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FUNCTIONAL ELECTRICAL STIMULATION OF PERMANENTLY DENERVATED MUSCLES, UPDATED 2020

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ABSTRACT
Spinal cord injury produces muscle wasting, which is especially severe after the complete and permanent damage of lower motor neurons that occurs in complete Cauda Equina Syndrome. Even in this worst-case scenario, we have shown that permanently denervated Quadriceps muscle can be rescued by surface Functional Electrical Stimulation and a purpose designed home-based rehabilitation regime. Here, our aim is to show that the effects are extended to both antagonist muscles and the skin of the thighs. Before and after 2 years of electrical stimulation, mass and structure of Quadriceps and Hamstrings muscles were quantitated by force measurements. Muscle gross cross section were evaluated using color computed tomography, muscle and skin biopsies by quantitative histology and immunohistochemistry. The treatment produced: a) an increase in cross-sectional area of stimulated muscles; b) an increase in muscle fiber mean diameter; c) improvements in ultrastructural organization; and d) increased force output during electrical stimulation. The recovery of Quadriceps muscle force was sufficient to allow 25% of the compliant subjects to perform stand-up and step-in place trainings. Improvements are extended to hamstring muscles and skin. Indeed, the cushioning effect provided by recovered tissues is a major clinical benefit. It is our hope that, with or without our advice, trials may start soon in Europe and Russia to provide persons-in-need the help they deserve.
Keywords: Spinal Cord Injury, denervated degenerating muscle, home Functional Electrical Stimulation, muscle co-activation, Color Computed Tomography, functional recovery, skin.

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ФУНКЦИОНАЛЬНАЯ ЭЛЕКТРОСТИМУЛЯЦИЯ ПОСТОЯННО ДЕНЕРВИРОВАННЫХ МЫШЦ, ОБНОВЛЕННАЯ В 2020 Г.

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РЕЗЮМЕ
Повреждение спинного мозга вызывает мышечное истощение, которое особенно тяжело после полного и постоянного повреждения нижних моторных нейронов, которое возникает при полном синдроме Кауда Эквина. Даже в этом худшем случае мы показали, что постоянно денервированные мышцы Квадрицепса могут быть спасены с помощью поверхностной функциональной электрической стимуляции и специально разработанного домашнего реабилитационного режима. Наша цель – показать, что эффект распространяется как на мышцы-антагонисты, так и на кожу бедер. До и после 2 лет электрической стимуляции, масса и структура мышц Квадрицепса и Хэмстрингса были квантитированы с помощью измерения силы. Мышцы валового поперечного сечения оценивались с помощью цветной компьютерной томографии, биопсии мышц и кожи с помощью количественной гистологии и иммуногистохимии. В результате лечения: а) увеличение площади поперечного сечения стимулированных мышц; б) увеличение среднего диаметра мышечных волокон; в) улучшение ультраструктурной организации; и г) увеличение выходной силы во время электрической стимуляции. Восстановление мышечной силы Квадрицепса было достаточным для того, чтобы 25% участников программы могли проводить тренировки в положении «стоя» и «шаг на месте». Улучшения распространяются на подколенные мышцы и кожу. Действительно, амортизирующий эффект, обеспечиваемый восстановленными тканями, является основным клиническим преимуществом. Мы надеемся, что вскоре в Европе и России, с нашими рекомендациями или без них, начнутся исследования для оказания нуждающимся людям той помощи, которую они заслуживают.
Ключевые слова: травмы спинного мозга, денервированные дегенерирующие мышцы, домашняя функциональная электрическая стимуляция, мышечная соактивация, цветная компьютерная томография, функциональное восстановление, кожа

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Introduction

Early aging and Aging muscle atrophy

Skeletal muscle atrophy is the loss of muscle size and strength, which occurs with prolonged malnutrition, bed rest, neural and skeletal muscle injuries, diseases such as chronic cardiovascular and respiratory failures, diabetes, sepsis, cancer, and occurs inexorably during late aging, even in obese persons [1]. It is a sad truth that human muscle tissues will naturally decline decade after decade past the age of 30 years [2]. There are innumerable neuromuscular disorders and systemic diseases, which induce muscle atrophy, impairing the mobility of both old and young patients. Ill people, and even the extreme elderly, may counteract muscle deterioration by working to maintain the majority of their skeletal muscles in the best possible shape [3]. However, because of the debilitation that often accompanies disease and advanced age, ill and elderly people generally spend very little to no time in daily physical activity. This decreased muscle use contributes to even further muscle loss. This consequent disuse muscle atrophy further limits patient independence and can culminate in confining people to wheelchairs, beds, and to prolonged hospitalizations. Thus, immobility-related muscle atrophy is associated with functional limitations, thromboembolism, and increasingly high medical costs [4].

Muscle atrophy countermeasures

All chronic and progressive muscle impairments need permanent management. An effective, low-cost option is to educate people-in-need about how to perform physical activity, whether it is volitional [5] or electrical stimulation-induced exercise for cases in which the persons are not willing or are unable to move as needed [6]. Indeed, cardiovascular and ventilation rehabilitation protocols for surgical patients are well established and a major component of these is designed to reverse muscle atrophy and weakness [8,9]. Although the balance between cost (time/capital investment/interference with daily living) and long-term benefits is still debated [10, 11], many practitioners and institutions recognize the value of electrical stimulation in their daily clinical practice [12–15].

During 2018, there was a new wave of papers in excellent journals (e.g., New England Journal of Medicine and Nature) about “Direct Spinal Cord Stimulation in Spinal Cord Injury”, which promises to revolutionize the management of thoracic-level Spinal Cord Injury (SCI) patients as far as their mobility is concerned [16–17]. There is no question that these approaches deserve to be duplicated as soon as possible by independent trials with more numerous participants. However, there is a small group (at least in aging European countries) of SCI patients who will never be enrolled in these new trials. These patients suffer from conus and cauda equina complete injury, a rare SCI syndrome in which there is basically a complete separation of the lower motor neurons of the spinal cord from skeletal muscles [7]. In these patients, there are no longer intact peripheral nerves to carry messages from an intrathecal or external electrically stimulated spinal cord to the leg muscles. Indeed, these patients suffer much more than typical muscle atrophy, eventually eventually experiencing the replacement of muscle tissue with fibrous and adipose tissue as their denervated muscles degenerate. denervated degenerated muscles. Nonetheless, in previous studies we have shown that, in SCI patients suffering with permanent and complete conus and cauda equina syndrome, denervated leg muscles were rescued by 2-years of home-based Functional Electrical Stimulation, when a specific-purpose developed electrical stimulator (now commercially available: “Stimulette den2x” of the Schuhfried Medizintechnik GmbH, Vienna, Austria) provided the needed high currents to large surface electrodes covering the Quadriceps muscles

[7, 18, 19]. Interestingly, we recently further demonstrated in these patients that skin, when exposed to 2 years of surface electrical stimulation, exhibits an improvement in epidermal thickness [20–22]. Here we add that the afore-described electrical fields also produced clinically relevant recovery in atrophic Hamstring muscles which were not in direct contact with the very large electrodes which are part of the Vienna Protocol of home-based Functional Electrical Stimulation for denervated degenerated muscles, validated by the EU Program: RISE [Use of electrical stimulation to restore standing in paraplegics with long-term denervated degenerated muscles (QLG5-CT-2001–02191)]. We see that a supposed drawback, the co-activation of non-targeted muscles, is indeed responsible for a major positive clinical result.

In short, our data show that permanently denervated Quadriceps muscles can be rescued by a purpose designed home-based functional electrical stimulation regime. Here our aim is to emphasize that the effects have multiple clinical results, extending positive effects to non-targeted antagonist muscles and to the skin.

Patients, home-based Functional Electrical Stimulation of denervated degenerated muscles, force, mass and extent of degeneration-recovery of thigh muscles

Patients suffering with a complete Conus and Cauda Equina lesion (up to 9.0 years of complete and permanent peripheral denervation) were enrolled in the RISE Program following the inclusion and exclusion criteria previously reported, together with their demographic details [18]. They were volunteers suffering with a Conus and Cauda Equina lesion who received detailed information and signed an appropriate informed consent document [23]. Clinical and functional assessments, as well as follow-up procedures and muscle biopsies, were performed at the Wilhelminenspital, Vienna (Austria). Quadriceps muscle biopsies were harvested before and after 2 years of home-based Functional Electrical Stimulation and analyzed by light and electron microscopy (respectively, in Padova and Chieti Universities, Italy). Complete denervation of right and left quadriceps muscles was assessed before and after 2 years of home-based Functional Electrical Stimulation by test electrical stimulation, needle electromyography, and both transcranial and lumbosacral magnetic stimulation [23]. Using a custom-designed stimulator and large surface electrodes designed and implemented in Vienna (Austria), we stimulated denervated atrophic leg muscles according to our published home-based Functional Electrical Stimulation strategy [7,18,23]. We determined both the mass and force of the stimulated Quadriceps muscles at each time point. Force was assessed by electrostimulation of the Quadriceps m. of patients seated on a custom-designed chair. The isometric knee extension torque was measured as movement from a 90 knee placement by activating the Quadriceps m. with a standardized stimulation program and the same electrodes used for the home-based training.

Using Quantitative Muscle Color Computed Tomography (QMC–CT), we determined the gross anatomy of the thigh muscles and the extent of their atrophy/degeneration [24–26]. QMC–CT uses CT numbers (i.e., Hounsfield Units) for tissue characterization. In the process of assessing muscle quality, soft tissues were discriminated as follows: subcutaneous fat, intramuscular fat, low-density muscle, normal muscle, and fibrous-dense connective tissue (Fig. 1). To evaluate the data further, pixels within the defined interval of Hounsfield Units values were selected and highlighted in colors (red for normal muscle tissue, yellow for intramuscular adipose tissue, green and blue for loose or fibrous connective tissue, respectively) while other tissues with Hounsfield Units values outside the threshold ranges remain black, including the extra-muscular adipose tissue [25].

Results of the EU Program: RISE

The EU Program: RISE [Use of electrical stimulation to restore standing in paraplegics with long-term denervated degenerated muscles (QLG5-CT-2001–02191)] resulted in improvement of thigh muscles in 20 out of 25 patients who completed a 2-year home-based Functional Electrical Stimulation program. The results revealed: 1) a 35% increase ($p < 0.001$) in cross-sectional area of the Quadriceps muscles; 2) a 75% increase ($p < 0.001$) in mean diameter of Quadriceps muscle fibers; and 3) improvement of the ultrastructural organization of contractile material and of the Ca2+-handling system (T-tubules and triads; 27–29 and Table 1).

Furthermore, there was an extremely impressive 1187% increase ($p < 0.001$) in force output during electrical stimulation that was sufficient to allow 25% of the end-point patients to perform home-based Functional Electrical Stimulation assisted stand-up exercises.

Results beyond the EU Program: RISE
Coactivation of the Hamstring muscles

Though not expected by bioengineers and physiatrists, who are more interested in selective electrical stimulation to control arm and leg functional movements, after the 2 years during which the compliant SCI patients performed home-based Functional Electrical Stimulation (5 days per week using large electrodes covering the Quadriceps muscles), the CT cross sectional area of the Hamstring muscles also improved, increasing from 26.9+/-8.4 to 30.7+/-9.8 cm2; this represents a significant 15% increase (p≤0.05). Thus, the Color CT analyses confirm that the home-based Functional Electrical Stimulation-induced muscle improvements, which were noted in CT of Quadriceps m., also occurred in Hamstrings (Figure 1 and Table 2).

Table 1. *Results of the EU RISE Project for home-based functional electrical stimulation (h-bFES) of denervated degenerating muscles in complete lumbosacral spinal cord injury (SCI): Use of electrical stimulation to restore standing capability in paraplegics with long-term denervated degenerated muscles (QLG5-CT-2001–02191)*

• The condition of none of the 20 patients who performed 2-year h-bFES worsened
• Quantitative muscle color CT shows that after two years of h-bFES, Hamstring muscles present an increased content of red, high-density tissue (normal-looking muscle tissue), even when starting h-bFES at 3 years after SCI
• CT cross sectional area of the Hamstring muscle group improved, increasing from 26.9+/– 8.4 to 30.7+/-9.8 cm2, a significant 15% increase (p≤0.05)
• Despite co-activation of the antagonists, the Quadriceps muscle presented a 1187% increase in h-bFES-induced knee torque output from 0.8 1.3 to 10.3 8.1 Nm (p<0.001)
• Over time 23 of the 25 patients performed knee extension from a sitting position
• Electrostimulation-induced force allowed 25% of patients to perform h-bFES stand-up exercises
• Many of the compliant patients achieved good results during the first year of h-bFES

Table 2. *Quadriceps muscles (Fig. 1 A, B and E, F) and Hamstrings (Fig. 1 C, D and G, H)*

		Colored Areas			Total Colored Area	
		% of Red	% of Orange	% of Blue	(m2)	%
Muscle						
Quadriceps	A, Pre h-bFES*	68	27	5	2041	
Quadriceps	B, Post h-bFES	93	5	2	2713	43
Hamstrings	C, Pre h-bFES	68	27	5	2013	
Hamstrings	D, Post h-bFES	82	5	13	2600	29
Quadriceps	E, Pre h-bFES	50	32	18	1452	
Quadriceps	F, Post h-bFES	94	4	2	3400	134
Hamstrings	G, Pre h-bFES	8	43	49	1426	
Hamstrings	H, Post h-bFES	52	17	31	2029	42

Densitometry of the color CT scan presented in Fig. 1. Total area and percent areas of normal density muscle tissue (red), loose degenerating muscle tissue (orange), and of loose and dense connective tissues (blue/green).
**h-bFES: Home-based functional electrical stimulation*

Comparison of left panels of Figure 1 provides strong evidence for the deterioration of permanently denervated muscles at 1 to 3 years post SCI. However, it is worth noting that, even starting at 3 years post SCI, home-based Functional Electrical Stimulation of denervated degenerated muscles is able to recover the Hamstrings to an impressive extent. This is strong evidence that co-contraction of dorsal and ventral thigh muscles induced by the large electrodes is a powerful mechanism behind the success of the Vienna Strategy for recovery of denervated degenerated muscles thigh muscles. This is a clinically relevant observation because an increase in bulk of the Hamstrings is an effective mechanism for preventing dermatological complications in conus and cauda equina syndrome, specifically pressure sores.

Home-based Functional Electrical Stimulation-induced recovery of skin thickness from SCI-induced skin atrophy

It is certainly worth noting, that we recently demonstrated, using skin biopsies harvested from the same series of RISE patients, that the skin also became atrophic and flattened (i.e., there were decreased numbers of papillae-like structures per mm of skin and a decreased interdigitation index of dermal-epidermal junctions) after several years of SCI [30], but that these issues recovered from atrophy and flattening after 2-years of home-based Functional Electrical Stimulation applied to treat denervated degenerated muscles [20–22].

Advantages and limitations

Patients suffering with SCI must use wheelchairs to gain some mobility independence and this results in them sitting on their Hamstring and Gluteal muscles several hours each day. The prolonged seating sadly contributes to the development of severe atrophy of the muscles and edema of the legs, with increased risks of decubitus ulcers and deep thrombophlebitis [31]. Of particular importance in SCI is whether the connection between the muscle and the nerve is preserved or the muscle is denervated as a result of complete peripheral nerve lesion. In the latter cases, the denervated muscle becomes unexcitable with commercial electrical stimulators and undergoes ultrastructural disorganization within a few months, while severe atrophy with nuclear clumping and fibro-fatty degeneration appears later within 3 to 6 years. Our work with home-based Functional Electrical Stimulation of denervated degenerated muscles is important because it leads to muscle recovery, even in the worst cases of complete, permanent lower motor neuron muscle denervation. Here we review data demonstrating that electrical stimulation by very large electrodes covering the full Quadriceps m., to activate the entire population of denervated muscle fibers of the human thigh, is able to recover both ventral (Quadriceps muscles) and dorsal (Hamstrings muscle group) muscles of the thigh. This conclusion is supported by the fact that compliant enrolled patients of the RISE Project are able to perform electrical stimulation-supported standing-up and walking-in-place trainings [7,18]. Furthermore, QMC–CT of thigh muscles treated for two years with home-based Functional Electrical Stimulation strongly support the efficacy of the Vienna Strategy for home-based Functional Electrical Stimulation of denervated, degenerated muscles. Interestingly, we developed QMC–CT as a by-product of the EU RISE project to complement follow-up in these extreme cases of muscle degeneration, as complete Conus and Cauda Equina syndrome.

A noteworthy point is that the Color CT scans taken at enrollment (before any home-based Functional Electrical Stimulation) seem to suggest that the Hamstrings are more atrophic and degenerating than the Quadriceps muscles. [18,27] It is thus not surprising that the effects of home-based functional electrical stimulation are more evident in the Quadriceps than in the co-activated Hamstrings. Nonetheless, the improvements noted in the Hamstrings muscle group are a clinically relevant effect of home-based Functional Electrical Stimulation because the recovered tissues of the dorsal thigh muscle contribute an important cushioning effect for the sitting position.

Furthermore, because we harvested muscle tissue through a skin biopsy, we had the opportunity to extend our analyses to skin. Excitingly, we found that the home-based Functional Electrical Stimulation-sustained improvements in muscle structure are extended to skin, whose thickness and flattening worsen in accordance with the extent of years of SCI, but are substantially recovered after 2-years of home-based Functional Electrical Stimulation [20–22]. The improvement of tissue trophism will be even more clinically relevant if patients add home-based functional electrical stimulation of Gluteal muscles to their training workout, as the Vienna Strategy for denervated degenerated muscles SCI strongly recommends. On the other hand, the only limitation of home-based Functional Electrical Stimulation for denervated degenerated muscles, is that it can be applied only in cases of completely denervated Cauda Equina, because the degenerating denervated muscles need a very high-intensity electrical stimulation, that is not comfortable for SCI persons with residual innervation/reinnervation.

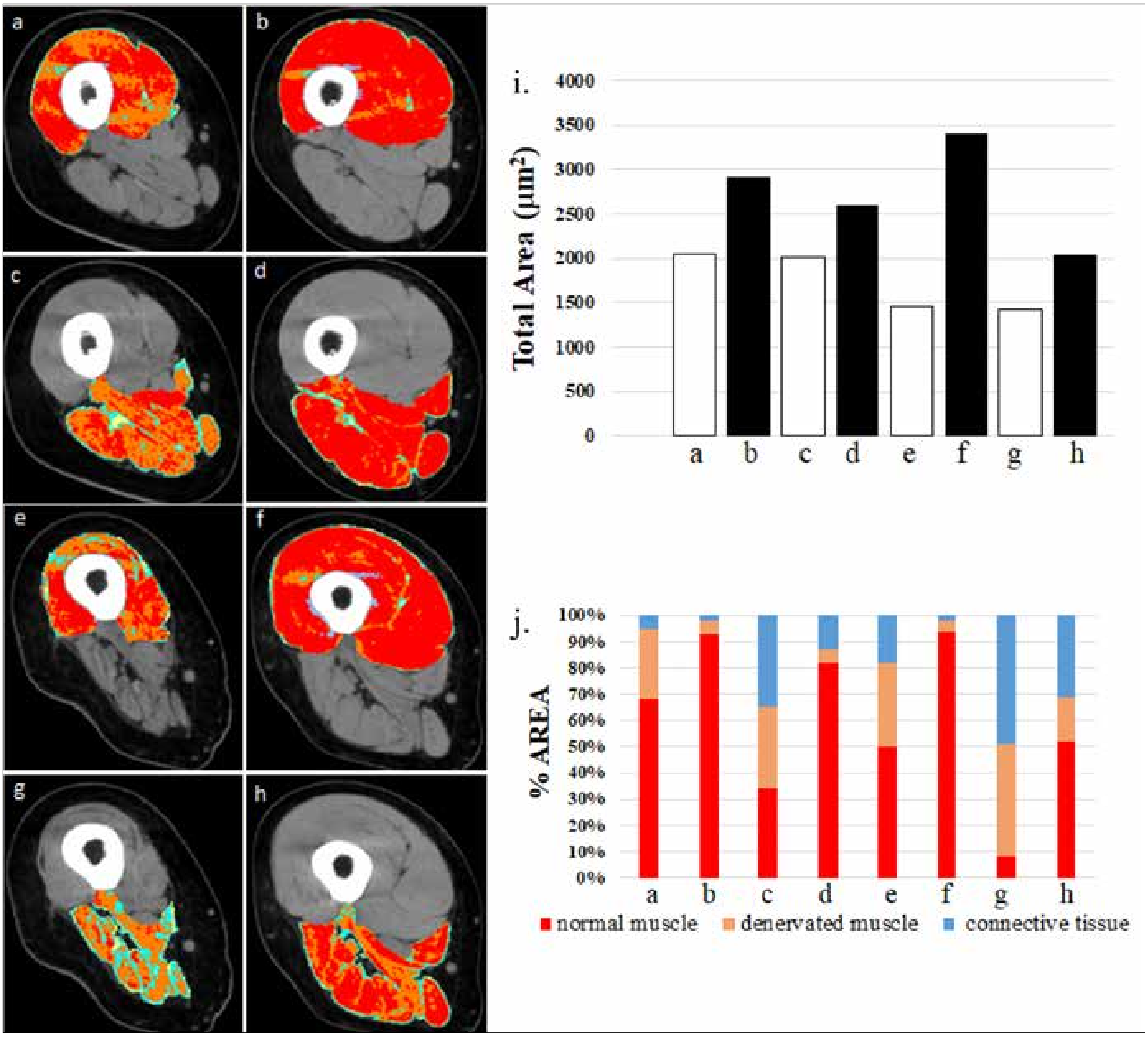

Fig. 1. *Both denervated Quadriceps and Hamstring muscle groups respond to home-based Functional Electrical Stimulation (h-bFES) years after injury.a. Quadriceps muscle at 1 year post spinal cord injury (SCI), No h-bFES.b. Muscle in panel "a" after 2 years of h-bFES.c. Hamstring muscle at 1 year post SCI, No h-bFES.d. Muscle in panel "c" after 2 years of h-bFES.e. Quadriceps muscle at 3 year post SCI, No h-bFES.f. Muscle in panel "e" after 2 years of h-bFES.g. Hamstring muscle at 3 year post SCI, No h-bFES.h. Muscle in panel "g" after 2 years of h-bFES.i. Total area of muscles a-h.j. Quantitative computed densitometric analyses of tomography, muscles a-h*

Byproducts

Based on these results, the Colleagues of Vienna have also designed and implemented stimulators for home-based neuromuscular electrical stimulation, especially suited for the requirements of elderly people [32]. As detailed in Kern et al., 2014 [33], older persons were exposed to regular neuromuscular electrical stimulation training at home. Results demonstrate that when training is done two times a week, for a total amount of 24 training sessions (3 × 10 minutes for each session), neuromuscular electrical stimulation for elderly persons is safe and effective. Using this approach, all subjects achieved neuromuscular electrical stimulation-induced full knee extension. The outcomes included a significant increase in muscle strength, which was associated with an increase in the number and size of fast muscle fibers, which are the first to respond to electrical stimulation and are well related to the power of skeletal muscle. In muscle biopsies, a significant increase in the number of Pax7-and NCAM-positive muscle satellite cells was also observed, but there were no signs of muscle damage and/or cellular inflammation. [34–44] Furthermore, there are many more applications of home or in hospital FES to manage disuse muscle atrophy related to several organ diseases, from chronic cardiovascular failures to functional electrical stimulation cycling in spinal cord injury. [45–59]

Conclusive remarks

In recent years, we have demonstrated the long-term clinical value of co-activation of thigh muscle by home-based Functional Electrical Stimulation training using large surface electrodes. Indeed, the Vienna Strategy is able to reverse, at least at clinically relevant levels, the adverse effects of aging and of SCI, even the effects of the worst case scenario of complete conus and cauda equina syndrome. Continued regularly, home-based Functional Electrical Stimulation for denervated degenerated muscles helps to maintain healthier leg muscles and skin, reducing the risks of life-threatening SCI complications. We have done our best to attract the attention of Colleagues to our results by publishing in top journals and by presentations at International Conferences. Thus, we are now hopeful that we will attract the attention of the international communities of physiatrists to organize independent trials of home-based Functional Electrical Stimulation for denervated degenerated muscles in SCI persons suffering with complete conus and cauda equina syndrome.

We hope that many Colleagues will share our desire to offer to these people-in-need the chance to live a better life, as they deserve.

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