CAN THE EFFICACY OF ELECTRICALLY STIMULATED PEDALING USING A COMMERCIALLY AVAILABLE ERGOMETER BE IMPROVED BY MINIMIZING THE MUSCLE STRESS–TIME INTEGRAL?

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ABSTRACT: *Introduction:* The cardiorespiratory and muscular strength benefits of functional electrical stimulation (FES) pedaling for spinal cord injury (SCI) subjects are limited because the endurance of electrically stimulated muscle is low. *Methods:* We tested new electrical stimulation timing patterns (Stim3, designed using a forward dynamic simulation to minimize the muscle stress–time integral) to determine whether SCI subjects could increase work and metabolic responses when pedaling a commercial FES ergometer. Work, rate of oxygen uptake ($\dot{V}o_2$), and blood lactate data were taken from 11 subjects (injury level T4–T12) on repeated trials. *Results:* Subjects performed 11% more work pedaling with Stim3 than with existing stimulation patterns (StimErg) ($P = 0.043$). Average ($\dot{V}o_2$) and blood lactate concentrations were not significantly different between Stim3 (442 ml/min, 5.9 mmol/L) and StimErg (417 ml/min, 5.9 mmol/L). *Conclusion:* The increased mechanical work performed with Stim3 supports the use of patterns that minimize the muscle stress–time integral to prolong FES pedaling.
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Functional electrical stimulation (FES) leg cycle ergometry is well suited as an exercise method for the spinal cord injury (SCI) population. Previous research has indicated that FES pedaling by activating the quadriceps, hamstrings, and gluteus muscle groups can lead to health benefits in SCI individuals by increasing cardiorespiratory activity,[1–5] improving circulation,[4,6–10] reducing muscle atrophy,[4,11] increasing muscle mass,[12] and improving a sense of well-being.[13] Although FES leg cycle ergometry is beneficial, the number of individuals who are able to elicit cardiovascular training from the activity using commercially available ergometers is limited due to the short duration and low work achieved when using these ergometers in trained subjects.[1,5,7,14–17]

Muscle endurance in FES applications is affected by several factors, but the condition of the muscles (i.e., degree of atrophy, fiber-type composition) and the stimulation waveforms used to activate the muscles are of primary importance.[14,17–22] Because the muscles themselves are not immediately alterable, previous efforts have been directed toward manipulating the electrical stimulation waveform (e.g., maximum intensity)[23–25] and on and off timing[23–27] delivered to the muscles as a means to increase the duration and work rate (i.e., power output) of FES pedaling. These approaches are supported by recent work showing that increased muscle strength does not lead to improved FES pedaling power output.[28]

An alternative means to increase the duration and work rate of FES pedaling is related to the force–time integral of the muscles. A relationship exists between the endurance of a muscle and the muscle force–time integral, which reflects the interaction between force amplitude, duration of contraction, and rest interval between contractions.[29–32] Bigland-Ritchie et al.[31] and Thomas et al.[32] used reduction in the force–time integral as a measure of muscle fatigue. In addition, it has been demonstrated that a reduction of the force–time integral for a single muscle group leads to an increase in the duration of the force-generating capacity of the muscle group.[29,30] Because a reduction in the force–time integral increases the endurance for a single muscle group, it is reasonable to consider that a similar outcome would be observed for multiple muscle groups. Accordingly, there has been a long-held association between the reduction of the muscle stress–time integral and the increased endurance of multiple muscles working together to perform a gross motor task such as walking or pedaling.[33–36] However, we know of no study that has tested the stress–time integral under conditions of multiple muscle coordination, such as FES pedaling, as a means to increase endurance and work performed.

To conduct such a test, two steps are necessary. One is to identify the muscle stimulation timing patterns that minimize the stress–time integral of the muscles involved in FES pedaling, and the other is to conduct experiments to determine whether these patterns increase endurance and work performed in FES pedaling. In a previous study,[37] we used a forward dynamic simulation to compute the stimulation timing patterns that minimized the stress–time integral of the upper leg muscles involved in FES pedaling, thus completing the first of these two steps. Based on the

Abbreviations: ANOVA, analysis of variance; ASIA, American Spinal Injury Association; EMG, electromyography; FES, functional electrical stimulation; GMAX, gluteus; HAMS, hamstrings; QUADS, quadriceps; SCI, spinal cord injury; StimErg, stimulation ergometer

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simulation, we expected the computed stimulation timing patterns to reduce the stress–time integral of the stimulated muscles by 17%.[37] The purpose of this study was to complete the second step. An advantage of increased endurance would be increased mechanical work performed by the muscles and increased metabolic responses to the exercise. Thus, our first objective was to test whether the computed stimulation timing patterns enable individuals with SCI to perform more work than that performed with existing FES ergometer electrical stimulation patterns. Because exercise involving increased mechanical work by the muscles increases short-term metabolic responses and can lead to long-term physiological adaptations,[3,4,15,38] a second objective was to determine whether the computed electrical stimulation timing patterns would lead to significant increases in the metabolic responses.

METHODS

Forward Dynamic Simulation. To satisfy these objectives, the electrical stimulation on and off times that minimized the muscle active stress–time integral and the difference in the active stress–time integral of the quadriceps, hamstrings, and gluteus muscle groups (referred to as Stim3) were tested in a clinical setting. These electrical stimulation on and off times were computed previously by means of a forward dynamic simulation of FES pedaling with the ankle joint fixed in the neutral position (the foot at a 90° angle with the shank). Detailed information on the forward dynamic simulation can be found in the study by Hakansson and Hull.[37] In brief, a forward dynamic simulation representative of FES pedaling on a commercial ergometer (ERGYS 2; Therapeutic Alliances, Inc., Dayton, Ohio) was developed. The muscle excitation on and off times that satisfied the performance criterion were computed and programmed into the FES ergometer controller. The performance criterion, J, was as follows:

$$J\sum_{i=1}^{p}\int_{t_{0i}}^{t_{fi}}(F_i/A_i)\,dt+\sum_{i=1}^{p}\sum_{j=1}^{p}\left|\int_{t_{0i}}^{t_{fi}}(F_i/A_i)\,dt-\int_{t_{0j}}^{t_{fj}}(F_j/A_j)\,dt\right| \quad \text{for } i\neq j \text{ and only different combinations of } i,j \qquad (1)$$

where F_i is the force of the ith muscle, A_i is the physiological cross-sectional area of the ith muscle, t is time, t_{0i} and t_{fi} are the on and off times, respectively, of the ith muscle, and p is the number of activated muscles. The physiological cross-sectional area was determined by normalizing the maximum isometric strength of the muscle by the maximum active muscle stress. The maximum isometric stress was defined as the specific tension divided by the cross-sectional area. A maximum active muscle stress of 250 kPa was used.[39] The optimal electrical stimulation amplitudes and on and off times were obtained by converting the optimal control problem into a parameter optimization problem[40] and using a simulated annealing optimization algorithm[41] to compute the excitation parameters that both minimized the cost, J, and satisfied a time constraint requiring an average pedaling rate within 1 rpm of the target 50-rpm pedaling rate. The cost, J, as given, minimized the stress–time integral and the difference in the stress–time integral across activated muscles.

Experiments. Experimental data were collected from subjects to test their performance using the computed electrical stimulation timing patterns, Stim3, compared with the stimulation timing patterns currently used by the ERGYS 2 computer-controlled leg cycle ergometer, hereafter referred to as StimErg (Fig. 1). Written informed consent was obtained from 11 individuals (8 men and 3 women) with complete spinal cord injury [American Spinal Injury Association (ASIA) A impairment classification], who volunteered for the 8-week study. The age of the subjects ranged from 18 to 48 years (mean 28 ± 9 years); height ranged from 1.55 to 1.85 m (mean 1.71 ± 0.10 m); body mass ranged from 42 to 89 kg (mean 65 ± 15 kg); and injury level ranged from T4 to T12. All subjects were at least 1 year post–spinal cord trauma (Table 1). None of the subjects had pedaled an FES ergometer prior to the study. The experimental protocol was approved by the institutional review board of the University of California, Davis.

Electrical stimulation pedaling was performed using a computer controlled FES ergometer (ERGYS 2). The subjects' feet were secured in padded boots connected to the pedals. The boots also served to fix the ankle joint in the neutral position (i.e., the foot and tibia form a 90° angle). The ergometer seat was positioned according to the manufacturer's recommendation, where the knee flexion angle was limited to 45° (full extension equals 0°), with the ankle in the neutral position. Pairs of self-adhesive 5 × 10-cm oval electrodes (TENS Products, Grand Lake, Colorado) were placed on the skin over each of the quadriceps (QUADS), hamstring (HAMS), and gluteus (GMAX) muscle groups on both legs. Electrode placements were based on the ergometer manufacturer's recommendations (Therapeutic Alliances) and muscle motor point locations.[42] The proximal and distal anterior thigh electrode centers were

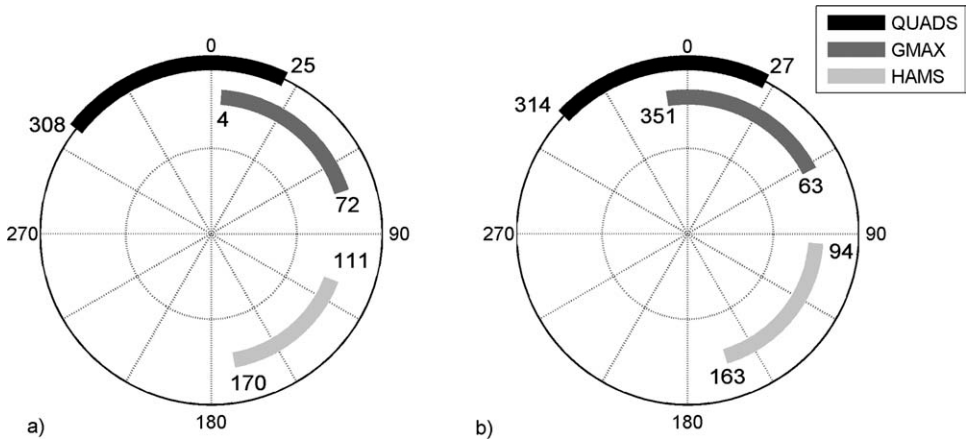

FIGURE 1. Plot of muscle electrical stimulation on and off timing as a function of crank angle for the: **(a)** commercially available electrical stimulation ergometer (StimErg); and **(b)** the minimized stress–time integral for the quadriceps (QUADS), gluteus (GMAX), and hamstring (HAMS) (Stim3) muscle groups. Top-dead-center indicates 0° and the beginning of the crank cycle. The on and off timing angles are listed at the beginning and end of the stimulation for each muscle group.

positioned lateral and medial, respectively, to the line representing the midline of the QUADS to best stimulate the rectus femoris, vastus lateralis, and vastus medialis muscles. The posterior thigh electrode centers were positioned along the line connecting the ischial tuberosity and knee center to best stimulate the biceps femoris, semimembranosus, and semitendinosus muscles. Electrode placement positions were measured with respect to bony landmarks to ensure that the electrodes were placed in the same position during each session.

The experimental protocol was designed to take 8 weeks to complete. Subjects pedaled the ergometer three times per week with a target of 30 minutes total per session during the first 3 weeks to acclimate to FES pedaling, and once per week during the last 5 weeks for experimental data collection. Experimental data were collected once per week to reduce potential training effects between sessions. Because the subjects were not experienced with metabolic tests, the data from the first experimental session for each subject were not used in the analyses. The last 4 weeks of the experimental data collection were divided into two 2-week time blocks. The order of the electrical stimulation timing patterns, StimErg and Stim3, was randomly assigned during the first 2-week time block. The order was then reversed during the second 2-week time block (e.g., week 1: StimErg; week 2: Stim3; week 3: Stim3; week 4: StimErg).

During the acclimation period, subjects pedaled using both the computed and existing stimulation patterns assigned randomly. The FES ergometer computer controller applied a biphasic sinusoidal waveform (500-μs pulse duration and 30-Hz frequency) to each of the electrode pairs. When the crank reached the stimulation on angle, the electrical stimulation ramped up to the set

Table 1. Descriptive characteristics of the subjects.

Subject	Age (y)	Height (m)	Mass (kg)	Injury level	Years postinjury	Gender	Average pedaling time (s)		Metabolic measure time (min)
							StimErg	Stim3	
1*	48	1.65	89	T4	6	M	364	414	—*
2†	18	1.85	57	T6	3.75	M	—†	—†	27–28
3†	20	1.65	64	T10	1.5	M	—†	—†	41–42
4*	30	1.73	55	T9	11	F	312	373	—*
5	26	1.68	61	T10	3	M	955	1018	13–14
6	27	1.73	74	T10	6.5	M	2499	2347	34–35
7	35	1.78	85	T6	1.25	M	1897	2324	27–28
8*	23	1.57	42	T6	6.5	F	268	360	—*
9†	20	1.80	60	T10	2	M	—†	—†	48–49
10	22	1.55	49	T8	3.5	F	1008	923	13–14
11	36	1.83	78	T7	17	M	467	515	6–7

Average pedaling time is tabulated for the two trials with each stimulation timing pattern. The 1-minute time period during which the metabolic measures used in the analysis were recorded is also tabulated.

**Subjects who did not pedal long enough to achieve steady-state metabolic response and were not included in the analysis indicated.*

†Subjects who chose to end at least one test session prior to reaching the 35-rpm termination criterion and were not included in the analysis indicated.

stimulation amplitude. Similarly, the electrical stimulation amplitude ramped down from the ergometer-controlled amplitude to the off angle. The ramp-up and -down portions of the applied electrical stimulation each covered 21° of the crank cycle. For all muscle groups and subjects, the maximum stimulation amplitude was set at 140 mA, which is the maximum output of the FES ergometer computer controller.

At the beginning of each pedaling session, an assistant manually turned the cranks on the ergometer at 44 rpm for 1 minute. After the 1 minute of manual pedaling, the stimulation amplitude was increased to a level such that the subject's muscles were able to pedal the ergometer at the 50-rpm target pedaling rate. The stimulation amplitude was increased (up to the maximum 140 mA) or decreased by the ergometer controller as needed to maintain the target pedaling rate. As muscle fatigue increased, the stimulation amplitude was increased to the maximum 140 mA so as to maintain the target pedaling rate. The controller ended the exercise session when the pedaling rate dropped to <35 rpm. External resistance was applied to the ergometer flywheel by means of an electromagnetic brake. During the acclimation sessions, external flywheel resistance was increased by small increments (0.06 kPa or approximately 3 W at 50 rpm) every 7 minutes once the subjects were able to pedal the ergometer for 15 minutes continuously without applied external resistance during the prior acclimation session. Upon completion of each pedaling run, the ergometer was manually pedaled for the subject for 2 minutes to permit the subject to cool-down.

Tests for the experimental data collection began a week after the final acclimation session. After positioning the ergometer seat and the electrodes, the subject was fitted with a low-dead-space mask for breath-by-breath respiratory gas analysis (MedGraphics CPX/MAX/D; Medical Graphics Corp., St. Paul, Minnesota). The metabolic cart gas oxygen and carbon dioxide analyzers and volume flow pneumotachometer were calibrated prior to each testing session. Respiratory gases data were recorded continuously for the duration of the session. Baseline breath-by-breath respiratory gases data were collected for 5 minutes. After 5 minutes of quiet sitting, baseline blood lactate (Lactate-Pro; Fact Canada, Quesnel, Canada) measurements were made from the subject's earlobe. The subject then underwent 1 minute of manual pedaling at 44 rpm. After 1 minute of pedaling, the stimulation was gradually increased over the first minute until the stimulation amplitude was high enough to permit the subject to pedal under his/her own power. The pedaling rate, stimulation amplitude, and applied external resistance were continuously recorded via custom-written software (MatLab; The MathWorks, Natick, Massachusetts). No external resistance was applied during the first 7 minutes. The external resistance to the flywheel was increased by 0.06 kPa (approximately 3 W) at the end of the first 7-minute period and every 7-minute period thereafter until the sessions were stopped due to the 35-rpm cut-off or the subject's request. At the end of the pedaling session, an assistant manually turned the cranks on the ergometer for 2 minutes to cool-down the subject. The 7-minute time step was chosen to account for the mean response time of oxygen uptake kinetics ($\dot{V}O_2$) to reach steady state.[26,43]

Data Processing and Analysis. The respiratory and pedaling data recorded from each of the subjects were time synchronized. Breath-by-breath $\dot{V}O_2$ data were collected and averaged over the final minute of each 7-minute period (i.e., between minutes 6 and 7, 13 and 14, and so on). Blood lactate concentrations were measured during the last minute of each 7-minute period for the duration of the testing session. At the end of the pedaling session, the subject was manually pedaled for 2 minutes to cool down. Resting baseline values collected during the 5-minute rest period were averaged and subtracted from the $\dot{V}O_2$ measures. Similarly, the resting blood lactate concentration was subtracted from the values collected while the subject actively pedaled. The recorded pedaling rate and external applied flywheel resistance data were combined with the internal friction of the ergometer[43] to calculate the instantaneous pedaling work rate (i.e., power). The pedaling work rate data were averaged over the same 1-minute period as the respiratory data. The total mechanical work performed over the duration of the testing session was computed by integrating the instantaneous pedaling work rate (i.e., determining the area under the power–time curve).

Statistical analyses were performed to address the two objectives of the study. A two-factor, repeated-measures, one-tailed analysis of variance (ANOVA) was used to test the hypothesis that electrical stimulation timing patterns that minimize the stress–time integral and the difference in the stress–time integral across activated muscles, Stim3, enabled an individual with SCI to generate more mechanical work on the FES ergometer than the existing timing patterns, StimErg.[44] The two factors were the electrical stimulation timing patterns at two levels (Stim3 and StimErg) and the 2-week time block during which the electrical stimulation factor was tested (first half and second half). The dependent variable was the log transformation of

the total work generated prior to cessation of the test (35-rpm cut-off pedaling rate). The log transformation was used to account for the increased variance associated with larger work values.[45] The one-tailed analysis was performed because the dependent variable (i.e., mechanical work) was expected to increase due to previous results with the parameters tested (i.e., stress–time integral).[30] A second set of analyses was performed to determine whether differences in the electrical stimulation applied to the muscles could have influenced the mechanical work performed. Two-factor, repeated-measures, one-tailed ANOVA was performed to identify whether there were differences in the electrical stimulation (i.e., current–time integral) delivered to the muscle groups (QUADS, HAMS, and GMAX) when pedaling with Stim3 and StimErg. Similar to the previous analysis, the two factors were the electrical stimulation timing patterns (Stim3 and StimErg) and the 2-week time blocks. The dependent variable was the log transformation of the total current–time integral delivered to the muscle group prior to cessation of the test.

A two-factor, repeated-measures ANOVA was performed to assess whether the average pedaling work rate could have influenced the metabolic measures. The two factors in this analysis were the electrical stimulation timing patterns and the 2-week time blocks. The dependent variable was the averaged pedaling work rate. Because there was not a significant difference in the averaged pedaling work rate, two-factor, repeated-measures ANOVAs were performed to determine whether Stim3 altered the metabolic demand on two metabolic measures, $\dot{V}O_2$ and blood lactate concentration, during the pedaling task. The two factors in these analyses were the electrical stimulation timing patterns and the 2-week time blocks. The dependent variables in these analyses were the 1-minute averaged $\dot{V}O_2$ and the blood lactate concentration. The 1-minute averages occurred over the same minute across all sessions for an individual subject and corresponded to the last minute of the highest 7-minute period reached by the subject in all of his or her experimental testing sessions (Table 1). The level of significance was $P < 0.05$. PASW Statistics, release 18 (SPSS, Inc., Chicago, Illinois), was used for all statistical calculations.

RESULTS

Three subjects terminated a test prior to the 35-rpm designated termination criterion. For the 8 subjects who pedaled until the termination criterion was reached (Table 1), Stim3 resulted in a significant increase ($P = 0.044$) in mechanical work performed compared with StimErg. Based on the difference of the within-subject averages normalized to the average work for all four testing sessions, 11% more mechanical work was accomplished with Stim3 than with StimErg. The average mechanical work accomplished by the 8 subjects with Stim3 was 18.3 ± 17.6 kJ, and with StimErg it was 16.9 ± 16.7 kJ. Of the 8 subjects included in the analysis, 6 generated more mechanical work with Stim3 than with StimErg (Fig. 2). For 4 of these 6 subjects, the increase in total mechanical work equaled or exceeded 10% of the average mechanical work generated over all four testing sessions. There was no significant interaction between the electrical stimulation timing patterns and the time blocks ($P = 0.378$). Analyses of the current–time integral indicate that there was no significant difference in electrical stimulation quantities delivered to the QUADS muscles when pedaling with StimErg and Stim3 ($P = 0.390$). Differences were observed in the electrical stimulation quantities delivered to the HAMS ($P < 0.001$) and GMAX ($P = 0.010$) muscle sets (Table 2). There was no significant interaction between the current–time integral and the time blocks for the QUADS ($P = 0.176$), HAMS ($P = 0.176$), or GMAX ($P = 0.176$).

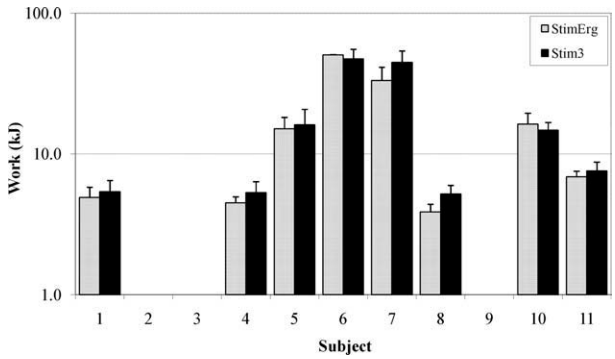

FIGURE 2. Bar chart of the mechanical work generated by the 8 subjects who pedaled the FES ergometer to the 35-rpm cut-off pedaling rate with the StimErg and Stim3 electrical stimulation timing patterns (Table 1). Each bar is the average of the two time blocks. The error bars denote 1 standard deviation.

Three subjects did not pedal long enough for gas-exchange kinetics to reach steady state during the first 7-minute period. For the 8 subjects who reached steady-state gas-exchange kinetics for at least the first 7-minute period (i.e., no external applied flywheel resistance) for each of the four testing sessions (Table 1), the electrical stimulation timing patterns did not have a significant effect on the average pedaling work rate ($P = 0.848$) (Table 3). The average work rate for pedaling with StimErg (21.0 ± 5.4 W) was similar to that for Stim3 (21.4 ± 5.2 W). The electrical stimulation timing patterns did not have a significant effect on $\dot{V}O_2$ ($P = 0.576$) or blood lactate ($P = 0.608$) (Figs. 3 and

Table 2. Measures of the electrical stimulation applied to the QUADS, HAMS, and GMAX muscle groups over duration of testing session.

		Current–time curve			
		Total	QUADS	HAMS	GMAX
Subject 1	StimErg	21.45	8.52	7.15	5.78
	Stim3	23.92	8.90	8.02	6.99
Subject 2	StimErg	—	—	—	—
	Stim3	—	—	—	—
Subject 3	StimErg	—	—	—	—
	Stim3	—	—	—	—
Subject 4	StimErg	15.90	6.32	5.30	4.29
	Stim3	18.78	6.86	6.31	5.61
Subject 5	StimErg	43.16	17.14	14.39	11.63
	Stim3	43.33	16.17	14.53	12.63
Subject 6	StimErg	129.96	51.61	43.32	35.02
	Stim3	121.68	45.27	40.81	35.60
Subject 7	StimErg	135.90	53.97	45.30	36.63
	Stim3	155.52	57.41	52.20	45.91
Subject 8	StimErg	11.65	4.63	3.88	3.14
	Stim3	12.33	4.53	4.14	3.66
Subject 9	StimErg	—	—	—	—
	Stim3	—	—	—	—
Subject 10	StimErg	40.44	16.06	13.48	10.90
	Stim3	39.73	14.93	13.32	11.49
Subject 11	StimErg	25.32	10.06	8.44	6.82
	Stim3	24.55	9.07	8.24	7.24

Quantities measured as the area under the current–time curve. Values are reported as Ampere-seconds.

4). The average $\dot{V}O_2$ and blood lactate concentration for pedaling with StimErg (417 ± 176 ml/min, 5.9 ± 2.3 mmol/L) were comparable to the corresponding averages for Stim3 (442 ± 214 ml/min, 5.9 ± 2.1 mmol/L). Although the interaction between the electrical stimulation timing patterns and the time blocks was nearly significant for the $\dot{V}O_2$ ($P = 0.079$), it was not important. The interaction for the blood lactate was not significant ($P = 0.563$).

DISCUSSION

To enhance the physiological benefits associated with FES pedaling for SCI individuals, it is desirable to increase their pedaling endurance and mechanical work output. Because previous research has demonstrated that the muscle stress–time integral is inversely related to muscle endurance and because a consequence of increased endurance would be an increased capacity for muscular work, the objectives of this study were to determine whether the stimulation timing patterns that minimize the muscle stress–time integral would enable an individual with SCI to generate more work and higher metabolic responses than existing FES ergometer electrical stimulation patterns. The key findings of this study are that the stimulation timing patterns that minimized the stress–time integral increased the mechanical work generated by 11% on average, but did not affect significantly either the rate of oxygen uptake or the blood lactate level.

Table 3. Average pedaling work rate for the subjects during the 1-minute period in which the metabolic measures used in the analysis were recorded.

	Pedaling work rate (W)
Subject 1	
StimErg	—
Stim3	—
Subject 2	
StimErg	22 (0)
Stim3	22 (0)
Subject 3	
StimErg	27 (0)
Stim3	26 (0)
Subject 4	
StimErg	—
Stim3	—
Subject 5	
StimErg	15 (3)
Stim3	15 (3)
Subject 6	
StimErg	24 (0)
Stim3	23 (2)
Subject 7	
StimErg	19 (2)
Stim3	21 (1)
Subject 8	
StimErg	—
Stim3	—
Subject 9	
StimErg	29 (0)
Stim3	29 (1)
Subject 10	
StimErg	17 (0)
Stim3	16 (2)
Subject 11	
StimErg	14 (0)
Stim3	15 (0)

Each value represents the average of the two trials (1 standard deviation).

Before addressing the importance of our findings, a discussion of the methodological limitations

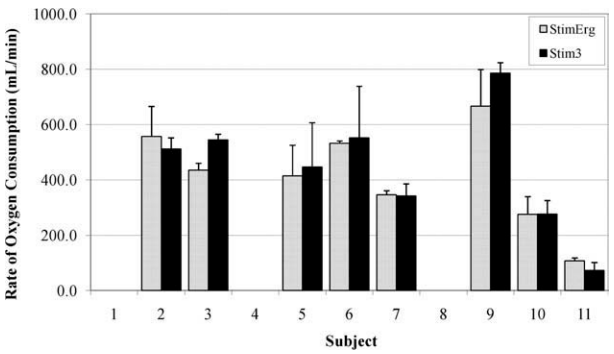

FIGURE 3. Bar chart of the rate of oxygen uptake ($\dot{V}O_2$) recorded from the 8 subjects who were able to pedal long enough with both the StimErg and Stim3 electrical stimulation timing patterns to achieve steady-state $\dot{V}O_2$ kinetics (see Table 1). Each bar is the average of the two time blocks. All values represent the change above resting baseline values. The error bars denote 1 standard deviation.

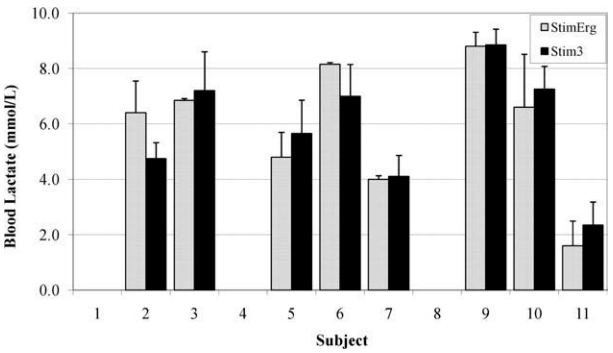

FIGURE 4. Bar chart of the blood lactate concentrations recorded from the 8 subjects who were able to pedal long enough with both the StimErg and Stim3 electrical stimulation timing patterns to achieve steady-state metabolic responses (Table 1). Each bar is the average of the two time blocks. All values represent the change above resting baseline values. The error bars denote 1 standard deviation.

of our study is warranted. The forward dynamic simulations used to determine the optimal electrical stimulation amplitudes and on and off times were developed based on a generic human musculoskeletal model and not subject-specific musculoskeletal models. Subject-specific simulations would have accounted for the muscle–tendon properties (e.g., maximum muscle force, fiber type distribution, fiber lengths, and tendon slack lengths) of the individual subjects in the calculation of the electrical stimulation amplitudes and on and off times and could have led to improved pedaling outcomes. However, the electrical stimulation amplitude-to-force relationship varies greatly among SCI individuals[19,46,47] and depends on many stimulation variables, including electrode placement, muscle strength, fiber-type distribution, and skin impedance. Because the aforementioned stimulation variables would have been difficult to measure and control in the experimental tests and unrealistic to measure in most clinical or home settings, the generic model was used. In addition, because the stimulation amplitude-to-force relationship for the individual subjects was not determined, only the electrical stimulation on and off timing was tested in this study.

A second methodological limitation pertains the control of the subjects' pedaling rate. The ERGYS 2 adjusted the electrical stimulation amplitude applied to the subjects to elicit the pedaling motion. As the muscles fatigued, the electrical stimulation amplitudes delivered to the muscle groups were increased up to the maximum delivered by the ERGYS 2 controller to best maintain the 50-rpm pedaling rate. During three trials—one trial each for 3 subjects— the sustained pedaling rate was below the 50-rpm target for at least 1 minute of the final 7-minute period. The forward dynamic simulation was designed to replicate steady-state pedaling at 50 rpm and did not account for pedaling rates of <50 rpm because we did not foresee that subjects would maintain a pedaling rate below the 50-rpm target. There were no observable negative effects (e.g., jerky pedaling motion or pedaling motion stoppages) as a consequence of pedaling below 50 rpm.

Notwithstanding these limitations, our approach in using a forward dynamic simulation to compute stimulation patterns overcame the disadvantages of previous methods. Previous efforts to determine electrical stimulation timing patterns from physiological measures have used electromyographic (EMG) recordings of non-disabled individuals as they pedal an ergometer.[27,48–51] This method is both convenient and practical and has been demonstrated to work; indeed, StimErg timing patterns are based on such recordings. Yet, there are several disadvantages associated with this approach. First, muscle timing of neurologically intact individuals is influenced by all the leg muscles that can contribute to pedaling. EMG will not address how the muscle timing will change when a subset of the leg muscles are activated, as in FES pedaling. Second, muscle strength and fiber-type composition in muscles of neurologically intact individuals differ from those of paralyzed individuals and may lead to differences in muscle timing. Third, force development timing differs in neurologically activated and electrically stimulated muscle.[20] An advantage of forward dynamic simulations is that the muscle parameters can be adjusted to address the aforementioned issues.

The stimulation timing patterns that minimize the stress–time integral differ from those that have been proposed or tested previously. Compared with StimErg, Stim3 on and off timing patterns shifted earlier in the crank cycle for the HAMS and GMAX and later in the crank cycle for the QUADS. Stim3 also resulted in a similar duty cycle (i.e., 19–20%) for the three muscle groups. In contrast to our approach, Janssen et al.,[52] using a similar ergometer, altered StimErg timing patterns by removing the ramped modulation. The change did not lead to a significant improvement in the total work performed. In a different study, Janssen and Pringle[25] increased the StimErg timing by 55° (20° before and 35° after) and the maximum stimulation amplitude from 140 to 300 mA. These modifications did not result in increased power output in untrained subjects. In another set of studies designed to maximize pedaling power, Gföhler et al.[53] determined subject-specific stimulation patterns using an adjustable FES pedaling ergometer, and Trumbower and Faghri[27] identified timing patterns based on EMG recordings of neurologically

intact subjects pedaling an ERGYS ergometer. To our knowledge, the timing patterns from these studies have not been tested experimentally. The timing patterns for the QUADS, GLUTS, and HAMS from these two studies, as well as several other simulation studies designed to maximize pedaling power,[54–56] enveloped those of both StimErg and Stim3. A disadvantage of increased stimulation duration is the associated longer duty cycle. Previous studies directed at the relationship between duty cycle and endurance in muscle activated by electrical stimulation in a time period similar to that observed in our pedaling study indicate that a duty cycle of 20% resulted in greater endurance than longer duty cycles.[19,57,58]

A majority of the subjects who pedaled to the stop criterion benefited from Stim3 with regard to the mechanical work that they were able to perform. The benefit was notable in that the percent difference in the work between Stim3 and StimErg increased by 6–30% (mean 17%). For the 2 subjects who performed less work with Stim3, the differences were from 6% to 10%. The results indicate that, although Stim3 did not benefit all subjects, for the 75% of those who did benefit, the average mechanical work performed more than doubled the reduction in work by the remaining 25% of the subjects.

The current–time integral analyses indicate the subjects received more electrical stimulation to their HAMS and GMAX muscles, but not to their QUADS when pedaling with Stim3 compared with StimErg. The increases in stimulation to the HAMS and GMAX were likely due to the increase in duty cycles for the HAMS (16% vs. 19%) and GMAX (19% vs. 20%) when pedaling with Stim3 as compared with StimErg (Fig. 1). The shift in duty cycle was driven by the second term of the cost function, Equation (1), which served to distribute the load more equally across the muscle groups. As a result of the differences in the duty cycles and on and off timing of the muscle groups, our theoretical model predicted that there would be an increase in the net mechanical energy generated by the HAMS and a decrease in the net mechanical energy generated by the QUADS and GMAX when pedaling with Stim3 as compared with StimErg.[37] The increased contribution in mechanical energy generation by the HAMS may have led to the increases in the mechanical work generated when pedaling with Stim3.

An earlier study we performed using a forward dynamic simulation of FES pedaling to determine the electrical stimulation timing indicated that Stim3 would increase the work performed by the HAMS and reduce the work of the QUADS and GMAX.[37] Another study on recumbent pedaling demonstrated that the QUADS and GMAX generated most of the work, followed by the HAMS (including the biceps femoris, short head).[59] Other investigators have shown that FES pedaling can be accomplished by the QUADS only,[60] the QUADS and GMAX,[3,61] or the QUADS and HAMS.[62,63] As such, Stim3 may have enabled the increased mechanical work by the 6 subjects through the reduction of the energy demands on the QUADS muscle group.

The findings that there were no differences in the measured $\dot{V}O_2$ and blood lactate concentrations were not surprising based on the experimental protocol design and the low FES pedaling intensity during the experimental testing sessions. Because the 1-minute average of the rate of oxygen uptake and the blood lactate concentration measures were taken over the same minute of the same 7-minute period across trials for each subject (Table 1), the measures were made as the subjects pedaled with the same externally applied flywheel resistance. Although it was possible for the pedaling work rates to have differed, which would have indicated different levels of mechanical work by the muscles and could have affected the metabolic measure, they did not (Table 3). Yet, a difference in the stimulation amplitude applied to the muscles to achieve steady-state pedaling with StimErg and Stim3 may have led to differences in the number of recruited muscle fibers and, in turn, to differences in metabolic responses. In addition, based on the FES pedaling study by Hunt et al.,[26] in which differences in the rate of oxygen uptake were observed between pedaling with two different stimulation timing patterns at the same work rate, we believed that it would be possible to identify differences in the rate of oxygen uptake with our similar experimental protocol. However, the low pedaling work rates during the experimental sessions (Table 3), which were influenced by muscle atrophy, fiber-type conversion associated with disuse from spinal cord injury, and the non-physiological recruitment of muscle fibers with surface electrical stimulation, evidently limited our ability to detect differences in the measured rates of oxygen uptake. The results of our study indicate that the differences in stimulation amplitude and duty cycle pedaling with StimErg and Stim3 were not large enough to change the rate of oxygen uptake.

Although the protocol design may have limited our ability to detect differences in the metabolic responses to StimErg and Stim3, it did not affect the quality of the results. The measured $\dot{V}O_2$ responses were within the range reported previously in other studies,[8,26,61] as were the measured blood lactate concentrations[15,64] and respiratory exchange ratios.[15,61]

Several subjects deviated from the experimental protocol, and thus some of their data could not be used in the statistical analyses. At the request of 3 subjects, at least one of the testing sessions was terminated prior to reaching the stopping criterion. As a result, there was no clear indication on how to appropriately determine the mechanical work they had performed. Consequently, the data for these subjects were not included in the analysis of total mechanical work performed. Also, 3 subjects were unable to pedal beyond 5 minutes during the first 7-minute period for at least one of the testing sessions. Previous research[26,43] and examination of the data indicate that the metabolic responses of these subjects had not yet reached steady state. As such, these subjects were omitted from the metabolic data analysis.

In conclusion, the results of our study hold promise for improving the efficacy of FES pedaling by individuals with SCI. That the mechanical work was significantly increased with Stim3 compared with StimErg indicates that relatively small changes in the stimulation timing patterns to drive the muscles in FES pedaling can lead to advantageous performance outcomes. The results of our study support the use of patterns computed with forward dynamic simulations, which minimize the muscle stress–time integral as a means to increase the efficacy of this exercise modality, provided that the pedaling rate is constant.

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