Functional electrical stimulation in neurological disorders

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Functional electrical stimulation (FES) refers to electrical stimulation of muscles in order to improve the impaired motor function. This is achieved by activating skeletal muscles with constant frequency trains of stimulations. This method has been found useful in various neurological disorders like hemiplegia, foot drop and paraplegia including spinal cord injuries. The first half of this review focuses on the broad clinical applications of functional electrical stimulation, its mechanism of action and the complications of this mode of therapy. Advanced Parkinson's disease (PD) is characterized by marked slowing of gait and frequent freezing episodes. Medical and surgical treatments are often ineffective in managing freezing episodes. The second half of this review discusses briefly the gait abnormalities in PD and the available treatment options. The possible role of FES in improving gait in parkinsonism and the importance of future research in this direction are highlighted.

What is FES?

Functional electrical stimulation (FES) has been described as the electrical stimulation of a muscle deprived of nervous control for providing muscular contraction and thereby producing a functionally useful movement. Liberson et al. in 1961, proposed, that electrical stimulation of the peroneal nerve could improve gait in hemiplegic patients [1]. Electrical stimulation of the anterior tibial muscles can be coordinated with the gait cycle, and can improve gait quality in patients with a central foot drop [1]. The motor nerves can be activated by surface or implanted electrodes. When these pulses are applied to motor nerves, action potentials are generated, which travel along the axon to the target muscle. The motor nerves of the targeted muscle must be intact for the action potentials to be propagated [2]. Repetitive electrical stimulation of the common peroneal nerve elicits lasting changes in corticospinal excitability, possibly as a result of co-activating motor and sensory fibers [3].

How stimulation is carried out

Several types of stimulator devices are available depending upon the purpose for which they are used [2]. The majority of these devices were developed for one specific treatment purpose, or to restore a single bodily function. If users want to use an FES system designed for one purpose to carry out another, they will be required to modify either the stimulator's hardware or software, or both. As such alterations are often impractical, many researchers and practitioners in the FES field were forced to develop their own stimulators. FES devices which can be used for multiple purposes have now been developed [4,5].

Functional electrical stimulation-assisted walking involves stimulating the relevant leg muscles in a coordinated fashion so as to perform the walking motion. The peroneal nerve is the main nerve to be stimulated. The lower-limb muscle groups that are activated include the hip flexors and extensors, knee flexors and extensors, and the ankle plantar flexors and dorsiflexors [6,7]. From a biomechanical point of view, FES of the ankle plantar flexors results in an increased ground clearance of the lower extremity [6]. Additionally, the FES-assisted lifting of the heel results in the elimination of extensor tone and thus shortening the swing time [6].

Studies have proved that the FES-assisted walking improves walking endurance, speed, and lower-extremity muscle strength [8,9]. Examples of stimulators available for assisted walking include Unistim or WalkAide (l-channel) devices and the Quadstim (four channel) device. The Unistim device employs a hand switch to turn stimulation on and off. With the Quadstim device, flexors are stimulated when a hand switch is pressed and extensors are stimulated when it is not [10].

Methodology

Conventional foot drop stimulator has a heel sensor which is connected to the stimulator with wires. Newer stimulators have radio frequency communication between foot sensor and stimulator. When the lower leg is tilted back at the end of stance phase, the tilt sensor

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turns on a train of stimuli. When the leg tilts forward just after the foot strikes the ground, the stimuli turns off. The surface electrodes are placed over common peroneal nerve (cathode) near the head of the fibula and over the tibialis anterior muscle (anode). Stimulator is attached around the upper part of the leg using a velcro. A foot sensor is placed in the shoe (or sole) so that it can detect and measure the pressure exerted by the heel on the ground as well as the tilt of the leg. A software is used to calculate the threshold for turning on stimulation for optimum results. Stimulation time and other time parameters are to be set manually or automatically [11].

**Current applications of FES**

Most FES systems today are pre-programmed to perform tasks specific to the needs of the individual. The major areas of application include: assisted walking in paraplegia [10,12,13], cases of spinal cord injuries [14–16] and in hemiplegic gait training [10,17–19]. The therapeutic effect of FES-assisted walking may derive from many factors such as plasticity of both the peripheral and central nervous system being the major one. Muscles activated by either electrical or voluntary means, undergo changes in the property of their fibers [20].

Other areas where FES has been used with success include quadriplegia [21,22], cerebral palsy [23], urinary incontinence [24,25], vestibular dysfunction [26], sexual dysfunction [14,27,28], and recurrent laryngeal nerve palsy [14,29].

**Long-term effects of FES**

Long-term use of FES in spinal cord injury has been shown to result in improvement in voluntary strength, decrease in energy cost, increase in maximum walking distance and speed, increase in step length and improvement in joint kinematics [30]. Many patients report a carry over benefit for several days even after turning off the stimulation [20,31]. The superiority of the FES method as compared with conventional physiotherapy in hemiplegic patients is mainly attributed to the enhanced motor learning accomplished by application of FES [32]. Osteopenia of the distal femur and proximal tibia and the loss of strength of the quadriceps also can be partly reversed by regular FES-assisted training in individuals with spinal cord injuries [33]. Subjects with walking speed deficits caused by spinal cord injury or cerebral damage who walk at less than 1 m/s obtain particular benefit from FES [34].

Long-term benefits of FES system has been questioned by some authors [35]. According to them, the skeletal muscle is a dynamic tissue, which continuously changes its properties in response to demand. This adaptive capacity should always be taken into account by those seeking to design stimulators for chronic use, and by those responsible for monitoring their effectiveness over time.

**Mechanism of benefit**

There are possible central as well as peripheral mechanisms, which contribute to benefit in functional electrical stimulation [36]. The peripheral mechanism of therapeutic benefit is by improvement in muscle strength, increase in muscle stretch and reduction of the spasticity [36]. One of the central changes implicated in mechanism of benefit is cortical reorganization and neuronal plasticity. This mechanism plays a major role in the recovery of stroke patients treated with FES [37]. FES, particularly when applied through surface electrodes, activates both motor and sensory nerve fibers. High-frequency sensory stimulation may in itself be capable of modifying cortical connectivity [38]. In studies on the rat, evidence has been put forward that this might occur through the expression of the c-fos gene, both in the brain [39] and in the dorsal horn of the spinal cord [40].

**Functional neuroimaging in FES**

Functional magnetic resonance imaging (fMRI) studies following electrical stimulation of the median nerve has revealed ipsilateral and contra lateral activation of somatosensory. The locations of the contra lateral and ipsilateral responses in somatosensory cortex differed, and the region of the ipsilateral response was located posterior to the region of the contra lateral response following stimulation of the median nerve [41]. Simultaneous electroencephalography (EEG) and fMRI measurements have been performed in healthy subjects to determine the representation of stimulation of the right thumb in somatosensory cortex. In all subjects, EEG-based dipole locations could be determined in primary and secondary somatosensory cortex [42]. The dipole located in the contra lateral primary sensory cortex was systematically more inferior to the blood oxygenation level dependent response seen in fMRI studies [42].

**Chemical changes**

Chronic electrical stimulation or FES exercise training of paralyzed human muscles results in an increase in muscle oxidative capacity, as indicated by an increase in oxidative enzymes [43]. Studies in humans and animals
have indicated that changes in glucose transporter protein levels precede changes in oxidative enzymes.

The long-term FES endurance exercise training results in an increase in GLUT-1 and GLUT-4 levels and in the oxidative capacity of paralyzed skeletal muscle in individuals with spinal cord injury (SCI) [43]. GLUT-4 is involved in insulin and exercise stimulated glucose uptake, and GLUT-1 is involved in glucose uptake in the basal, non-insulin-stimulated state. Evaluation of tissue health measured through monitoring tissue oxygen levels in the ischial region and measuring interface pressures at the seating support interface showed a quantifiable benefit following FES use [44].

Functional electrical stimulation also results in a significant rise in norepinephrine levels in plasma [45]. Histochemical analysis of quadriceps after FES showed that the size and number of type IIa fibers increased significantly [46]. FES is also found to increase the endothelin and creatine kinase level in patients with spinal cord injury [43,47]. Elevation in the endothelin level is particularly important in maintaining baroreceptor-mediated blood pressure control after spinal cord injury [47].

Mean serum testosterone levels significantly increased with FES-assisted resistance training in SCI and no significant changes were noted in hematocrit, sex hormone binding globulin, Prolactin, epinephrine, and cortisol levels [48,49].

Disadvantages of FES

Most current FES systems employ a simple stimulation pattern, i.e., a constant frequency train with equally spaced pulses, with frequencies ranging from 20 to 50 Hz. However, muscles get fatigued rapidly as a result of artificial activation. Clinicians often increase the stimulation frequency or intensity to maintain the needed forces as the muscles fatigue. Unfortunately, both high stimulation frequency and intensity accelerate the rate and level of fatigue [50]. Thus, it is important to optimize the stimulation strategy to minimize energy expenditure and fatigue.

The ‘catch like’ property of skeletal muscle is the force enhancement produced when a brief, high frequency burst of pulses (2–4 pulses) is added to a subtetanic train of pulses [51]. Stimulation trains that take advantage of the ‘catch like’ property have been shown to produce greater forces than trains commonly used during clinical application of functional electrical stimulation [51]. The variable frequency and short duration trains of electrical pulses, which makes use of the ‘catch like’ property, may provide significant advantages over any constant frequency trains of stimulation, in reducing fatigue [52].

A few patients reported pain in using the system and discontinued its usage [53]. Some patients reported skin irritation secondary to stimulation. In order to prevent these complications and to make the system more user friendly, implantable systems with implantable batteries have been designed [54].

In spite of reports of marked psychological improvement in some patients [55,56], an unrealistic expectation about improvement following FES use may result in depression and hostility in patients [55].

Clinical trials with FES

A multicentric non-randomized study which tested 26 patients with central foot drop of more than 1 year duration reported that walking speed improved 15% after 3 months, 32% after 6 months and 47% after one year [57]. Eighty-seven percentage of the patients were satisfied with the therapy on a ‘satisfaction questionnaire’ [57].

In a non-randomized study, Merletti et al. reported clinical improvement in 76% of 50 hemiplegic patients treated with FES [58]. Kim et al. compared functional electrical stimulators with ankle-foot orthosis in subjects with incomplete spinal cord injury and reported that FES has an advantage over ankle-foot orthosis in increasing foot clearance values [59].

A randomized study involving 29 patients to look at the efficacy of implantable peroneal nerve stimulator reported a 23% improvement in the walking speed in stroke patients treated with this method [60]. Though this is an incomplete list of studies with FES, it can be seen that most of the studies were non-randomized and involving small number of patients. Large-scale randomized trials with FES system will be required for getting wider clinical acceptance for this mode of therapy.

FES and Parkinsonism

Gait in Parkinsonism

Gait hypokinesia (slowness) is a characteristic feature of Parkinson’s disease (PD). Festinating gait was first associated with Parkinsonism by Sir James Parkinson, in his original essay on ‘The Shaking Palsy’.

Parkinson’s disease gait is characterized by a particular difficulty with the internal regulation of stride length [61]. Cadence control (steps/min) remains unaffected throughout its entire range [62]. The gait hypokinesia is directly attributable to an inability to internally generate sufficiently large steps [62]. PD subjects have a higher cadence rate than control subjects for any given velocity; however, this increased
Freezing of gait

Freezing of gait (FOG) can be defined as a transient halt in motor activity, wherein the patient appears as if nailed to the floor. Freezing episodes and related phenomena or motor blocks (MBs) are a poorly understood, a particularly disabling and a therapeutically frustrating problem in PD [65]. The prevalence of freezing in PD increases with disease duration, occurring in up to 53% of the population after 5 years of illness [66]. Studies have revealed that FOG may occur in very early stages of idiopathic PD, in up to 26% of patients who were not yet exposed to levodopa (L-dopa) [67].

Five types of FOG can be identified according to the subgroup classification of Fahn, (i) start hesitation, when freezing was detected as the patient initiated walking, (ii) turn hesitation, when the feet appeared to become stuck whilst making a turn, (iii) apparent hesitation in tight quarters (i.e., when FOG was noted when the patient passed through a narrow space), (iv) destination-hesitation, when the feet appeared to freeze as the patient approached a target (the final 2 m of the task), and (v) open space hesitation (i.e., when the patient experiences a spontaneous freezing episode whilst walking in an open space without an apparent provoking factor such as a doorway) [68]. Freezing was found frequently in patients with vascular parkinsonism (57%), normal-pressure hydrocephalus (56%), and generally in the group of patients who had parkinsonism (progressive supranuclear palsy, multiple system atrophy, and corticobasal ganglionic degeneration; 45%) [69].

When PD presents as a gait disorder without tremor, there is higher risk of FOG [70]. Some authors have suggested a significant association between the existence of MBs and levodopa-induced dyskinesia, suggesting a similar pathophysiology [65].

Yanagisawa and colleagues studied electromyographic (EMG) activity of leg muscles in PD patients with FOG. In these patients, they observed ‘a unique but non uniform patterns of EMG’ and suggested that rhythmic contraction of leg muscles beyond a certain rate is a factor causing FOG [71]. The presence of complex rhythmic oscillations during FOG may reflect a coordinated, but ineffective attempt to overcome freezing. Consistent patterns of premature timing of tibialis anterior and gastronomies activity occurred before freezing, which was interpreted as a disturbance of central gait cycle timing [72]. The total amount of EMG activity was reduced in both the lower limb muscles because of the shortened time in which the muscles were active. In contrast to gastrocnemius, activity in TA showed increased amplitudes of the EMG bursts, indicating a compensation strategy of pulling the leg into swing. These changes contribute to insufficient forward progression, deceleration and eventually a breakdown of movement [72]. Strides performed just before FOG are characterized by decreasing stride length (with stable cadence) and suggest that failure to time and control the sequence of gait cycles causes a diminishing stride length which, in turn, leads to freezing [73]. FOG is related to asymmetric gait performance and reduced bilateral motor coordination of gait [74]. The treatment of FOG is often frustrating to the patient as well as treating physicians.

Pharmacological and surgical approaches

Freezing of gait that appears predominantly during ‘off’ states, improves with levodopa, in contrast to the ‘on’ state FOG, which is worsened by levodopa [75]. Levodopa treatment only increases the threshold at which FOG occurred, but did not change the basic pathophysiology. Dopamine agonist treatment was associated with an increased frequency of FOG in two double blind prospective studies in early PD [67,76,77]. Both unilateral and bilateral sub thalamic stimulation can alleviate off state FOG, but on state FOG may not improve much [67].

Injection of botulinum toxin into the calf muscle has been attempted to improve freezing in PD [78]. A clear relationship between botulinum toxin A injections into the calf muscles of parkinsonian patients and the resulting improvement of FOG was noted in the pilot study [78].

Non-pharmacological approaches

The Research into Cueing (RESCUE) trial investigated the effects of a home physiotherapy program based on rhythmical cueing on gait and gait-related activity. Small but significant improvements were found after intervention. Severity of freezing was reduced by 5.5% in freezers only. Gait speed and step length showed improvement [79]. Different types of visual cue for subjects with PD produced an improvement in gait and helped some of them to prevent or overcome freezing episodes. Stripes placed on the walking surface may draw attention to the stepping process, if patients are encouraged to put their feet on the stripes [80]. Optical stimulating glasses that provide different types of continuous optical flow (backward or forward) and
intermittent stimuli synchronized with external events in the peripheral field of view, have been used to overcome freezing [81]. Assistive devices, specifically based on visual cues, are not consistently beneficial in overcoming ‘on’ freezing in most patients with PD [82]. The basal ganglia and their frontal projections may be one of the essential lesion sites for FOG. A recent study using single-photon emission tomography revealed enhanced lateral pre-motor cortex (PMC) activity during paradoxical gait in PD, suggesting that PMC can compensate for the impaired function of the medial frontal cortex when cued by visual input [83].

Rhythmic auditory stimulus (RAS) training also can improve functional locomotor patterns of walking in parkinsonism [84,85]. Faster RAS produced significant improvement in mean gait velocity, cadence, and stride length in PD patients. Close synchronization between rhythm and step frequency in PD patients suggest evidence for rhythmic entrainment mechanisms even in the presence of basal ganglia dysfunction [84]. EMG patterns in tibialis anterior and vastus lateralis also changed significantly in patients on rhythmic auditory stimulation [85].

The future

Both PD patients and normal controls showed a marked increase in the force and velocity of their movements when a cutaneous cue was used as a ‘go’ signal [64]. Dopaminergic therapy and an external stimulus similarly improved the deficient force production for the anticipatory postural adjustments associated with step initiation in PD [64]. Usefulness of botulinum toxin in FOG shows that altering the contractile property of the lower limb muscle could relieve FOG, though it involves a central pathology. Moreover, EMG studies during FOG have shown that there is evidence of rhythmic contraction of leg muscles at the onset of FOG. So, it is logical to think that if we alter the activity of the muscles especially tibialis anterior and gastrocnemius, at the onset of a freezing episode, using a FES, it could initiate a new gait cycle. This can be achieved with the help of a switch attached to the waist band, which can be operated by the patient or the caregiver to turn on the FES device. FES may also improve slowness of gait in PD if used on a continuous basis.

A PubMed search on use of functional electrical stimulation in PD yielded no related articles. As FES is a non-invasive treatment, it would be interesting to test FES in PD patients with gait abnormalities, for any beneficial effect. An FES software, which can stimulate tibialis anterior and gastrocnemius in PD patients would need to be developed, for this specific purpose.

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