
Functional Electrical Stimulation of Skeletal Muscles in Aging and Premature Aging

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11.1 Structural and Molecular Markers of Muscle Weakness and of Recovery Induced by h-b FES

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Aging is an unavoidable process, if lethal diseases do not prematurely end survival. A final evidence of this obvious concept has been recently provided by Gava et al. [1], describing the power decay of the series of world records obtained by master athletes (from 30 to 100 years). Skeletal muscle power begins to decline at the age of 30 years and continues, almost linearly, to zero at the age of 110 years. During aging, many factors contribute to the decline of the skeletal muscle, including sub-clinical and reversible muscle denervation/reinnervation [2]. Recently, we added evidence that denervation contributes to atrophy and slowness of aged muscles by comparing muscles of lifelong active seniors to those of sedentary elderly people. We found that the sportsmen have more muscle mass and slow fiber groupings, providing in this way evidence that physical activity maintains slow motoneurons, which reinnervate muscle fibers [3–5]. A premature muscle atrophy/degeneration occurs in irreversible and complete *conus* and *cauda equina* syndrome consequent to a lumbar/sacral spinal cord injury, determining a complete loss of muscle fibers within 5–8 years [6–8].

The impact of muscle denervation on aging skeletal muscle fibers is a relatively orphan topic [9, 10]. This is related in part to the difficulties in determining by molecular approaches whether motoneurons release chemical neurotrophic agents to the muscle fibers of the motor units. It is well known that such mechanism contributes to neuromuscular junction development and maintenance. However, if and which chemical trophic factors influence the synchronized expression of the hundreds of nuclei belonging to a single muscle fiber remains a subject of hypotheses. The synchronized spread of muscle action potential seems to be, on the contrary, a more rational mechanism [11]. On the other hands, the conclusions of recent reviews

[8, 9, 12] are that FES is poorly used in rehabilitation of elderly patients. Aging skeletal muscle presents both a loss of muscle mass and a conspicuous reduction in myofiber plasticity [9, 12–14] and alterations in muscle-specific transcriptional mechanisms. During the aging process, protein synthetic rates decrease, and an increase in protein degradation follows [15, 16], affecting muscle fibers [17]. It is generally recognized that an ineffective damage repair is a contributory cause of functional impairment during aging [18–20] and promotes the detrimental replacement of functional contractile muscle with fibrous tissue [17]. Volitional physical exercise can reverse these damaging processes. Interestingly, it has been shown that both acute and prolonged resistance exercises stimulate the proliferation of satellite cells in healthy sedentary elderly subjects [21]. This fact may be explained by the increased levels of myostatin, a negative regulator of muscle mass. An increase in autophagy in the muscle of athletic people has been reported, suggesting that exercise may activate an important system that detoxifies muscle cells [22]. Another important factor that is associated with physical exercise is insulin-like growth factor 1 (IGF-1) [23]. The evidence suggests that training and regular exercise can increase muscle strength and attenuate sarcopenia by modulating expression of autophagy, myokines (IL-6), and IGF-1 [24].

Unfortunately, elderly people may be unable or reluctant to adequately participate in physical exercise. We therefore suggested that FES could be an alternative approach. A stimulator for neuromuscular electrical stimulation (ES), which especially suits elderly people requirements, was designed. As detailed in Kern et al. [15], older persons were exposed to regular neuromuscular ES training for a period of 9 weeks, starting two times a week for the first 3 weeks and then switching to three times a week for the next 6 weeks, for a total amount of 24 training sessions (3×10 min for each session). After detailed instructions, ES training was performed by the subjects themselves at home, using a two-channel custom-built battery-powered stimulator [25]. The subjects applied two conductive rubber electrodes (9×14 cm, 126 cm²) which were attached to the skin by wet sponge on the anterior thigh on both sides (left/right). The electrode pairs for the left and right thigh were connected to the two channels of the stimulator. This allowed independent activation of the left and right thigh muscles, which were alternatively stimulated. Each repetition (muscle contraction) was evoked by a 3.5 s train (60 Hz) of electrical pulses (rectangular, biphasic, width 0.6 ms). Consecutive contractions of the same thigh were separated by 4.5 s off intervals. In this study, constant voltage stimulation devices were applied. The subjects were also instructed to increase the stimulation intensity until their maximal tolerance was reached. Using this intensity, a full knee extension was achieved in all subjects. Nevertheless, the applied current and voltage were recorded by the stimulation device for each training session (the mean stimulation current was 128 ± 16 mA and voltage of 39 ± 14 V). The outcome was an increase in muscle strength, associated with an increase of fast fibers, which are the first to respond to ES and are related to the power of the skeletal muscle [14, 15]. We found that ES increases expression of IGF-1, the markers of satellite cell proliferation and extracellular matrix remodeling, downregulating the expression of proteases [14, 58]. There is also a collagen remodeling during both volitional physical

exercise and ES. Three different forms of collagen are upregulated in electrically stimulated muscle [14, 15], but the increase in collagen does not likely stimulate fibrosis, as is shown by both morphological evidence and the increase in expression of miR29 [26]. The INTERREG IVa project recruited sedentary seniors with a normal lifestyle who were trained for 9 weeks with ES. Functional tests of trained subjects showed that ES induced improvements of leg muscle strength and mobility [27, 28]. ES significantly increased the size of fast-type muscle fibers and the number of Pax7- and NCAM-positive satellite cells. Moreover, no signs of muscle damage and/or inflammation were observed in muscle biopsies [14, 15]. Altogether, the results here summarized demonstrate that physical exercise, either voluntary or induced by ES, improves the functional performance of aging muscles. Of course, physical training can't stop the aging process, but ES is a safe home-based method that is able to counteract atrophy of fast-type muscle fibers.

Age-related muscle power decline is partially attributable to a loss of innervation, and it can be delayed by a lifelong high-level activity [3–5]. Diseases involving permanent denervation show a similar, but premature, aging process and a much more severe muscle deterioration. Despite doubts and criticisms of related literature [29, 30], we have shown that, with appropriate protocols, h-b FES can even inhibit degeneration of denervated muscle and even reverse it [31–33]. Therefore, the use of h-b FES should be extended in critical care units, rehabilitation centers, and nursing facilities and at home of elderly persons in presence of peripheral nerve lesions to improve hopefully muscle reinnervation [34–37].

11.2 FES for Partially Denervated Muscle and FES Protocols for Training of Denervated–Degenerated Skeletal Muscle

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Functional electrical stimulation (FES) was introduced more than 50 years ago to identify those applications of electrical currents to organs and tissues of humans and other large mammals to obtain responses mimicking and/or restoring lost functions [38]. Spinal cord injury causes loss of functions and muscle wasting, which are especially severe after lower motor neuron (LMN) lesions. During the last decades, a great attention has been paid to denervated muscles, numerous studies focusing on the changes in gross anatomy, mechanical properties, and potential for reinnervation of skeletal muscle when the lesions involve the LMN. Results in literature are at best contradictory, and claims suggest that electrical stimulation of partially denervated muscles may even interfere with nerve regeneration [7]. During the last decade, we studied the effects of physical exercise induced by FES in spinal cord injury (SCI) with complete *conus* and *cauda equina* syndrome, in which denervated leg muscles are permanently and completely disconnected from the nervous system.

Denervated human muscles become refractory to the electrical stimulation developed by the common electrical devices and undergo ultrastructural disorganization within few months, while severe atrophy with nuclear clumping and fibro-fatty degeneration appears within 3 and 6 years [8, 9]. To counteract these progressive changes, a novel therapy concept for paraplegic patients with complete LMN denervation was developed in Vienna: the home-based FES (h-b FES) for denervated–degenerated muscles. New electrodes and a safe stimulator have been designed to reverse severe atrophy by delivering high-intensity (up to 2.4 J) and long-duration impulses (up to 150 ms) to stimulate contractions in long-term denervated skeletal muscle fibers. A specific clinical assessment and training, based on sound evidence from animal experiments, was developed at the Wilhelminenspital in Vienna, Austria. After 2-year training using h-b FES, the patient showed (1) significant increase of muscle mass and myofiber size with striking improvements of the muscle ultrastructural organization; (2) recovery of tetanic contractility with significant increase in muscle force output, during electrical stimulation; and (3) capacity to perform FES-assisted stand-up and stepping-in-place exercise. In conclusion h-b FES of permanent denervated muscle is an effective home therapy that results in rescue of muscle perfusion, mass, and function. Additional benefits are reduced leg edema, prophylaxis of thromboembolism, and enhanced cushioning effect for seating [32]. In our clinical experiences, nerve regrowth is not inhibited by FES of partially denervated muscles. On the contrary, we observed sensory or motor reinnervation (or both) during the application of high intensive stimulation training even 2–5 years after injury [39]. The complex response of muscle tissue to denervation is one of the most studied processes in muscle physiology and pathology. One of the important conclusions of pioneering studies is that, after a certain period of time (6 months in the rodents), denervated muscle undergoes some irreversible changes that inhibit its full restoration even after reinnervation. Findings from different experimental models, including free autotransplant, led to the same conclusion: after 2–7 months of denervation the restorative capacity of the muscle declines progressively in rat [40]. These observations were translated to the macroscopic behavior of the denervated human muscle and its potential for reinnervation, establishing a dogma that continues to negatively influence clinical management of denervated muscle. Despite countless published results [41], our recent studies in animal models and humans are enlightening several unrecognized characteristics and behaviors of the complex processes that occur during permanent LMN denervation of the human muscle tissue. These results are strengthening the rational basis of FES to maintain/recover permanently LMN denervated muscles. Some of the effects of long-lasting (in terms of years) LMN denervation of the human muscle we recently described were unexpected. In contrast to the well-known rodent model, the LMN denervated human muscle presents simple atrophy up to 1 year after SCI [7]. On the other hand, the characteristic denervation-induced muscle fiber disorganization in the atrophying muscle, documented by electron microscopy, occurs much earlier [7]. The ultrastructural disorganization of the muscle fibers that appears much earlier than severe atrophy in both animal models [42, 43] and humans [6, 7, 32, 44] explains the early functional impairments of the LMN denervated muscle. Until

today, muscles of the extremities in *conus* and *cauda equina* syndrome were commonly not treated with FES, because it was widely recognized that long-term and completely denervated muscles cannot be effectively stimulated. On the other hand, our studies in animal models and humans indicate that (1) severe atrophy does not occur in rats for at least 3–4 months [40, 41]; (2) in rabbit, the degeneration of muscle tissue does not appear in the first year after denervation [43]; and (3) muscle tissue degeneration starts from the third year onward, in humans [32, 33, 42, 44]. Our findings that the long-term denervated rat muscle maintains L-type Ca²⁺ current and gene expression of the related proteins longer than functional contractile machineries [45] provide the molecular, structural, and functional rationale of a rehabilitation training for human permanently denervated muscles, which was developed as a result of empirical clinical observations [32]. The FES device stimulates muscle fibers in the absence of nerve endings and after prolonged denervation, determining (1) restoration of muscle fiber ultrastructure, (2) recovery of conduction velocity of the excitation–contraction apparatus up to a level that allows tetanic contraction, and (3) the maintenance/recovery of muscle mass and fiber size. Before this, electrical stimulation was believed to be effective only when started very early after LMN lesion, and FES was used only to delay muscle atrophy, since long-term denervated muscles (6 months onward) do not respond, when stimulated by surface electrodes and standard commercial electrical stimulators developed for innervated muscles. The results of the EU RISE Project [32, 33, 42, 44], and of the related animal research [43, 45], provide different perspectives.

11.2.1 Stimulation Devices and Electrodes

During the last 20 years, clinicians and engineers developed in Vienna novel rehabilitation concepts for paraplegic patients with complete LMN denervation of the lower extremity due to complete lesion of the *conus* and *cauda equina*. To counteract the progressive changes that transform muscle into an unexcitable tissue, these new rehabilitation managements became possible due to the development and optimization of new stimulation devices for h-b FES. They have been specifically designed to reverse longstanding and severe atrophy of LMN denervated muscles by delivering high-intensity and long-duration impulses that can directly elicit contraction of denervated skeletal muscle fibers in absence of functional neuromuscular endplates. These new stimulators and the large surface electrodes needed to cover large denervated muscles were developed by the Center of Medical Physics and Biomedical Engineering at the Medical University of Vienna, Austria [46–48]. Based on these prototypes, an electrical stimulator for denervated muscle is now commercially available, the “Stimulette den2x” of the Schuhfried Medizintechnik GmbH, Vienna, Austria [49]. Patients were provided with stimulators and electrodes in order to perform stimulation at home for 5 days per week. Large (180 cm²) electrodes (Schuhfried Medizintechnik GmbH, Mödling, Austria) made of conductive polyurethane were placed on the skin surface using a wet sponge cloth (early training) and fixed via elastic textile cuffs. As soon as the skin was accustomed to the

necessary high current density, gel was used under the polyurethane electrodes to achieve minimal transition impedance. The electrodes were flexible enough to maintain evenly distributed pressure to the uneven and moving skin, thus providing homogeneous current distribution throughout the entire contact area. In parallel, specific clinical assessments and training settings were developed at the Wilhelminenspital Wien, Austria [50–54].

11.2.2 Training Protocol

Details of the four phases of this rehabilitation strategy are summarized in Table 11.1 and Fig. 11.1. The rehabilitation training for complete denervated muscles was validated by the clinical outcome, strongly supported by the results obtained from light and electron microscopy muscle biopsies' analyses performed in Padua and Chieti Universities (Italy), respectively, and described by Kern et al.

Table 11.1 FES training of relatively short-term denervated (1–2 years) human muscles (Adapted from Kern et al. *Neurorehabil Neural Repair*. (2010); 24:709–21)

Training time (months)	Functional class	Stimulation parameters	Training parameters
3–4	I or II	120 ms ID /500 ms IP ; 5 s SD /2 s SP 40 ms ID /10 ms IP ; 3 s SD /3 s SP	5 × 3 min 5 d/week 3 × 3 min 5 d/week
5–6	II or III	120 ms ID /400–500 ms IP ; 5 s SD /1 s SP 40 ms ID /10 ms IP ; 3 s SD /3 s SP	5 × 4 min 5 d/week 3 × 3 min 5 d/week
6–8	III	120 ms ID /400 ms IP ; 5 s SD /1 s SP 40 ms ID /10 ms IP ; 3 s SD /3 s SP	5 × 4 min 5 d/week 3–4 × 3 min 5 d/week + ankle weight 2×/week
8	III or IV	120 ms ID /400 ms IP ; 5 s SD /1 s SP 40 ms ID /10 ms IP ; continues + switch	5 × 4 min 5 d/week Stand-up–sit-down exercise Stand-up–stepping–sit-down exercise
16	V	120 ms ID /400 ms IP ; 5 s SD /1 s SP 40 ms ID /10 ms IP ; continues + switch	5 × 4 min 5 d/week Walking exercise

Functional Classes

0 No torque measureable, no contraction/twitch visible

I No torque measureable, but contraction/twitch visible

II Torque measured between 0.1 and 2.9 Nm

III Torque measured more than 3.0 Nm, but not able to stand

IV Able to stand in parallel bars/standing frame

V Able to walk with an aid

ID impulse duration, *IP* impulse pause, *SD* stimulation duration, *SP* stimulation pause, *d* days, *rep* repetition in one set of stimulation

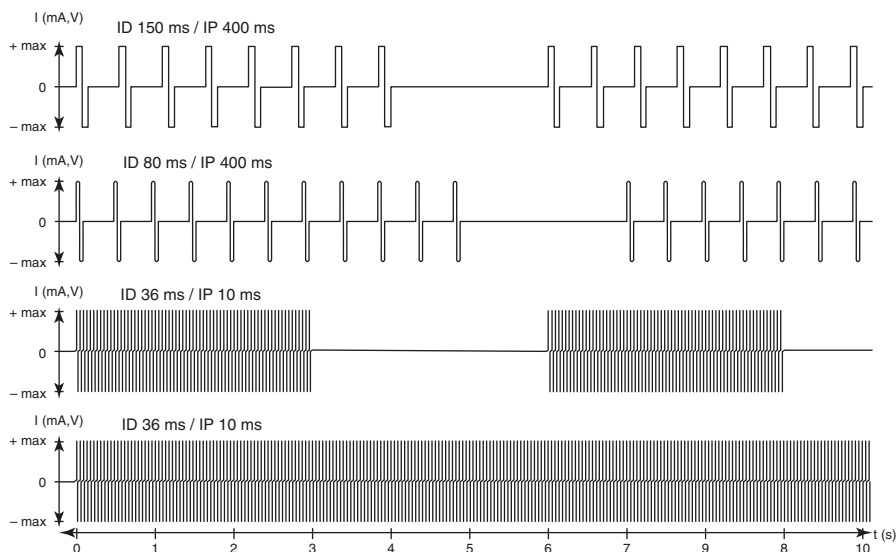


Fig. 11.1 Parameters for progressive home-based functional electrical stimulation (h-b FES) training of long-term fully denervated human muscles. Figure shows a sample of a progressive FES training according to the described training in Table 11.1. It starts with bursts of a stimulation duration (SD) of 4 s and a stimulation pause (SP) of 2 s containing impulses with an impulse duration (ID) of 150 ms and an impulse pause (IP) of 400 ms for 4 months (it can be reduced if the time of denervation is under 6 months) to activate poor denervated muscle fibers. According to the enhanced activation, the ID can be reduced to 80 ms and SD increased to 5 s for another 4 months approximately. The next training phase implements tetanic bursts of 3 s SD and 3 s SP with impulses of 36 ms ID and 10 ms IP to increase muscle fiber diameter, muscle mass, density, and force, with leg extensions with and without additional weights on the ankles of the patients. If a good condition is achieved, depending not only to the training but also to the time span of denervation, standing, stepping-in-place, and walking exercises can be performed with continuous stimulation (controlled by an external switch) with 36 ms ID and 10 ms IP

in his longitudinal prospective study [32]. The training strategy consisted of two progressive stimulation programs (Fig. 11.1), and positive changes and effects of FES on structural, functional, histological, and ultrastructural parameters were described in detail by Kern et al. in 2010 [32]. FES treatment can be integrated into daily life of patients without too much interference on their daily activities. The reduction of leg edema [55], the improved cosmetic appearance of lower extremities, the enhanced cushioning effect for seating, and the ability to perform home exercises are additional effects of FES. We are thus confident that it will be possible to translate into a wider population of diseased subjects and to aged people the knowledge of our interdisciplinary group of European scientists and clinicians. In fact, current studies suggest that electrical stimulation of the LMN denervated muscles could be extended to patients with incomplete lesions or elderly persons and could reduce secondary complications related to disuse and impaired blood perfusion (reduction in bone density, risk of bone fracture, decubitus ulcers, and thromboembolism) [55–57].

Key Points

- Elderly and mobility-impaired patients may develop severe limitations to their independence after arm and leg immobilization or being bedridden.
- Education and support of patients to perform daily exercises in the hospital and then at home is an effective and low-cost measure to limit disability and improve physical and mental being of older patients, but when persons are reluctant or hampered to perform volitional exercise, functional electrical stimulation in the hospital and then at home is an alternative worth to be tested in many patients.
- Section 11.1 discusses structural and molecular markers of muscle weakness and protocols of FES-induced recovery in aging and neuromuscular impairments.
- Section 11.2 presents detailed protocols of h-b FES for denervated–degenerated muscles.

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