devices. With the GUI, we could customize the following parameters of the NMES treatment: selection of NMES device, total repetitions, on and rest times for each contraction (duty cycle), the pulse width, and the individual voltage for each of the eight MSUs. The metabolic analyzer used in this study was the K5 Wearable Metabolic System (COSMED, Rome, Italy), which reliably measured the oxygen consumption ($\dot{V}O_2$) and the carbon dioxide production ($\dot{V}CO_2$).[30]

Procedures

Each participant underwent two separate in-lab sessions (i.e., walking and NMES). The two sessions were scheduled to be roughly 24 h apart. Subjects were asked to avoid caffeine at least 6 h prior to either session and to avoid strenuous exercise for 24 h prior to each session. Strenuous exercise was defined as any intensity that would elicit noticeable fatigue or soreness that would necessitate a reduction in intensity or a rest day.

For the walking test, subjects used a treadmill located in the MIT HSL (**Fig. 1A**). The treadmill was fitted with an emergency stop button and we instructed subjects on how to safely enter and exit the treadmill during the administration of the test. After donning the K5 metabolic analyzer, we began the test. The test consisted of three bouts of 5 min of walking at various speeds: slow (2 mph), brisk (3 mph), and incline (2 mph at a 6° incline), with a 15-min rest between the bouts. The order of the walking bouts was randomized for each participant to minimize the confounding error. Prior to the first and after the last bout, the participant would sit for 10 min to obtain a steady state resting (baseline) condition. Additionally, 1 min prior to each of the walking bouts, subjects performed 30 s of bodyweight squats in order to ensure the subjects reached a metabolic steady state during the 5 min. Bodyweight squats were selected because during the NMES test, the only warm-up activity able to be performed while attached to the NMES devices was bodyweight squats. The protocol is depicted graphically in **Fig. 1C**.

For the NMES test, we applied NMES to eight muscles, four on each leg: the quadriceps rectus femoris (RF), hamstrings complex (HM), tibialis anterior (TA), and gastrocnemius (GN). These muscles were selected based on prior studies in order to produce a countermeasure that would target the femur and tibia. The RF and HM were the muscles used in the previous strain model and comparable strains should be expected at the proximal femur as this study used similar NMES intensities and subject population.[1] While no strain model of the distal femur or tibia have been developed, repetitive contractions in the GN and the quadriceps have been shown to reduce bone loss in the tibia[33] and distal femur,[12] respectively, in SCI patients. Additionally, stimulating the agonist-antagonist muscle pair of a particular limb segment (e.g., channels 1 and 2 on left RF and HM) can minimize movement[26] and muscle pain that may result from the rapid and powerful muscle shortening.[6] We selected the RF over the other quadriceps muscles specifically because the muscle would counter the hip extension associated with HM as well as contribute to a hip joint reaction force. The configuration and approximate locations of the corresponding electrodes for each muscle are illustrated in **Fig. 2**. We used maximal electrode spacing to attenuate the effects of body fat and therefore minimize discomfort.[11] Each participant sat in a custom built, adjustable rig that was constructed in the MIT HSL (**Fig. 1B**). This rig allowed the easy attachment and detachment of the electrodes, provided support for the foot to help minimize movement of the ankle and to reduce potential GN pain, and also replicated the position astronauts exhibit while floating in microgravity. Prior to beginning any NMES treatment, we provided safety instructions and emergency stop signals and procedures.

We then calibrated the strength of the NMES contractions, one agonist-antagonist pair at a time. Using sets of three NMES pulses set to a duty cycle of 1 s on/3 s off, we gradually increased the pulse amplitude of channel 1 until achieving the "maximum

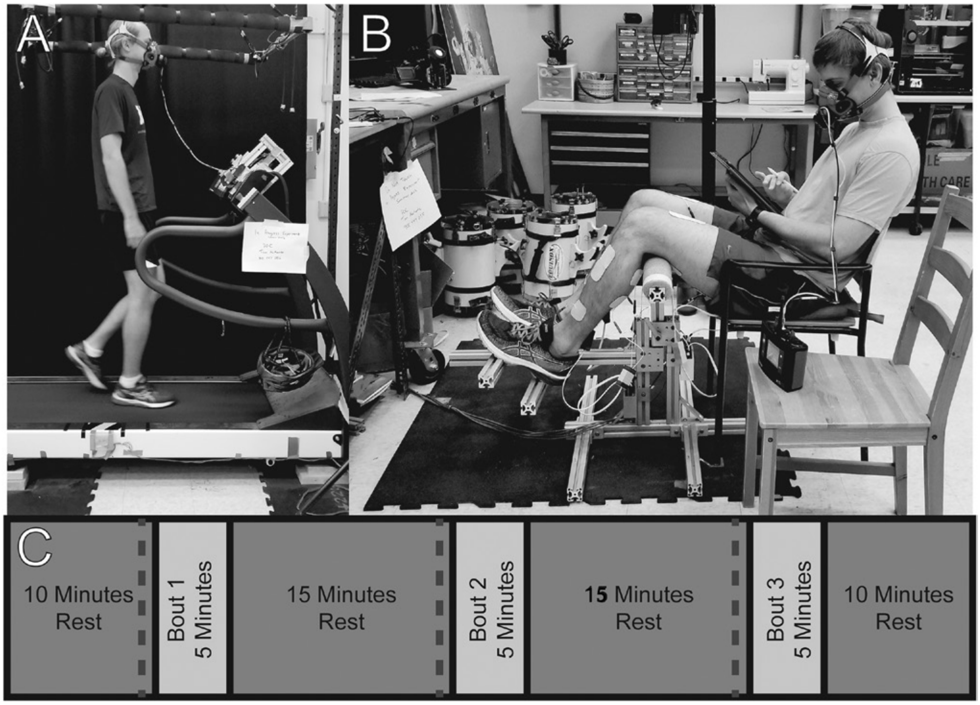

Fig. 1. Experimental design. A) A photo of a participant using the treadmill during day 1. B) A photo of the NMES setup and rig. Subjects sat in a chair with their legs draped over an adjustable leg rest and feet placed on an adjustable footrest. C) Graphical representation of the experimental procedures. The dotted line in the rest blocks represents the initiation of the warm-up bodyweight squats.

tolerable comfort level," which was a subjective metric where the participant felt they could withstand repeated contractions without pain or significant mental distraction. This was then repeated with channel 2 and then again with both channels on simultaneously to produce the agonist-antagonist cocontraction. Any modifications (increase or decrease) to the pulse amplitudes during the cocontraction were applied as needed to minimize discomfort or any excessive limb movement.

Last, once all eight MSUs were calibrated, we administered practice runs of the NMES testing protocols. The testing protocol involves an alternating contractile pattern of two groups with four muscles each: the left thigh (RF and HM) and the right lower limb (TA and GN) contract together, followed by the right thigh and the left lower limb. The alternating pattern results in the second group activating halfway during the rest period of the first group. This grouping was selected to minimize any potential knee pain that could result from a simultaneous contraction of the RF, HM, and GN. We delivered a set of three contractions at the fastest testing duty cycle (1 s on/3 s off), adjusting the pulse amplitude of any of the eight MSUs as required. We then delivered sets of 6, 10, 15, and 20 contractions, adjusting pulse amplitudes as required after each set to ensure that, during the actual testing protocol, the participant would not be in pain or discomfort. The pulse frequency and width used during the calibration and subsequent testing was 50 Hz and 400 μs, respectively. These values were chosen to aid in ensuring tetanic contractions while minimizing fatigue.[23]

After a period of rest, we began the testing protocol and the participant would don the portable K5 system. The NMES protocol was similar to the walking protocol. Three bouts of 5 min of NMES were delivered with duty cycles of varying speeds and, therefore, repetitions (1 s on with: 3 s off, 75 repetitions; 4 s off, 60 repetitions; or 5 s off, 50 repetitions), with the bouts occurring in a randomized order and with 15 min rest between each bout. We chose 5 min for the duration as prior research

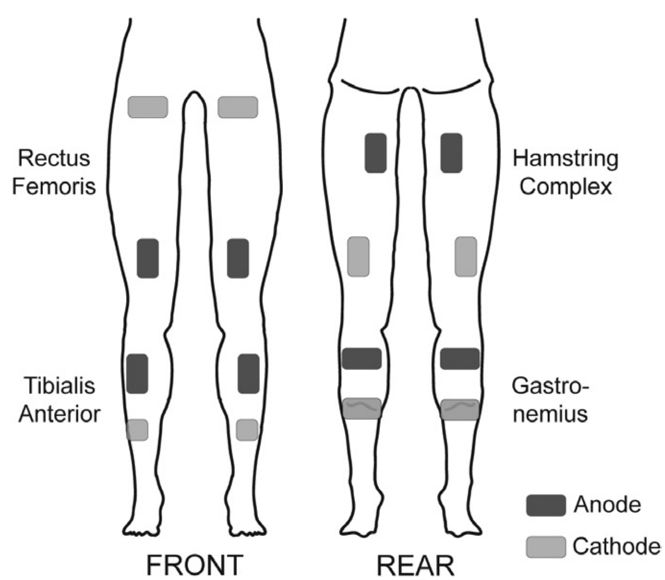

Fig. 2. Location of the electrical stimulation electrodes. The black electrodes denote the anode connection, placed over the muscle bellies. The gray electrodes denote the cathode connection, placed with maximum separation on same muscle. All electrodes but the tibialis anterior (TA) were 10 x 5cm rectangular electrodes. The TA was a 5 x 5 cm square electrode (Ultrastim X, Axelgaard, Fallbrook, CA, USA).

demonstrated that the muscles in most individuals will begin to fatigue at this point.[2] During all rest periods, the subjects were able to move their legs out of the rig and sit normally. Additionally, 1 min prior to each of the NMES bouts, subjects performed 30 s of bodyweight squats in order to ensure the subjects reached a metabolic steady state during the 5 min. The protocol is depicted graphically in Fig. 1C.

If at any time during the test the participant felt uncomfortable or was in pain, that particular bout would be stopped. If the participant felt they could continue, the noted MSU's pulse amplitude would be lowered and the 5-min bout would be restarted after a 10-min rest. If after the completion of an NMES bout, the subjects noted that they were beginning to experience or anticipated muscle pain, the pulse amplitude of the noted MSU for the following 5-min bout would be lowered slightly. We expected this latter scenario to occur with the GN and HM from a prior pilot study and we, therefore, attempted to minimize the likelihood of either of these scenarios with the final practice runs at the fastest duty cycle prior to the administration of the test. Additionally, during each of the 5-min NMES bouts, we instructed the subjects to perform a work-related task (technical work or reading a scientific paper). After the end of each bout, we then asked them to rate the level of distraction the NMES bout was on a scale from 1 to 5. If they felt they could not perform a work-related task, they were instructed to read anything leisurely of their choosing. The metrics for this scale are displayed in **Table I**.

We processed the experimental data from the K5 system using MATLAB (The MathWorks, Inc., Natick, MA, USA). $\dot{V}O_2$ and $\dot{V}CO_2$ were filtered using a fourth order Butterworth filter with a cutoff frequency of 0.50 Hz. It should be noted that it takes several minutes for the metabolic rate ($\dot{V}O_2$ and $\dot{V}CO_2$) to stabilize. The participant's warm-up squats raised the metabolic rate rapidly, shortening the time to reach a steady state. In order to ensure that the metabolic rate reflected that of a steady state condition for walking or NMES, we allowed an additional stabilization period. The first 3 min of each 5-min bout were dropped from the data and we calculated the average $\dot{V}O_2$ and $\dot{V}CO_2$ for each walking or NMES bout with the last 2 min of each bout. We additionally used a 5-min period (3 to 8 min) from the initial 10-min baseline as the resting metabolic data to compare each of the walking and NMES bouts respectively. This 5-min period was used to avoid any nonresting conditions that were still present from before the test or in anticipation of the first bout.

Table I. Distraction Survey Given to Each Participant After Each Bout of Electrical Stimulation in Which They Either Read or Performed Work of Their Choosing.

	SCALE	WORKLOAD REFERENCE
1	Not Distracting at all	No impedance to technical work
2	Slightly Distracting	Slight impedance to technical work
3	Somewhat Distracting	Great impedance to technical work
4	Very Distracting	Unable to perform technical work, but can perform leisure activities
5	Extremely Distracting	Unable to perform any task

For this study, we calculated the metabolic cost (M) using the Brockway equation,[9] excluding the nitrogen term:

$$M = 16.58\,\dot{V}O_2 + 4.51\,\dot{V}CO_2$$

where $\dot{V}O_2$ and $\dot{V}CO_2$ are in $L \cdot s^{-1}$ and M is in W. We normalized M to each participant's body mass in kilograms (M_{bw}). Additionally, $\dot{V}O_2$ was normalized to each participant's body weight and converted to $ml \cdot min^{-1} \cdot kg^{-1}$ ($\dot{V}O_{2bw}$), and $\dot{V}CO_2$ was converted to $L \cdot min^{-1}$ for use in the analysis. Last, we calculated the percent increases in M_{bw}, $\dot{V}O_{2bw}$, and $\dot{V}CO_2$ for each of the three walking bouts and the three NMES bouts with respect to the baseline condition for each respective day ($\overline{M_{bw}}$, $\overline{\dot{V}O_{2\,bw}}$, $\overline{\dot{V}CO_2}$).

Statistical Analysis

Our study had three dependent variables: $\overline{M_{bw}}$, $\overline{\dot{V}O_{2\,bw}}$, and $\overline{\dot{V}CO_2}$. We performed two-tailed t-tests on all dependent variables to assess whether there are any significant differences between each walking speed and each of the three NMES duty cycles. We used a one-way ANOVA to determine if there were any significant differences between any of the three NMES duty cycles (i.e., 5 s vs. 4 s, 5 s vs. 3 s, 4 s vs. 3 s). All statistical analyses were performed using JMP Pro 16 (SAS, Cary, NC, USA), with statistical significance concluded when $P < 0.05$.

RESULTS

The mean and standard deviation of the absolute $\dot{V}O_{2bw}$, $\dot{V}CO_2$, and M_{bw} during the baselines and the walking and NMES bouts are presented in **Table II**. No significant difference was observed in the baseline measurements between each day. The $\overline{M_{bw}}$ with respect to each day's baseline was 120.4 ± 26.5%, 189.3 ± 59.5%, and 281.7 ± 66.8% for the slow, brisk, and incline walking, respectively, and 57.4 ± 30.6%, 53.0 ± 35.8%, and 64.9 ± 52.8% for the 5-s rest, 4-s rest, and 3-s rest NMES duty cycles, respectively. The $\overline{M_{bw}}$ for all three NMES bouts were significantly less than that during the incline walk ($P < 0.0001$), the brisk walk ($P < 0.0001$), and the slow walk ($P < 0.05$). No significant difference in $\overline{M_{bw}}$ was observed between any of the three NMES bouts.

Similar results were observed with $\overline{\dot{V}O_2 bw}$ and $\overline{\dot{V}CO_2}$. Each NMES bout was significantly less than all walking speeds ($P < 0.01$), with the exception of the $\overline{\dot{V}CO_2}$ between the slow walk and the 3-s rest NMES duty cycle. No significant differences were found in $\overline{\dot{V}O_2}$ or $\overline{\dot{V}CO_2}$ between any of the NMES bouts. The individual data for $\overline{M_{bw}}$, $\overline{\dot{V}O_{2\,bw}}$, and $\overline{\dot{V}CO_2}$ are shown in **Fig. 3**.

The results of the subjective distraction survey are presented in **Table III**. Of the 10 subjects, 4 noted a decrease in distraction between the first and last treatment, 2 noted an increase, and 4 noted no change. Statistical analysis was not performed on this data, nor was any potential trend analyzed based on the particular randomized order of NMES duty cycles received.

Table II. The Mean (SD) of the Consumed Oxygen Rate ($\dot{V}O_2$), Produced Carbon Dioxide Rate ($\dot{V}CO_2$), and Metabolic Cost (M) During Walking and Neuromuscular Electrical Stimulation (NMES) Trials.

	WALKING				NMES			
	BASELINE	SLOW	BRISK	INCLINE	BASELINE	1/5 s (50 rep)	1/4 s (60 rep)	1/3 s (75 rep)
$\dot{V}O_{2bw}$ ($mL \cdot min^{-1} \cdot kg^{-1}$)	4.97 (1.09)	10.75 (1.76)	13.88 (1.91)	18.55 (2.90)	5.05 (1.25)	7.61 (1.59)	7.31 (1.55)	7.76 (1.67)
$\dot{V}CO_2$ ($L \cdot min^{-1}$)	0.29 (0.08)	0.64 (0.16)	0.83 (0.22)	1.06 (0.24)	0.28 (0.07)	0.48 (0.14)	0.47 (0.13)	0.50 (0.14)
M_{bw} ($W \cdot kg^{-1}$)	1.68 (0.37)	3.66 (0.60)	4.72 (0.64)	6.27 (0.95)	1.70 (0.43)	2.62 (0.55)	2.53 (0.52)	2.69 (0.59)

DISCUSSION

Bone health and maintenance is thought to be dictated by the DSS, which is the daily summation of all strain loading cycles.[29] In microgravity, exercise is the predominate source of skeletal strain, but astronauts lack the lower strain loading cycles that are present on Earth from typical daily activity, such as walking, that contribute to DSS. Repetitive tetanic contractions from NMES have been shown to produce strains in the femur similar to that of walking and, therefore, NMES could be used to supplement the exercise regimen on a long duration mission to Mars by reintroducing the strains from typical daily activity that are absent, thus increasing the DSS and potentially reducing bone loss[1] and subsequent fracture risk.[36] However, as the exercise regimen incurs a high metabolic cost due to its intensity and duration, any supplement countermeasure must have a metabolic cost sufficiently low enough that it would not increase the risk of a negative energy balance.[20]

Our study findings demonstrated that the metabolic cost of repetitive tetanic contractions to the lower limbs, even at a relatively rapid duty cycle (1 s on/3 s off), was less than the metabolic cost of walking. Therefore, if NMES were to be used in this manner as a bone loss countermeasure in microgravity, it is unlikely that it would increase the daily caloric expenditure to a degree that would heighten the risk of the negative energy balance. As the metabolic costs during the NMES bouts were significantly less than that of slow walking, we predict that a regimen that uses multiple short sets at a relatively rapid duty cycle, spread throughout an entire workday could be used. This would add a high volume of distributed loading cycles, adding to the DSS and accounting for habituation, potentially reducing bone loss.[29,31] Additionally, our results indicate there was an insignificant difference in the metabolic cost between the slowest and fastest duty cycles, implying that any regimen design would be more limited by an individual's muscle fatigability[2] rather than metabolic cost. It is also likely that the NMES protocols recommended to maintain muscle mass and strength in space[24] would not exacerbate the risk of negative caloric balance as well; however, confirmation studies with the specific recommended NMES protocols would be required.

While doing a task of their choosing (technical work, reading scientific papers, or reading for leisure), a majority of subjects noted that the NMES treatment was only somewhat distracting (3 on a subjective scale) at worst, and that technical work could still be performed. The variation in the survey responses, despite all subjects being calibrated to a "maximum tolerable comfort" level, is likely due to an inability to predict how one's comfort can translate to an ability to perform work simultaneously. Four of the subjects noted a decrease in the distraction as the experiment progressed and two noted an increase, while four noted a consistent level of distraction. We are not able to interpret why some individuals felt it became less distracting with each subsequent bout; however, those who noted an increase in distraction or noted the NMES as very or extremely distracting experienced near cramping in either their GN or HM muscles as the muscles became increasingly fatigued. In a long-term space-based countermeasure, we anticipate this issue would be less prevalent for two primary reasons. First, a countermeasure could and should be implemented with greater than 15 min rest between bouts. The muscle fatigues rapidly with NMES[7] and therefore satisfactory rest would be required. Second, a prior study has shown that with repeated NMES treatments, the likelihood of cramping can decrease.[6] The ability to do technical work, albeit slower, further highlights the potential benefit of an NMES-based countermeasure. In addition to the energy expenditure constraint limiting the addition of more exercise, there are operational and scientific demands that astronauts must attend to.[32] Being able to perform simultaneous tasks will limit any impact of a countermeasure. These results are consistent with a prior space-based NMES study conducted aboard Mir, which revealed that the cosmonauts were still able to perform tasks during the stimulation.[26]

We initially expected that there would be significant differences between the NMES bouts, as the fastest duty cycle had 50% more contractions than the slowest during the 5 min (75 vs. 50 repetitions). While our small sample size might have contributed to the lack of significance, there was also large variation between subjects. The variation in the increase in the metabolic cost between individuals can be attributed to two main reasons. First, the degree of muscle activation that can be accomplished with NMES will vary between individuals as differences in neuromuscular anatomy will affect how many motor end plates can be within the influence of the generated electric field with a given electrode.[7,8] Second, individuals can experience different levels of discomfort, which will affect the subjective "maximum tolerable comfort level" and,

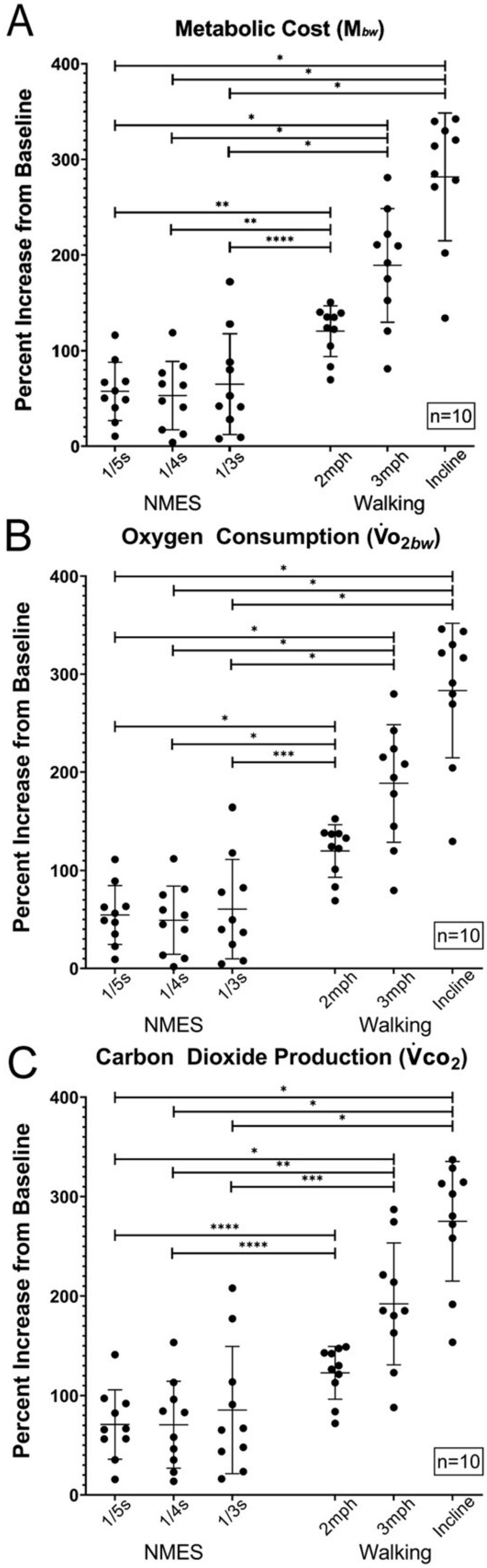

Fig. 3. Individual data points for the percent increase with respect to baseline in A) metabolic cost, normalized to body mass (M_{bw}); B) oxygen consumption, normalized to body mass ($\dot{V}o_{2bw}$); and C) carbon dioxide production ($\dot{V}co_2$). Data sets are presented with mean and standard deviation error bars ($^{*}P < 0.0001$, $^{**}P < 0.0005$, $^{***}P < 0.01$, $^{****}P < 0.05$).

Table III. The subjective Distraction Level of Each Neuromuscular Electrical Stimulation (NMES) Bout in Order of Delivery, as Noted by Each Participant Immediately Following Each 5-min Treatment.

	LEVEL OF DISTRACTION BY NMES BOUT (IN ORDER OF DELIVERY)		
PARTICIPANT	FIRST	SECOND	THIRD
1	3	2	3
2	3	3	2
3	3	3	2
4	4	4	4
5	3	3	3
6	5	4	4
7	2	2	2
8	3	2	2
9	4	4	4
10	3	3	4

Note that 1 and 5 represent the least and greatest degree of distraction, respectively. The comparative metric given to each participant in the determination of distraction can be found in Table I.

consequently, the potential strength of a contraction. This subjectivity is in part influenced by differences in skin characteristics, hair, and body fat thickness,[11] as well as pain tolerance. While our study did not include repeated NMES treatments over multiple days, soreness from prior NMES could also affect the subjective discomfort; however, this has been shown to lessen over time.[28] This inherent variation in muscle activation and the resultant increase in metabolic cost imply the potential application of an NMES-based countermeasure will be highly individualized. This aspect is further emphasized by the variations in comfort, which will affect how the various NMES sessions can be integrated into a work schedule, as well as the variations in potential strain, as noted by a previous study.[1]

To the best of our knowledge, our study was the first to compare the metabolic cost during NMES to that of walking in healthy, active individuals. Our findings are consistent with prior studies showing that NMES can increase the metabolic cost and, therefore, caloric expenditure when compared to the rest.[5,18,37] However, as our results show that the increase is less than that of slow walking, the degree to which NMES can serve as an effective cardiovascular exercise supplement in active individuals is arguable. More likely, NMES could be used as a self-directed tool to increase caloric expenditure during prolonged periods of sitting.[10] Regardless, NMES still presents itself as an effective clinical tool to replace or supplement cardiovascular exercise for those unable to perform vigorous exercise (e.g., spinal cord injury patients)[17] or those at risk of injury during vigorous exercise (e.g., obese individuals).[16]

Limitations

Our study used subjects that had no prior experience with NMES and, therefore, there may have been an increase in discomfort or anxiety. This could have altered breathing during the trial and contributed to the high variability in the results during the NMES bouts. Prior familiarization can reduce subjective discomfort, allowing for a stronger NMES amplitude and subsequent muscle contraction[28] and, therefore, incurring greater metabolic cost. This lack of familiarization along with our small sample size likely contributed to the absence of the expected trend or significant differences between the different NMES duty cycles. Second, we did not control for or measure the subcutaneous fat thickness of the legs of subjects. Body fat will reduce the electrical signal reaching the muscle, resulting in a weaker contraction, as well as increased discomfort.[11] While we attempted to control for this by having all subjects calibrate NMES to a maximum tolerable level, it is likely that body fat additionally contributed to the high variability in metabolic cost during NMES. Additionally, due to our small sample size, we did not perform an analysis between men and women, which might have highlighted this issue, as women tend to have greater lower body fat. Third, the walking speeds on the treadmills were not adjusted for height. This could have impacted the data as stride lengths can affect cadence and, therefore, metabolic cost at the same speed.

Last, it should be noted that our findings are specific to the particular NMES parameters and duty cycles used. Other studies on healthy individuals have used high-frequency nonfused contractions[5] that may increase metabolic activity significantly more than the tetanic contractions used in our methods, or have used larger muscles or a greater number of muscles, which would increase oxygen demand. Differences in the NMES frequency or current, or the regimen duty cycle, can increase the rate of fatigue[22,23] and therefore the metabolic response as well. The specific NMES protocol selected in our study was selected with the optimization of ease of application, minimal joint movement, and maximum joint reaction forces to serve as a bone loss countermeasure rather than maximizing metabolic activity to serve as a cardiovascular countermeasure.

This study serves as an initial investigation into how an NMES-based bone loss countermeasure would affect the risk of a negative caloric balance. The results of our study suggest that if such were to be used on a long duration mission to Mars as a supplement to the exercise regimen, the increase in metabolic cost resultant from the countermeasure would not increase the risk of a negative caloric balance as the metabolic cost observed was less than even that of slow walking. Therefore, an NMES regimen using numerous short bouts of repetitive tetanic contractions to the lower limbs could be used to add a high volume of loading cycles and increase the accumulation of daily strain to the lower body, which could potentially reduce bone loss in the hip, femur, and tibia. However, as using NMES for bone loss in space is a relatively novel idea, numerous follow-on studies are recommended, including a long-term head down tilt bed rest study in order to observe the long-term effects of NMES on BMD in the femur and tibia when used in conjunction with exercise, confirming the total metabolic cost when repeated sets are used throughout a given day, and investigating the BMD and metabolic effects of the muscle-targeting regimens in order to develop a potential whole musculoskeletal system regimen.

ACKNOWLEDGMENTS

We would like to extend our gratitude to Dr. Paulo Melo, who designed the NMES devices used in this study, and Jim Burns-Montante, who was instrumental in the procurement and programming of the additional devices necessary for this study. We also extend our thanks to all subjects who volunteered to participate in this study, as well as the Massachusetts Institute of Technology staff who aided in recruitment.

Financial Disclosure Statement: This study was funded and supported by The Charles Stark Draper Laboratory, Inc., Draper Scholars program. No conflicts of interest, financial or otherwise, are declared by the authors.

Authors and Affiliations: Thomas J. Abitante, B.S., and Dava J. Newman, SM, Ph.D., Massachusetts Institute of Technology, Cambridge, MA, USA; Mohammad M. Alemi, B.S., Ph.D., Department of Orthopaedic Surgery, Harvard Medical School, Boston, MA, USA; and Thomas J. Abitante and Kevin R. Duda, SM, Ph.D., The Charles Stark Draper Laboratory, Inc., Cambridge, MA, USA.

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