Review: Clinical Benefits of Functional Electrical Stimulation Cycling Exercise for Subjects with Central Neurological Impairments

Chih-Wei Peng[1,2,†] Shih-Ching Chen[1,2,†,*] Chien-Hung Lai[1,2]
Chao-Jung Chen[1] Chien-Chih Chen[3] Joseph Mizrahi[4] Yasunobu Handa[5]

[1]Department of Physical Medicine and Rehabilitation, Taipei Medical University, Taipei 11031, Taiwan, ROC
[2]Department of Physical Medicine and Rehabilitation, Taipei Medical University Hospital, Taipei 11031, Taiwan, ROC
[3]Department of Physical Therapy, Kaohsiung Medical University, Kaohsiung 80708, Taiwan, ROC
[4]Faculty of Biomedical Engineering, Technion-Israel Institute of Technology, Haifa 32000, Israel
[5]Division of Developmental Neuroscience, Graduate School of Medicine, Tohoku University, Sendai 980-8575, Japan

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Abstract

Functional electrical stimulation (FES) cycling ergometer has been utilized in recent decades for rehabilitation by sequentially stimulating the large leg-actuating muscles of paralyzed leg muscles to produce cyclical leg motion. A number of studies reported physiological adaptations after regular FES-cycling exercise (FESCE) training in subjects with spinal cord injury, stroke, cerebral palsy and other conditions. This article provides a comprehensive overview of general aspects of FES cycling systems and clinical applications of FESCE. The studies cited in this article provide supportive findings for the potential clinical efficacy of FESCE for reducing the risk of secondary medical complications in subjects with paralysis. The potential therapeutic benefits of FESCE include conditioning the cardiopulmonary, muscular, and skeletal systems, and improving other physiological and psychological performances. Our recent pilot study also indicated that the decrease of leg spasticity in subjects with cerebral palsy is one of the acute effects of FESCE. In conclusion, we recommend that FESCE is of benefit in a variety of aspects to improve the general condition and to prevent deterioration in subjects with central neurological impairments.

Keywords: Functional electrical stimulation, Cycling exercise, Spinal cord injury, Stroke

1. Introduction

Individuals with a spinal cord injury (SCI) typically lose motor control and muscle mass of the lower limbs, consequently have limited opportunities for conditioning their lower extremities, and are destined to lead a relatively sedentary lifestyle. This can precipitate secondary disabilities associated with inactivity, such as cardiovascular diseases, bone demineralization, and bedsores [1,2]. Traditionally, physical therapy was administrated to paraplegic patients as functional limb training. However, this requires many medical human resources, and has inadequate clinical efficacy. In recent years, various functional electrical stimulation (FES) techniques have been developed, which can provide alternative and efficient approaches for achieving the activities of daily living (ADLs) and improve the physical fitness of paraplegic subjects. FES is the application of an electrical current to excitable tissue to improve or restore functions lost in neurologically compromised subjects [3]. Currently, FES research for restoring functions to paralyzed lower extremities can roughly be divided into three fields: standing, walking, and cycling.

FES standing is achieved by simultaneously activating both sets of quadriceps and glutei muscles for knee and hip extension, which enables paraplegics to stand from a seated position and transfer to another surface [3]. Currently, there are no commercial FES-standing systems but the Cleveland VA Medical Center and CWRU group is developing an implantable FES standing system with an 8-channel stimulator. The system is now in the multiple clinical trial stage. The first FES systems for restoration of walking in paraplegics were developed in the late 1970s [4]. In later studies, Kralj et al. invented approaches that elicit a flexion withdrawal reflex of the hips, knees, and ankles by stimulating the peroneal nerve, which can produce a

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† These authors contributed equally to this work
* Corresponding author: Shih-Ching Chen
Tel: +886-2-27372181 ext. 1236; Fax: +886-2-55589880
E-mail: csc@tmu.edu.tw

suitable swing-phase gait of the lower extremities [3,5]. Presently, there are several available FES walking systems [6,7].

In contrast to FES standing and walking systems, an FES-cycling system uses stimulator cycling software to control sequential stimulation of the large leg-actuating muscles of paralyzed leg muscles to produce cyclical leg motion. Currently, FES cycling exercise (FESCE) is often used in rehabilitation therapy. There are a number of subsequent investigations reporting physiological adaptations after regular cycling exercise training, which demonstrated that cycling exercise increases muscle strength and endurance and bone density, suppresses spasticity, improves cardiopulmonary function, and provides many other physiological and psychological benefits for subjects with an SCI. This paper provides a comprehensive review of the research findings, including the general aspects of FES cycling system; the therapeutic benefits of FESCE in subjects with SCI; clinical efficacy of FES in subjects with stroke; a pilot study of FESCE in subjects with cerebral palsy; and future developments of FESCE.

2. General aspects of the FES cycling system

2.1 Principles of the FES cycling system

The FES cycling system uses stimulator cycling software to control sequential stimulation of the large leg-actuating muscles of paralyzed leg muscles to produce cyclical leg motion, as shown in Fig. 1. Typically, the quadriceps, hamstrings, and gluteus groups are activated in an appropriate sequence which is out of phase bilaterally to maintain a forward driving torque (Fig. 1(a)). The level of stimulation applied to the muscles (which, in turn, determines the amount of torque and cadence produced at the pedals) is controlled by the stimulation software (Fig. 1(b)). The advantage of FES-cycling over FES-walking and standing exercise is that individuals with paralysis can perform the exercise [8], and it can also enhance an individual’s suitability for FES standing and walking.

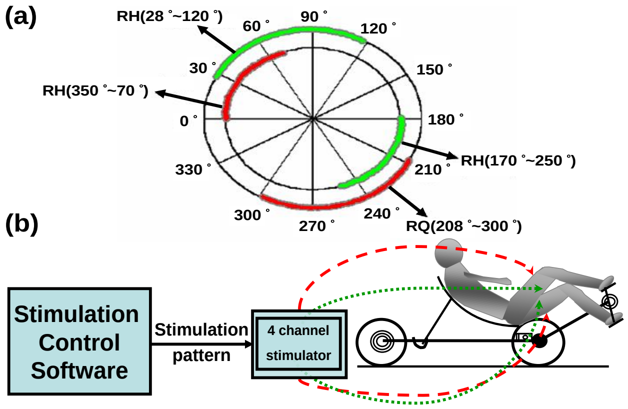

Figure 1. An example of functional electrical stimulation (FES) cycling stimulation control. (a) Schematic of the stimulation control used by stimulator cycling software. (b) Typical stimulated muscle groups and activation angles. 0° is defined when the crank arms are horizontal and the left knee is in extension. RQ, right quadriceps; LQ, left quadriceps; RH, right hamstrings; LH, left hamstrings.

2.2 Development of the FES cycling system

Pioneering work in the application of FES for leg cycling exercise for people with an SCI was first conducted in the early 1980s. The FES cycling device has been first designed for subjects with an SCI [9,10]. Presently, there are many commercial FES cycling ergometers available, such as the BerkelBike (BerkelBike BV, AV's-Hertogenbosch, the Netherlands), Ergys and Regys (Therapeutic Alliances, Fairborn, Ohio, USA), and Motomed (Reck, Betzenweiler, Germany). In general, FES cycling ergometers can be divided into two major types, mobile and stationary types, as tabulated in Table 1. The mobile type, a locomotion device, focuses on muscle training as well as giving some mobility to subjects whose muscles can still be excited. Several research groups have developed a mobile cycling system using standard or recumbent tricycles for SCI subjects [11-13]. Usually, the mobile type of cycling ergometer is an open-loop system, which is not only a rehabilitation modality but also a recreational activity [14].

Table 1. Characteristics of two major types of FES-cycling ergometers.

	Mobile type	Stationary type
Candidate patient	Incomplete SCI	SCI, stroke
Commercially available	No	Yes
Control method	Open loop	Close loop
Physical size	Large	Large, small for home-use
Application	Locomotion, therapeutic training, and recreation	Aerobic exercise training and symmetrical training

The stationary type of cycling ergometer is usually used for aerobic exercise training in subjects with an SCI to condition their muscle strength and enhance cardiopulmonary function. Recently, it was also used in symmetrical limb-movement training in subjects with a stroke [90]. Figure 2(a) shows a typical stationary FES cycling system with closed-loop control software (developed at National Cheng Kung University, Tainan, Taiwan), which has been used in many clinical centers [15]. Sometimes FES cycling devices are combined with certain accessories for specific purposes, e.g., an arm-crank for the purposes of upper-extremity training or warm-up exercise, as shown in Fig. 2(b) [16].

2.3 Considerations of FESCE training

It is well known that extreme inactivity due to paralysis can lead to physical deconditioning and produce medical complications. On the other hand, FESCE training might be a safe and efficient means to help subjects with paralysis to improve their physical fitness. However, most subjects with an SCI initially find it difficult to pedal the FES-cycle crank due to the muscle deconditioning of the bilateral paralyzed legs. In order to prepare the paralyzed muscles for FES-cycle training, subjects usually need to undertake a series of isometric FES training exercises on the bilateral paralyzed leg muscles in advance. Muscle conditioning is performed until subjects are capable of pedaling on an FES-cycle system without significant

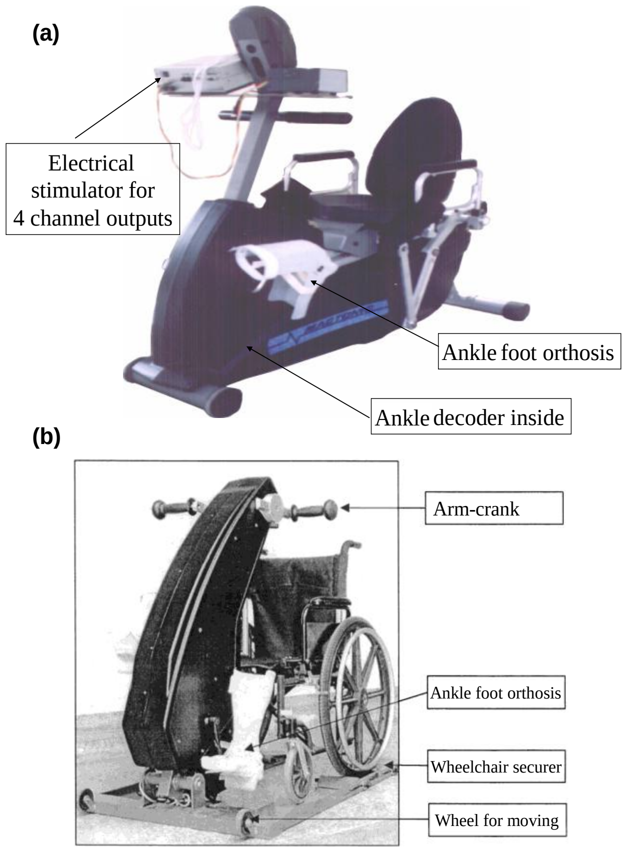

Figure 2. Types of stationary FES-cycling ergometer developed at National Cheng Kung University, Taiwan, including (a) a traditional ergometer for clinic center use and (b) a hybrid ergometer for home use [16].

resistance, which usually takes at least 1~2 weeks of isometric training [17].

From another aspect, the time course and training frequency are major factors that determine the therapeutic effects of cycling exercise. However, there are still no consistent verdicts about the minimum training time course for subjects with an SCI to achieve significant physical fitness. This is because after deconditioning, the training course of different physical organs may vary in order to achieve therapeutic adaptation. For example, studies demonstrated that cardiovascular adaptations were observed after 2 weeks of FESCE training [18]; whereas, to obtain therapeutic benefits of the skeletal system usually requires several months of cycling training [19]. In addition, the exercise intensities of cycling training such as the crank resistance, pedal cadence, and duration of each training session may also affect therapeutic outcomes. Regardless of the training time course and exercise intensities, it is commonly recommended that subjects with an SCI receive at least 2-3 times per week and 30 min per time in a cycling rehabilitation program. This is based on an exercise physiological viewpoint that the exercise training should persist for more than 30 min to reach the anaerobic threshold [20]. In addition, it was reported that detraining from cycling exercise can soon induce a quick reversal of physical fitness within 1 week [18]. Thus, subjects with an SCI need to continue the FESCE as a daily activity to maintain the therapeutic benefits.

The selection of electrical stimulation parameters is also an important issue considered in FESCE studies. Commonly, the FES cycling stimulation current is delivered to the large paralyzed leg muscles via surface electrodes. The stimulation output can either be regulated current or regulated voltage, which depends on the control design of the FES cycling stimulator. Generally, the regulated current approach is independent of the electrode-tissue impedance. A regulated-current stimulus (of magnitude of I) with pulse with t will deliver a fixed total charge Q per stimulus, such that $Q = It$. Regardless of electrode impedance and potential shift, because the current of the stimulus is regulated, the electrical field seems to be consistent in the area of the stimulated tissue. Therefore the regulated current approach is easy to reproducibly apply to the motor control of leg muscle activation. However, regulated current stimulation can possibly produce skin burns due to an increase in the current density if the surface electrode becomes dislodged or broken. Unlike the regulated current approach, the electrical field around the electrode-tissue interface is hard to predict for regulated voltage and the activation of the stimulated muscles may be less reproducible. However, it is not likely to incur skin burns even if the electrode becomes dislodged from the skin (i.e. an increase of impedance and a decrease of magnitude of current). Nevertheless, before conducting any FESCE, it is important to make sure that subjects have a good arrangement for the surface electrodes.

Moreover, the leg pedaling power output is usually controlled by modulating the intensity of the stimulating current with fixed values of the stimulation pulse width and frequency. Commonly, the stimulation frequency is selected in the range of 10~50 Hz. However, a relatively higher stimulation frequency (> 50 Hz) can produce higher forces and therefore higher power for pedaling the ergometer compared to lower stimulation frequencies (10~50 Hz). But higher stimulation frequencies may rapidly result in ATP depletion at neuromuscular junctions and cause muscle fatigue [21]. Therefore, when choosing stimulation parameters for cycling training, one should consider a subject's physiological condition as well as the intended cycling performance.

3. Clinical efficacy of FESCE in subjects with SCI

3.1 Therapeutic effects on the cardiopulmonary system

Subjects with paralysis are consequently destined to a relatively sedentary lifestyle, which can result in marked adaptations of cardiac deconditioning and vasomotor dysregulation [22,23], such as structural and functional adaptations in the peripheral vascular system of the paralyzed limbs, as tabulated in Table 2. These cardiopulmonary adaptations include a reduction in conduit artery diameters [18,24-26], diminution in capillarization [27,28], and decreases in the baseline and peak blood flows to the legs [27,29,30]. On the other hand, these adaptations also reflect a reduction in activity, a decrease in the subject's ability to utilize oxygen (aerobic capacity), and a predominant decrease in the oxidative capacity of the fast-twitch muscles [31,32].

Table 2. Therapeutic effect of FES-cycling studies on cardiopulmonary system.

	Before FESCE training	After FESCE exercise training
SCI subject's physiological conditions	↓Conduit artery diameters [19,25-27] ↓Capillarization [28,29] ↓Blood flow to the legs [28,30,31] ↓Oxidative capacity in leg muscles [32,33]	↑Cross area of arteries and density of capillary [34-37] ↑Blood inflow volume to legs [34-37] ↑Aerobic capacity and ventilation [42-45] ↑Oxygen uptake kinetics [9,46] ↑Left ventricular mass, left ventricular end-diastolic volume, and LDL [48,49]

LDL: low-density lipoprotein.
(↓) indicates a dramatic decrease compared to control data; (↑) indicates a dramatic increase compared to control data.

Currently, FESCE training is the most feasible approach for subjects with an SCI to effectively exercise their paralyzed legs and reverse the impaired blood flow to the paralyzed limbs. Many studies have reported that FESCE training can increase the cross-sectional area of the arteries and the density of capillaries and improve the blood inflow volume to the lower limbs [33-36]. This increased vascular capacity is primarily attributed to peripheral adjustments, such as vascular growth or altered vascular control in response to exercise-induced mechanical or metabolic changes, and may be partly responsible for the improved exercise performance seen during FESCE training [33]. The time course and training intensity are important factors determining the therapeutic effects of these cardiovascular adaptations. Some studies indicated that at least 2~4 weeks of FESCE can lead to arterial adaptations in subjects with an SCI [18,34,35]. However, other studies concluded that 6~8 weeks of FES-cycling training is a suitable time course to obtain therapeutic effects [27,33,37,38]. This discrepancy might result from different intensities of FESCE training. In addition, a recent study further indicated that detraining rapidly reversed these vascular adaptations within 1 week [18].

In the clinic, the aerobic capacity is commonly assessed by the peak oxygen uptake (V_{O2}) and oxygen uptake kinetics [39,40]. Several studies reported that after 12~26 weeks of FESCE training, 20%~35% elevations in the peak oxygen uptake (aerobic capacity) and ventilation were seen in subjects with an SCI [41-44]. Peak V_{O2} values after training were approximately l L/min. This is equivalent to the O_2 cost for an able-bodied 70-kg man walking at a pace of 3.5 mph or cycling at 50 watts (W). Besides the therapeutic benefit of the peak oxygen uptake, some studies also indicated that FES training in subjects with an SCI significantly elevated their oxygen uptake kinetics, such as increasing the forced vital capacity (FVC), forced expiratory volume at 1 s (FEV_1), forced inspiratory capacity (FIC), cardiac output (CO), and stroke volume (SV) [9,45].

According to several studies, subjects with an SCI are at higher risks of developing cardiovascular diseases [1,46]. This can result from the SCI significantly reducing a subject's metabolic and cardiopulmonary functions as well as their peripheral and central hemodynamic responses [22,24]. However, data predict that the risk of cardiovascular disease in subjects with an SCI can significantly be reduced after long-term regular FESCE training. Studies indicated that subjects with an SCI increased the left ventricular mass by 4.1%, the left ventricular end-diastolic volume by 2.5%, and high-density lipoprotein by 6% after 12~20 weeks of training [47,48]. All these results suggest that FESCE can improve the cardiopulmonary capacity as well as reduce the risk of cardiovascular disease, as tabulated in Table 2.

3.2 Therapeutic effects on the muscular system

Based on an exercise physiological viewpoint, it is recommended that exercise should persist for more than 30 min to reach the anaerobic threshold [20]. However, many untrained SCI subjects have difficulty in performing prolonged FESCE, since their sedentary lifestyle has led to a decreased oxidative capacity, weak muscle strength, and poor fatigue resistance [8]. As indicated above, deconditioned cardiovascular functions of subjects with an SCI can be reversed by FESCE. Therefore, it is reasonable that the muscle endurance and peak power output of subjects with an SCI will improve after several months of FESCE training [49-51]. Moreover, FESCE training can also increase the muscle mass and muscle strength in subjects with an SCI [52,53].

On the other hand, several studies reported that FESCE training converted the skeletal muscle fiber-type toward more oxidative (slow-twitch) muscle fibers [54,55], due to increases in the concentration of oxidative enzymes and mitochondria in the paralyzed muscle groups. The muscle fiber-type conversion can alleviate the phenomenon of muscle fatigue during FESCE. In addition, several studies showed that FES-cycling training can increase the circumference of the lower limbs resulting from hypertrophy of the thigh and leg muscles [56-58]. Hence, the gained training benefits of muscle fatigue-resistance and muscle hypertrophy may be the reasons why FESCE training improves a subject's muscle endurance capacity and power output during cycling. Additionally, subjects paralyzed by an SCI are characterized by increased body adipose tissue and reduced lean body mass. However, it was found that FESCE can efficiently increase the muscle-to-adipose tissue ratio in the thighs and calves [58,59].

Subjects with an SCI usually suffer from severe spasticity, which commonly occurs in their affected extremities, and this often leads to muscle and joint contractures, severe functional impairment, significant discomfort, and disruption of ADLs. Studies have evaluated the effects of FESCE training on changes in spastic muscle tone, but the results are still controversial. Several results demonstrated that FES cycling training can effectively reduce spasticity; these were from subjects' groups of small sample sizes [60-63]. However, other study indicated that FESCE may reduce the period and frequency of spasticity, but subjects often reported that their spasticity became more intense [8]. This might have resulted from the increased muscle strength after FES-cycling training.

Table 3. Therapeutic effect of FES-cycling studies on muscular system.

	Num. of patients	Mean age (range)	Post-injury average year	Training intensity	Training duration	Lesion level	Effect on BMD
Griffin et al. [51] (2009)	18	34(27-57)	11	30min/2-3 day/wk	>2.5 mo.	C4-T7	↑Lean muscle mass
Donaldson et al. [52] (2000)	1	52	10	21min/7day/wk	16 mo.	T11-T12	↑Muscle mass, muscle power
Szecsi et al. [50] (2009)	11	46.8	10.9±8.1	30 min./3 days/wk	~1.5 mo.	None	↑Muscle power output
Murphy et al. [54] (1999)	3	37.3(26-48)	14.3±7.5	30min/2 day/wk (drug T'x)	0.5 mo.	C6-T4	↑muscle mass, ↑muscle strength
Sipski et al. [57] (1993)	28	None	None	5~30min/2days/wk	4 mo.	None	↑Muscle mass, endurance,↓spasticity
Scremin et al. [58] (1999)	13	34.0(24-46)	10.0±5.0	30min/2days/wk	12 mo.	C5-L1	↑Muscle mass
Krause et al. [62] (2008)	5	46.(37-66)	7.3±2.1	60-100 min/day	1 day	T3-T7	↓Spasticity
Skold et al. [53] (2002)	15	33(21-48)	9	30 min./3days/wk	6 mo.	None	↑Muscle mass

(↓) indicates a dramatic decrease compared to control data; (↑) indicates a dramatic increase compared to control data.

Table 4. Therapeutic effect of FES-cycling studies on skeletal system.

	Num. of patients	Mean age (range)	Post-injury years	Training intensity	Training duration	Lesion level	Effect on BMD
BeDell et al. [77] (1996)	12	34 (23-46)	9.7±5.1	30 min/day, 3 days/wk	> 4 mo.	C5-T12	↑LS, (=)T, (=)WT, (=)FN,
Hangartner et al. [78] (1994)	15	25 (18-46)	6.3±4.8	30 min/day, 3 days/wk	3-12 mo.	C5-T10	↑DT, ↑PT
Leeds et al. [75] (1990)	6	23.6 (18-27)	2 to 9	30 min./day, 3 days/wk	7 mo.	C4-C6	(=)FN, (=)WT,(=)T
Chen et al. [20] (2005)	15	28.6 (23-37)	2 to 13	30 min/day, 5 days/wk	6 mo.	C5-T8	↑DF, ↑PT
Mohr et al. [79] (1997)	10	35 (27-45)	2 to 24	30 min/day, 3 days/wk	12-18 mo.	C6-T4	(=)FN, (=)LS,↑ PT
Bloomfield et al. [2] (1996)	9	28.2 (21-39)	6.0±1.2	30 min/day, 3 days/wk	9 mo.	C5-C7	↑LS, (=)FN, (=)DF, (=)PT
Belanger et al. [76] (2000)	14	32.4 (23-41)	9.6±6.6	60 min/day, 5 days/wk	6 mo.	C5-T5	↑DF, ↑PT
Sloan et al. [74] (1994)	2	47.3 (39-54)	0.6 to 4.5	30 min./day, 3 days/wk	6-12 mo.	C5-T12	(=)FN, (=)LS

LS: lumbar spine; T: trochanter; WT: ward triangle; FN: femoral neck; DT: distal tibia; PT: proximal tibia; DF: distal femur.

(↑) indicates a dramatic increase compared to control data; (=) indicates no significant difference between before and after FESCE training.

When investigating the joint range of motion (ROM), many studies reported that FESCE is effective in increasing the knee-joint ROM, and the therapeutic benefits might be attributed to alleviation of muscle contracture in subjects with an SCI, but few studies have been done on stroke populations [62,64,65]. The benefits of FESCE training on the muscular system are listed in Table 3.

3.3 Therapeutic effects on the skeletal system

Osteoporosis is a well-known complication in people with paralysis [66,67]. Loss of bone mineral density (BMD) is predominant in paralyzed limbs. Several studies reported a consistent verdict of the extent and timing of the loss of bone mass after an injury [17,68-70]. During the first year after an SCI, the BMD drops by close to 20% at multiple sites in the femur, and during the next 5 years at approximately 2%~6% per year in the femoral neck, femoral mid-shaft, and distal end. Subjects with an SCI have an increased risk of fractures as a result of minor trauma [17], and the estimated incidence of fractures is twice that of able-bodied people [71,72].

Many studies have evaluated the effects on BMD of subjects with an SCI after FESCE training, but the results are controversial [2,19,73-79]. Several studies found no differences in BMD of the lower limbs between before and after several months of FESCE [74,76,77]. However, other studies suggested that a reduced rate of SCI-induced bone loss or even an increase in bone density of paralyzed limbs occurred after chronic FES-cycling training, as shwon in Table 4 [2,19,77,78].

A study by Chen et al. showed that the distal femur and proximal tibia significantly increased in BMD after 6 months of FESCE training [19]. Similarly, studies reported increases of 10%~18% in the BMD of the distal femur or proximal tibia in subjects with an SCI who use a higher power output of training, but no increase in subjects after lower power output training or a short period of training [2,78]. Therefore, the magnitude of FESCE loading might directly affect the therapeutic effects on BMD. Thus, FESCE can potentially reverse neurogenic osteoporosis and subsequently reduce pathological fractures in subjects with an SCI, although there is still a lack of clarity about the optimal level of FESCE training to obtain therapeutic effects on BMD. From another aspect, long-term immobilization of joints can result in some abnormal changes to lower limb joints, such as a reduction in the joint-loading ability and degeneration of articular bones and cartilage. One study revealed that FES-induced exercise may contribute to alleviating these problems [80].

3.4 Other therapeutic benefits

Studies indicated the prevalence of type 2 diabetes mellitus (DM) conditions in subjects with an SCI was higher than that in able-bodied subjects, since the paralyzed muscles in the lower limbs significantly reduced glucose tolerance and exaggerated hyperinsulinemia during glucose loading [59,81]. Studies indicated that FESCE training has substantial benefits of increasing insulin sensitivity and preventing insulin-resistance syndrome in subjects with an SCI [50,82]. This is because the effect of insulin on glucose uptake in skeletal muscles is improved [83].

From another aspect, pressure sores are a common problem in subjects with an SCI, and they usually occur in the areas of gluteal soft tissue over bony prominences. These represent great health risks to subjects with an SCI [84]. A study by Petrofsky [85] indicated that the prevalence of pressure sores in subjects with an SCI who participated in regular FESCE was dramatically reduced by approximately 90%. The therapeutic effects resulted from FESCE increasing the capillary density, blood circulation, and muscle mass of the gluteal soft tissue. Recent studies further indicated that surface electrostimulation of gluteal muscles can effectively release interfacial pressure and restore blood flow in this region [86]. Thus, these results indicated that FESCE should be helpful for preventing pressure sores in subjects with an SCI. Moreover, several studies indicated that the functional performance, including dressing, transferring, standing, walking, and ADLs, of subjects with an incomplete SCI or stroke improved after 1~16 months of FESCE training [50,51,73,87]. Those improvements may have resulted from general improvements in cardiopulmonary fitness and the aerobic reserve capacity achieved by FESCE training. In addition, many studies reported that FESCE training has psychological benefits such as improving self-reliance, one's self-image, and social abilities [88,89].

4. Clinical efficacy of FES in subjects with stroke

For FESCE training in subjects with stroke, multiple therapeutic effects were demonstrated in many clinical studies. A study indicated a 6-week FESCE training program can markedly improve aerobic capacity in subjects with chronic stroke, evidenced by increases of V_{O2} peak and P_{Omax} by 13.8% and 38.1%, respectively [87]. On the other hand, postural imbalance or asymmetrical limb movement between affected and unaffected limbs are commonly observed in post-stroke subjects [90-92]. Recently, leg cycling exercise was considered a possible modality to overcome the asymmetrical lower limb movement in subjects with a stroke [91,93,94]. This was demonstrated by a recent study which found that an FES-cycling ergometer for training symmetrical movements in stroke subjects significantly increased symmetrical performance by 10% as well as improved the smoothness of cycling [90].

Approximately 80% of subjects poststroke recover some locomotor functions. However, many present with significant gait deficits, including reduced gait speeds [1] and spatiotemporal abnormalities. In general, effective gait training is among the goals of neurological rehabilitation after stroke. Many investigators indicated that hemiplegic patients received functional gait trainings at early stage of post-stroke is more effective than at chronic stage [95], and the functional recovery from stroke becomes inefficient beyond 5 months after the onset of stroke [96]. Thus, the FESCE can be a feasible rehabilitative tool for acute stroke patient to early receive pre-ambulation training. This is because the cycling exercise is a less balance requirement activity compared to conventional over-ground gait training in clinic, and thus it reduced the risk of falling. In addition, the electrical current of FESCE stimulated on paretic legs could produce repeated sensory inputs and enhance brain plasticity and cortical motor output.

In addition to FESCE and conventional over-ground gaiting, the robotic-assisted locomotor training (or called the body weight-supported treadmill training) is a newly developed pre-gait training device, which was first reported in the early 1990s. The device may improve overground walking in subjects with central neurological disorder, such as subjects with incomplete SCI, cerebral palsy, multiple sclerosis, and stroke. During clinical training, the device offered various settings to alter stepping speed, limb loading, mechanical assistance for stance and swing, step length, joint angles and other parameters. Thus, stepping was assisted in the way of the passive mechanical assistance of a robotic gait orthosis, thereby eliciting precise gait-specific proprioceptive input-information that is thought to facilitate motor learning by contributing to the development of an accurate internal representation for the movement experience. In addition, studies have now documented that sensorimotor activity in one leg affects the motor output of the opposite leg. Many studies indicated that the training has been shown to yield greater increases in locomotor ability than conventional rehabilitation protocols [97,98]. A study by Hornby et al. [99] showed that the robotic-assisted locomotor training facilitated improvements in walking speed and duration of the single limb stance time in subjects with chronic stroke. Recent studies reported that a modest dose of the robotic-assisted locomotor training is effective for improving overground walking speed and gait symmetry, and other lower extremity impairments and physical function in subjects with chronic hemiparesis post-stroke [97]. Similarly, a study by Macko et al. [100] reported that the aerobic training by the robotic-assisted locomotor trainer improves both functional mobility and cardiovascular fitness in patients with chronic stroke and is more effective than reference rehabilitation common to conventional care. Mayr et al. [98] further indicated the robotic-assisted locomotor training significantly improve the function of lower extremities, including walking speed, endurance, muscle strength, and muscle tone in subjects with stroke.

Some studies further combined FES in the robotic-assisted locomotor training [101,102]. Ng et al. [101] linked two FES stimulators to the control box of a gait training device, which were set to synchronize the gait phase and the stimulation timing for the quadriceps and the common peroneal nerve, respectively. The subject’s quadriceps in the paretic side were stimulated in the stance phase to facilitate weight acceptance, and his or her common peroneal nerve in the paretic side was stimulated during the swing phase to elicit ankle dorsiflexion and knee flexion. This study indicated a higher effectiveness in poststroke gait training that used the robotic-assisted locomotor training combining FES compared with conventional over-ground gait training. The training effect was sustained through to the 6-month follow-up after the intervention. Another study indicated that the combined use of FES with robotic-assisted locomotor training led to a significant improvement in motor recovery and the gait pattern of subjects with hemiparesis [102].

Table 5. Therapeutic effects of various pre-gait trainings in subjects after stroke.

	Num. of patients	Mean age (Range)	Post-injury years	Therapeutic modality	Training intensity	Training duration	Effect on BMD
Janssen et al. [87] (2008)	12	54.2±10.7	1.0±0.5	FESCE	30 min/day, 2 days/wk	1.5 mo.	↑WS, ↑aerobic capacity
Szecsi et al. [90] (2008)	39	68.7±10.9	2.8±5.9	FESCE	30~50 min/session	1 session	↑cycling power, ↑symmetry
Hornby et al. [99] (2008)	24	57.0±10.0	4.2±4.1	RALT	30 min/session	12 session	↑WS, ↑ST
Westlake, Patten [97] (2009)	8	58.6±16.9	3.6±2.2	RALT	30 min/day, 3 days/wk	1 mo.	↑WS, ↑SL, ↑balance
Mayr et al. [98] (2007)	8	65.6±11.7	0.3±0.3	RALT	30 min/day, 5 days/wk	1.5 mo.	↑WS, ↑MS, ↑MT
Ng et al. [101] (2008)	16	62.0±10.0	<0.1	RALT-FES	20 min/day, 5 days/wk	1 mo.	↑WS, ↑balance, ↑LF
Lindquist [102] (2007)	8	56.6±10.2	17.3±10.9	RALT-FES	45 min/day, 3 days/wk	2.2 mo.	↑WS, ↑ST, ↑SL
Lo et al. [63] (2009)	17	56.4±7.3	<0.1	LPWE	60 min/session	1 session	↓Spasticity
Tsai et al. [103] (2007)	15	53.0±9.5	1.5±0.8	LPWE	30 min/day, 3 days/wk	0.7 mo.	↑Cardiopulmonary function

RALT: robotic-assisted locomotor training; RALT-FES: robotic-assisted locomotor training combined FES; LPWE: leg-propelled wheelchair exercise.

(↑) indicates a dramatic increase compared to control data; (↓) indicates a dramatic increase compared to control data.

WS = walking speed; MS = muscle strength; MT = muscle tone; ST = stance time of impaired leg↑; SL = step length↑; LF = function of lower extremity.

In contrast to the robotic-assisted locomotor devices for pre-gait training, some innovative leg-propelled wheelchairs were developed for subjects after stroke. The innovative wheelchairs were propelled with one's legs instead of one's arms. Makino et al. [103] proposed a wheelchair with 2 pedals propelled by both legs. Bloswick et al. designed knee-extension wheelchairs that can be propelled using residual legs functions for elderly, which might be able to be operated with the unaffected leg by stroke patients [104]. Recently, Tsai et al. developed two types of unilaterally leg-propelled wheelchairs [105], and Lo et al. designed a FES-assisted leg-cycling wheelchair [63]. The above studies have demonstrated that leg exercise provides higher physiological efficiency than arm exercise with respect to wheelchair propulsion. Although there is still fewer studies reported the clinic benefits of these innovative wheelchairs, it is believed that, besides the locomotion function, the leg exercise of the wheelchair may also improve one's physical fitness. The therapeutic effects of FES, the robotic-assisted locomotion, and leg-propelled wheelchairs on pre-gait exercise training are tabulated in Table 5.

5. Pilot study of FESCE training on spastic conditions in subjects with CP

A preliminary study of the effects of FESCE training on the spastic condition of the lower extremities in children with CP was conducted in Taipei Medical University Hospital. Spasticity can severely impede joint ROM and functional abilities in the lower extremities of children with CP. Recent studies demonstrated that FESCE in subjects with an SCI can reduce lower-extremity spasticity [60-63]. But few studies have explored the physiological effects of FES cycling on CP subjects. Therefore, it is worth examining the potential clinical benefits of FESCE on CP subjects.

In this pilot study, three young children with CP (with a mean age of 3.0 years, range 2~3.5 years) participated in an FESCE program. The inclusion criteria were: having quadriplegic CP; having muscle responses to trial electrical stimulation; and never having undergone FES therapy. The exclusion criteria were: unhealed or recent bone fractures; the presence of muscle contractures in a lower extremity; poorly controlled autonomic dysreflexia; heterotopic ossification; severe spasticity; a range of lower-limb mobility that limited safe cycling; a history of cardiovascular disease; a history of pulmonary disease; a recent history of psychological disease; a history of parathyroid or thyroid disease; and an injection of botulinum toxin-A in the lower extremities.

Stimulation parameters of FESCE were a pulse frequency of 20 Hz and a current amplitude of 30 mA. The stimulation intensities were controlled by the current pulse duration (100~300 μs) via a multi-channel stimulator (Hasomed, Magdeburg, Germany). Electrical stimulation was sequentially applied to the bilateral quadriceps and hamstrings to achieve a rhythmic pedaling motion. FES cycling programs were conducted 30 min per time three times a week. The individuals required an exercise protocol based on the muscle status of their lower limbs. Initially, an individual pedaled with a minimal resistance load, and the load during exercise was gradually increased. The modified Ashworth scale (MAS) [106], leg drop pendulum test, and myotonometric measurements were conducted each time before and immediately after the FESCE training.

The MAS was used to evaluate the severity of spasticity of the bilateral extensor muscles of the legs (quadriceps muscles). The data of MAS were independently measured by two investigators, and then averaged. During the test, subjects sat on a bench that allowed the lower leg to freely swing against the upper leg. The investigator passively moved the lower leg against the upper leg to detect an increase in the spastic muscle tone.

For the pendulum test, a subject sat in an upright position. An electrical goniometer was placed on the knee joint to record the free swinging movements of the lower leg against the upper leg. These movements normally consist of a damped pendular swinging. The analogous output of the goniometer was connected to an analog to digital converter (ADC) to digitize and store the data for offline analysis on a personal computer. Five complete pendulum tests were performed with each leg, and the average value was further analyzed.

A myotonometer (Neurogenic Technologies, Missoula, MT, USA) is an instrument to measure tissue compliance to evaluate spastic conditions. The instrument consists of a probe that noninvasively pushes onto a muscle. Transducers within the probe measure the amount of underlying tissue displacement per unit of force applied to the muscle by the probe. Length-tension curves are generated from these recordings that show the amount of stretch to the muscle per unit of applied force. Tissue compliance meters were shown to be valid and reliable measures of muscle tone and compliance [107]. Myotonometer measurements were taken of the bilateral rectus femoris muscles at rest and during maximal voluntary isometric contraction (MVC).

In this study, the spastic conditions of the lower extremity (LE) were evaluated before and immediately after a session of FESCE. Our preliminary results showed all measured MAS scores decreased after FESCE, as shown in Fig. 3. The results implied that FESCE might acutely alleviate spastic conditions of the LE in children with CP.

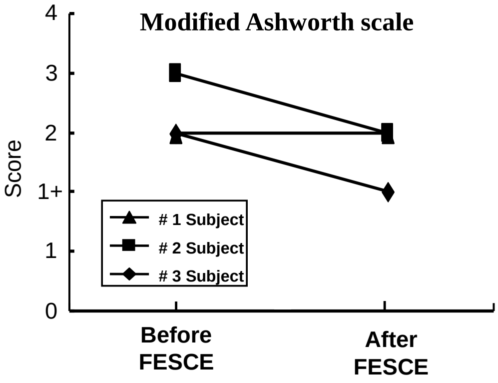

Figure 3. Acute effects of FESCE on the spastic condition of the lower extremities measured by the modified Ashworth scale. Data were taken from three subjects before and after FESCE.

Meanwhile, pendulum testing was also conducted to determine the immediate effects of FESCE on the severity of spasticity of the legs. Two parameters were measured from the raw data, including the relaxation index (RI) and average velocity. The RI is expressed as the ratio of (the first flexion angle – the onset angle) to (the resting angle – the onset angle) [62]. The average velocity is represented as the ratio of (the first flexion angle – the onset angle) to (the time interval from the onset angle to the first flexion angle). Our results showed that after an FESCE intervention, all RI and average angle velocity values exhibited an increase tendency compared to the those of before FESCE (Fig. 4).

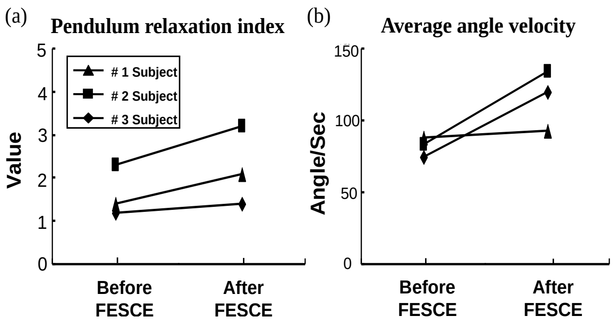

Figure 4. Acute effects of FESCE on the spastic condition of the lower extremities evaluated by pendulum testing. (a) The relaxation index and (b) velocity calculated from recorded data (taken from three subjects before and after FESCE).

An example of myotonometer recordings (0.025~2 kg) of the rectus femoris muscle at rest and at the MVC is shown in Fig. 5(a). The areas under the receiver operating curves (AUCs) generated during resting and MVC conditions were computed, respectively. Then the difference between two AUCs was further calculated. The smaller the difference between the two AUCs, the more severe the spasticity of the tested muscle was. Figure 5(a) shows an example of the difference in the AUC before FESCE, which was 1.3 mm × kg, which was smaller than that (2.0 mm × kg) immediately after a session of FESCE. Figure 5(b) shows the difference in the AUC before and after FESCE, which were derived from three subjects. The results indicated that the average difference in the AUC increased with an FESCE intervention, although no statistical significance was found. This pilot study demonstrated that FESCE might be a feasible modality for reducing the leg spasticity in subjects with CP.

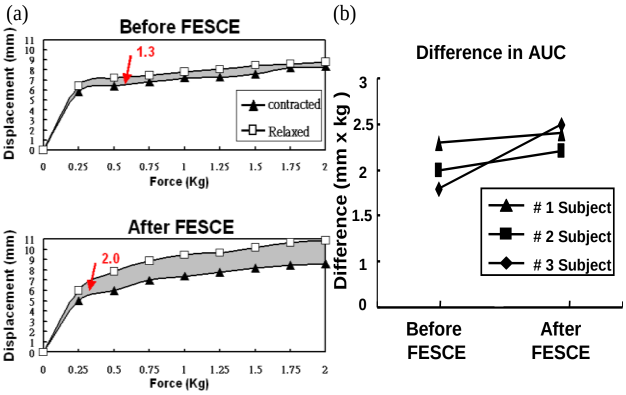

Figure 5. An example of myotonometer recordings of the rectus femoris muscle (a) before and immediately after a session of FESCE. Measurements were taken during resting and maximal voluntary isometric contraction at force levels of 0.25~2 kg. (b) Calculated results of the difference in the area under the curve (AUC) were taken from three subjects before and after FESCE.

6. Future developments

This article offers a comprehensive review of the research findings that recommend that lower-limb FESCE training can provide multiple health benefits for subjects with paralysis. In addition, studies showed that FESCE is safe, effective, and accessible to subjects with SCI, CP or stroke. Although the potential therapeutic benefits of FESCE training are immense, cycling exercise is currently still not widely prevalent among subjects with paralysis. Because most subjects find it difficult to travel back and forth daily to a clinical center, which may reduce the feasibility of participating in cycling exercise training. Therefore, development of an in-home, low-cost FES-cycling ergometer might be a feasible way to promote the wide use of the cycling device among subjects with paralysis.

The device can also be combined with communication transmission techniques, which can wire the recorded training data to a clinic to evaluate a subject’s cycling performance and readjust their training protocol. If the FES cycling device can be successfully applied as a home-use unit, cycling exercise would become an integral part of an individual's lifestyle. This can make the therapeutic benefits of FESCE more efficient. As the goals are accomplished, we might expect a great reduction of medical costs by FESCE.

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