# Upper and Lower Motoneuron Lesions in Tetraplegia

# Diagnostic and Therapeutic Implications of Electrical Stimulation

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**Upper and Lower Motoneuron Lesions in Tetraplegia - Diagnostic and Therapeutic Implications of Electrical Stimulation**



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When you run into something interesting, drop everything else and study it.

B.F. Skinner (1904 – 1990)

# Upper and Lower Motoneuron Lesions in Tetraplegia

# Diagnostic and Therapeutic Implications of Electrical Stimulation

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## ABSTRACT

The overall objective of this thesis was to improve outcomes and predictability of the treatment of upper extremity function in patients with cervical spinal cord injury and tetraplegia by advancing the diagnostic and therapeutic tools employed in upper and lower motor neuron lesions. An overview is presented of the current knowledge about the principles of electrical stimulation and its usefulness and proven effects on the upper limb. Initially a technique was developed to map the topographic distribution of the motor points of extensor and flexor forearm muscles in able-persons. The mapping system for selected muscles on the dorsal and palmar aspect of the forearm led to remarkable findings when electrical stimulation was applied to patients with cervical spinal cord injuries. One of the main findings was that flexors are noticeably more often denervated than extensors due to lower motoneuron lesions. The findings may explain the clinical observation of better functional outcome after surgical nerve transfer to extensors compared to relatively disappointing results after nerve transfer to the flexors. The continuation of the research project was an interventional study to investigate the possibility to increase the thickness and to influence the structure in denervated forearm and hand muscles by direct electrical muscle stimulation. The case series report showed that this was possible. A reasonable interpretation is that the viability of the motor end-plate pool can be maintained through direct electrical muscle stimulation and that it is likely that an early onset of stimulation improves the conditions for successful reinnervation after nerve transfer. In addition, the time between spinal cord injury and nerve transfer may be prolonged without impairing the outcome. In order to identify the effect of electrical stimulation on neuromodulation it was analysed how robotic-controlled exercises combined with functional electrical stimulation could increase the voluntary

strength of movements in people with spinal cord injury. The only available system for robotically controlled training is adapted to the lower limbs and therefore this study was performed on the lower extremities. The combination of electrical stimulation and robot-controlled, voluntary initiated training increased the recruitment of motor units and muscle strength in the legs.

**Keywords**: Electrical stimulation, Tetraplegia, Upper motoneuron lesion, Lower motoneuron lesion, Motor point topography, Nerve transfer

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# SAMMANFATTNING PÅ SVENSKA

En halsryggmärgsskada förorsakar ofta en total eller partiell förlamning av armar och ben (tetraplegi). Förutom förlusten eller begränsningen av gångförmågan leder skadan till försämrad hand- och armfunktion vilket medför stora aktivitetshinder i det dagliga livet för den drabbade individen.

Rehabiliteringen vid tetraplegi syftar till att hjälpa den ryggmärgsskadade att återfå maximal självständighet och träningen av övre extremitetens funktioner är avgörande för att nå det målet. I den här avhandlingen studeras hur elektrisk stimulering kan användas för att topografiskt kartlägga det exakta motoriska bortfallet vid tetraplegi. Såväl utbredning som typ av nervskada kan bestämmas och en individuell kartbild av bortfallet kan framställas. Denna kartbild tjänar som vägledning vid val av kirurgisk metod för rekonstruktion av handfunktion; omdirigering av muskler och senor (sentransferering), nerver (nervtransferering) eller en kombination av dessa båda tekniker. Avhandlingen undersöker principer och mekanismer för hur elektrisk stimulering påverkar hjärnan, ryggmärgen, nerverna och musklerna hos personer med hög ryggmärgsskada.

Två kliniskt viktiga kartbilder skapades via elektrisk stimulering av nyckelfunktioner som påverkar handens rörelser dvs sträckning och böjning för tummen och fingrarna. Studierna visade att vid hög ryggmärgsskada är den perifera nervskadan mer uttalad för böjarna än för sträckarna. Den motoriska kartbilden underlättar för kirurger att ge patienten både en säkrare prognos oavsett val av behandling men även direktiv för bästa behandlings- och rehabiliteringsalternativ.

Utifrån de upprättade motoriska kartbilderna undersöks om det är möjligt att återuppväcka förlamade, slappa muskler. I en behandlingsstudie studerades effekten vid direkt muskelstimulering av hand- och underarmsmuskler. Resultaten visade att genom elektrisk stimulering kan förlamade muskler återfå och bibehålla sin struktur vilket i sin tur förbättrar förutsättningarna för framgångsrik nervtransfereringskirurgi.

I en s.k. neuromoduleringsstudie under den akuta och subakuta fasen efter ryggmärgsskada analyseras hur kvarvarande funktioner i den förlamade kroppsdelen kan stimuleras till neurologisk återhämtning. Benmusklerna hos personer med ryggmärgsskador tränades med elektrisk stimulering via ett stationärt robotsystem. Studien visade att kraften i musklerna förbättras, både

med viljemässig aktivering och elektrisk stimulering. Användning av denna metod för förbättring av arm- och handfunktioner startar inom kort.

# LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Bersch I, Fridén J.

**Role of functional electrical stimulation in tetraplegia hand surgery**

Archives of Physical Medicine and Rehabilitation 2016;97(6 Suppl 2):S154-159

II. Bersch I, Koch-Borner S, Fridén J.

**Electrical stimulation – a mapping system for hand dysfunction in tetraplegia**

Spinal Cord. 2018 May;56(5):516-522

III. Bersch I, Koch-Borner S, Fridén J.

**Motor point topography of fundamental grip actuators in tetraplegia – implications in nerve transfer surgery**

Journal of Neurotrauma. 2019 Jun 25. doi: 10.1089/neu.2019.6444. [Epub ahead of print]

IV. Bersch I, Fridén J.

**Electrical stimulation of denervated upper limb muscles – effect on muscle morphological properties – a case series report**

Manuscript

V. Bersch I, Koch-Borner S, Brust AK, Fridén J, Frotzler A.

**Robot assisted training in combination with functional electrical stimulation for improving lower limb function after spinal cord injury**

Accepted for publication in Artificial Organs, 2018

# CONTENT

# ABBREVIATIONS

| | |
|---|---|
| ADL | Activity of daily living |
| APL | M. abductor pollicis longus |
| ATP | Adenosine triphosphate |
| BR | M. brachialis |
| CNS | Central nervous system |
| COPM | Canadian occupational performance measure |
| CPG | Central pattern generator |
| CSA | Cross sectional area |
| cSCI | Cervical spinal cord injury |
| DNA | Deoxyribonucleic acid |
| ECR | M. extensor carpi radialis |
| ECU | M. extensor carpi ulnaris |
| EDC | M. extensor digitorum communis |
| EMG | Electromyography |
| EPL | M. pollicis longus |
| ES | Electrical stimulation |
| FDP | M. flexor digitorum profundus |
| FES | Functional electrical stimulation |
| FCSA | Fibre cross sectional area |
| FPL | M. flexor pollicis longus |

| | |
|---|---|
| GRT | Grasp release test |
| LMN | Lower motoneuron |
| LMNL | Lower motoneuron lesion |
| MNL | Motoneuron lesion |
| MP | Motor point |
| MRC | Medical research council scale |
| ms | Milliseconds |
| NMES | Neuromuscular electrical stimulation |
| PA | Pennation angle |
| PT | M. pronator teres |
| rpm | Revolutions per minute |
| rTHAS | Reconstructive tetraplegia hand and arm surgery |
| SCI | Spinal cord injury |
| tSCS | Transcutaneous spinal cord stimulation |
| UMN | Upper motoneuron |
| UMNL | Upper motoneuron lesion |
| US | Ultrasound |
| µsec | Microseconds |

# 1 INTRODUCTION

## 1.1 DESCRIPTION OF THE CLINICAL CHALLENGE

A cervical spinal cord injury (cSCI) leading to tetraplegia is a catastrophic event with life-changing consequences for the autonomy of a human being. It implies that all four extremities are inoperable. Regarding the neurological situation there is a difference between the upper and lower limbs. While the lower limbs typically demonstrate reflex activity as the only remaining motor response after an upper motoneuron lesion (UMNL), the upper limb deficit presentation is much more complex in motoneuron lesions (MNL). In the zone of damage in the spinal cord, upper motoneurons (UMN) as well as lower motoneurons (LMN) can be destroyed. Therefore, the combination of innervated, partially denervated and denervated muscles has to be considered. The specific pattern of neurological failure influences the muscle structure, tone, elasticity and consequently the residual motor function, shape and control of the hand as well as the treatment strategies. Regaining hand function is the mostly expressed wish among persons with tetraplegia, far before the ability to walk. Thus, one important goal of the interprofessional rehabilitation team should be, to provide all clinical and science-based treatment options to regain the best functional outcome of the upper extremities for each individual patient. Hence the early knowledge about the type and characteristics of MNL in the hand and forearm muscles, mainly of those that are key actuators for hand closure and opening, is crucial. This knowledge enables to elaborate a schedule for the treatment whether conservative or surgical. Hereby electrical stimulation (ES) could serve as a diagnostic tool for the differentiation between an UMNL and LMNL. In addition, the application of direct muscle ES as a treatment might also have an impact on the muscle properties in case of a LMNL in the upper extremities. If degeneration could be avoided by ES it would enlarge the number of tetraplegic patients who could benefit from a nerve transfer. In case of an UMNL ES could be used for e.g. strengthening or motor learning and either optimise the residual function or serve as a treatment tool to prepare for nerve and tendon transfers.

## 1.2 HISTORY OF ELECTRICAL STIMULATION (ES)

*"Once upon a time it was the therapeutic fashion to put the legs of patients into buckets of torpedoes or electric eels."* (1)

ES in humans has a long history beginning in the first century A.D. where the roman physician Scribonius Largus used the torpedo fish to treat chronic headache by placing the fish on the spot of the pain (2). The greek physician Dioscorides (76 A.D) transferred the so called " torpedo therapy" and treated haemorrhoids, gout, depression and epilepsy (3). In the middle of the 18$^{th}$ century the feasibility of electrotherapy became easier and more common with the invention of the electrostatic generator and the Leyden jar by the Dutch Pieter van Musschenbroek 1745. Most experimental treatment with ES was applied on the brain in case of seizures, tumours, hemiplegia, epilepsy and depression. In 1752, Benjamin Franklin treated successfully but painfully a 24 years old woman suffering of seizures (4). Moist electrodes were invented a century later by Duchenne, called as "the father of electrotherapy" (5). Furthermore, Franklin recognised the therapeutic effect of electric shocks and tried to cure paralysis. But he noted, though paralyzed limbs appeared to gain strength and move that these effects were only temporary. His patients went home disappointed. His studies about electricity included basic principles of electrostatics and he developed terms as e.g. charge and discharge, plus and minus, condenser and battery that are still in use (6, 7). According to Turrell (8) four phases of electrotherapy should be mentioned. First, the application of static or atmospheric electricity characterized by high voltage and low amplitude using a machine that induced sudden shocks, called *Franklinism*. Second, the Galvanic current, called *Galvanism.* This allowed the application of direct dynamic current via nerve without sudden shocks but with the severe side effect of tissue necrosis. Third, the *Faradism,* after Michael Faraday, with the new discovery that the flow of current could be induced intermittently and in alternate directions. With the short pulse duration, less than 1 millisecond, the risk of tissue damage could be reduced. Fourth, the high frequency current particularly used for pain treatment, allowed stimulations without excitation of muscles (9).

Rolando first showed that electrical stimulation of the cerebral cortex in pigs can evoke movements (10). The era of mapping the cortex in animals and later on in humans began. Until this time the cortex yielded as unexcitable (3). In 1874 Robert Bartholow could provoke arm and leg movements, muscle contractions of the neck and eye movements by stimulating the cortex with a needle electrode during a brain operation in a woman (11).

It took further 60 years until 1931 the first detailed representation of man's motor cortex was published by Krause and Schum (12).

Since the 1960's a lot of information has been published on functional electrical stimulation (FES) for neurorehabilitation and neuromotor plasticity. Vodovnik has been reported with his attempt to bring recent FES developments to the attention of physiotherapists. He wanted to encourage more frequent use of FES in clinical practice and a critical evaluation of this technique by clinicians (13). Furthermore, the group of Vodovnik (13) highlighted some clinical objectives of FES:

1. Support and promotion of spontaneous recovery of impaired motor function due to a central nervous system (CNS) damage.

2. Development of motor function in children with cerebral palsy

3. Restoration of basic reflex motor mechanisms that are mainly involved at the spinal cord level

4. Substitution of motor functions that are lost due to a CNS damage

5. Prevention and/or correction of locomotor dysfunction because of changes in sensorimotor mechanisms integrated at various levels of the CNS.

The current term *"functional electrical stimulation"* has been brought up and established by Moe and Post 1962. They intended to describe the electrical stimulation of muscles deprived from neural motor control to cause a functionally useful contraction (14). The term neuromuscular electrical stimulation (NMES) is used similarly. In some papers the authors want to differentiate between therapeutic purpose and functional purpose and use the term NMES. NMES may lead to an effect that enhances function but does not directly provide a function. However, in both cases the LMN has to be intact to activate paralyzed or paretic muscles (15).

## 1.3 HISTORY OF ES IN SPINAL CORD INJURY (SCI)

Electricity was applied on patients with spinal paralysis more than 200 years ago. In the literature there are two notes by Brockliss 1782 and Mauduyt 1784 from France. They both recommended the use of early treatment with electrotherapy for patients paralyzed from the waist downwards (16). Unfortunately, the treatment was not described in detail. In the end of the 19th century four cases of incomplete paralyzed patients were described, one by William Gull from London, England and three by William Heinrich Erb from Heidelberg, Germany. The patient from William Gull, an incomplete tetraplegic patient was described regarding his neurological situation quite well, in contrast the treatment with electrotherapy was only noticed as *intense* (17).

Erb described his three cases, all incomplete paraplegics, more in detail regarding the electrical treatment. They were all treated with galvanic current from 10 – 22 therapy sessions with surface electrodes placed on the skin over the spine. All patients improved in muscle strength after receiving electrotherapy. All patients recovered the ability to walk and one experienced pain relief. One patient died six months after injury but three survived and were discharged later (18). If the neurological recovery in those incomplete cases was elicited by the stimulation is doubtful. During this period no cases of electrical treatment in complete lesions were reported because these persons died soon after injury before any treatment could be applied (16).

In the sixties of the 20th century Dimitrijevic and colleagues established another milestone by the hypothesis that programmed stimulation achieves facilitation of the spinal motor neurons. The afferent input to the spinal cord and the suppression of inhibitory interneuron activities result in functional motor improvement (19). Furthermore, Vodovnik investigated if FES may provide a patterned motor activation through the simultaneous stimulation of sensory receptors (20) Even if supra-spinal control would be missed or impaired, as in SCI, the propriospinal system would be able to integrate afferent input to provide coordinated movement and postural control (21). Between 1970 and 1990 studies about stimulation parameters were published.

All tried to achieve FES without problems of fatigue and tissue reactions under the electrodes (22, 23). An implanted device for enhancing hand function was developed at the Case Western Reserve University in Cleveland and marketed by NeuroControl in 1997. The Freehand System was implanted in 200 C4 – C5 tetraplegic patients (24).

However, actually more studies have investigated the effect of electrical stimulation in humans regarding structural alterations of muscle properties and the functional improvement in the lower extremities (n = 377, 1968 – 2017). Fewer were investigating the human upper extremities (n = 234, 1971 – 2017). From these 234 studies 125 were related to the hand and forearm.

## 1.4 APPLICATION OF FUNCTIONAL ELECTRICAL STIMULATION (FES) IN SCI

FES offers three different options. The transcutaneous application, by using surface electrodes, the percutaneous stimulation by using needle electrodes and the implantable stimulation systems.

FES treatment has been shown to improve lower (25-28) and upper limb function (29-33) as well as trunk stability and function (34-36). Furthermore, FES can improve breathing in high – level tetraplegia (37-43). In addition, FES might improve bladder, bowel, and sexual function (44), cardiovascular fitness by increasing aerobic capacity (45-48), decrease body fat mass (49) and prevent and treat pressure ulcers by increasing muscular blood flow and muscle mass (50-54) as well as the granulation and re-epithelialization and the enhancement of cellular activities like ATP concentration, collagen and DNA synthesis (55,56).

FES may also have an influence on neuronal plasticity, as animal studies have shown (57-58). In humans the motor learning process can be supported by combining electrical stimulation and action observation to increase the excitability of cortical motor areas (59).

## 1.5 FES RESEARCH AND IMPLEMENTATION IN SCI THERAPY

FES for some domains are effectively implemented in clinical treatment. Mostly implantable devices are used as those for the treatment of neuropathic pain, the sacral root stimulation for treatment of the neurogenic bladder dysfunction and the diaphragm stimulators for breathing. In the musculo–skeletal system, neuroprostheses are less widespread in clinical application and are typically restricted to research projects. One of the reasons is the small number of patients who can benefit from individualized and functional specified devices. Consequently, the economic incentive is low for commercial distributors. The freehand system was implanted in >250 persons with C5-C6 tetraplegia lesions (60). Even though an improvement in grasp and release, pinch force and activities of daily living was reported, the system was taken off the market for economic reasons (61). The technical research field provides numerous stimulation systems for upper and lower limb function and for trunk stability. The results of research are promising but the transfer into clinical practice is often difficult (62). Furthermore, there remains a gap between technical facilities and clinical application. The stimulators often offer sophisticated functions that require considerable technological knowledge by therapists. The time required for setting up and operating a system is substantial. The time assigned for treatment and rehabilitation is, however, often reduced step by step. This conflict might be one reason why in most clinical settings FES is used but not integrated in therapeutic interventions although the combination provides the best outcome (63,31).

Incorporation of engineering expertise in clinical teams, continuous education of therapists and development of more “user-friendly” devices are probably key components for establishing better clinical integration.

The International Functional Electrical Stimulation Society (IFESS) therefore has announced the mission to promote the awareness, knowledge, and understanding of both electrical stimulation technologies and their implementation. Furthermore, the society intends to bridge research, application and healthcare to enhance quality of life through advocacy, education, organization of international scientific meetings and facilitation of interprofessional collaborations.

# 1.6 PRINCIPLES OF ES

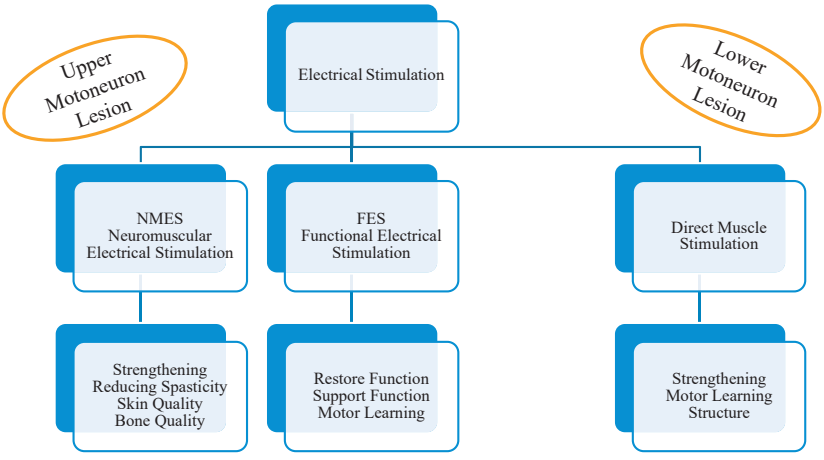


*Figure 1. Visualization of the different ES applications*

ES can be divided in two fields of application. The therapeutic ES or neuromuscular electrical stimulation (NMES) and the FES. The first aims to improve tissue health, including muscle structure and voluntary function by inducing physiological changes that remain after the stimulation treatment. In FES current is applied on excitable tissue to support or replace a function that is lost due to a neurological impairment.

In the literature very often for both types of stimulation the term *FES* is used.

In SCI rehabilitation ES opens a wide field of treatment.

### 1.6.1 DIFFERENCES BETWEEN UPPER MOTONEURON LESION AND LOWER MOTONEURON LESION

The UMN extends from the cerebral cortex (gyrus praecentralis) via the pyramidal tracks to the motoric anterior horn cells in the spinal cord whereas the LMN extends from the anterior horn cell of the spinal cord via the ventral roots of the spinal nerves into the peripheral nerves to the motor end plates of a muscle (Figure 2).

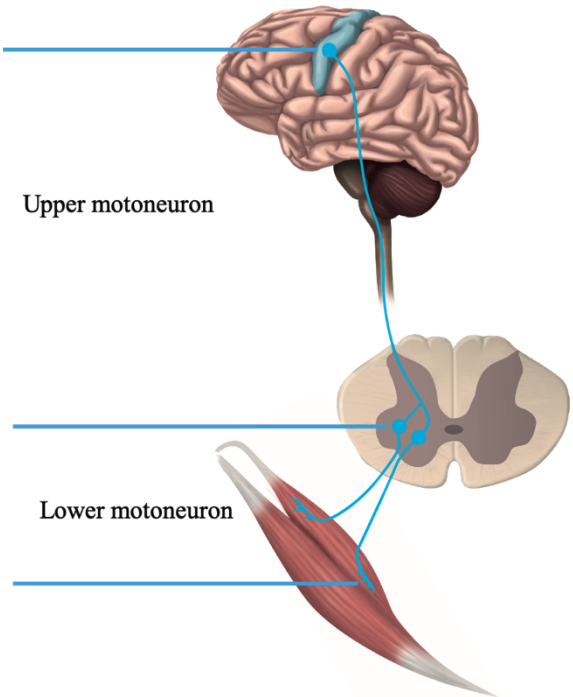


*Figure 2. Depiction of the upper and lower motoneurons*

In case of cervical spinal cord injury (cSCI) there is a three-level hierarchy of muscle innervation. First, the area above the lesion where the innervation is undisturbed. Muscles have normative strength and are under voluntary control. Second the muscle innervation at the level of lesion which shows characteristics of both, UMNL and LMNL. Hereby the extent is variable due to the severity and variety of the UMNL (64). Thirdly the innervation of the muscles below the lesion show an UMNL with an intact LMN.

In clinical practice the situation is more complex. There is a border area, where the combination of a UNML and LMNL exists. This border area comprises mostly one additional level above and below the actual level of lesion and can be detected by electrodiagnostic testing or ES (65-67).

There are combinations of disturbed blood flow and ischemia, glial scar formation, demyelination and remyelination in the tissue at the level of the spinal cord injury (68). A differentiation between an UMNL and LMNL due to cSCI cannot reliably be determined within the first 8 to 10 days after injury. That is based on the fact that an acute damaged axon can continue to conduct action potential up to 8-10 days (69).

### 1.6.2 ES IN UPPER MOTONEURON LESION AND LOWER MOTONEURON LESION

Depending on the localization of the lesion, the stimulation current can be transmitted via nerve, in case of an UMNL, or via muscle, in case of a LMNL. When surface electrical stimulation is applied, an artificial electric field is generated under the electrodes on the skin. The electric field depolarizes the cell membranes of the close neurons or elicits muscle fibre action potentials (70). Both lead to a muscle contraction (Figure 3). Nerve fibres react earlier than muscle fibres. This is because the threshold charge for producing action potentials in neurons is much lower than that for directly exciting muscle fibre action potentials (71). If a nerve has been excited the conduction of the action potential and the synaptic chemical transmission with processes of neurosecretion and chemoreception is actuated. This is regardless whether the excitation is of physiological origin or achieved by ES artificially. Thus, ES can create a muscle contraction, including the process of excitation and synaptic transmission, very similar to that evoked by voluntary activity. Nerve fibres are excitable from 50 µs (0.05 ms) pulse duration, whereas muscle fibres require longer impulse durations; above 10 ms.

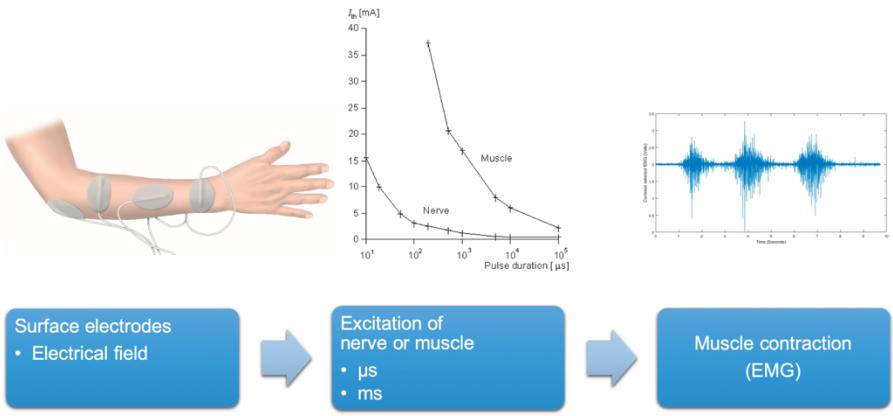


*Figure 3. Visualization of electrical stimulation*

Accordingly, depending on the type of lesion the stimulation parameters differ. In case of an UMNL, the stimulation is performed with a pulse duration of 200-400 µsec and a frequency within a range of 20-50 Hz. The wave form is biphasic rectangular. In contrast, the direct muscle stimulation is chosen in case of a LMNL. Here the pulse duration is about thousand times longer than in an UMNL and reaches from 35-200 ms and the frequencies from 0.25-22 Hz. The wave form can be modified between biphasic triangular to biphasic rectangular (Table1).

*Table 1. Stimulation parameters of an upper and lower motoneuron lesion*

| **Stimulation parameters** | **UMNL** | **LMNL** |
|---|---|---|
| **Pulse duration** | 250-400 µsec | 35-200 ms |
| **Frequency** | 20-50 Hz | 0.25-22 Hz |
| **Amplitude** | 20-80 mA* | 20-60 mA* |
| **Wave form** | Biphasic rectangular | Biphasic triangular<br>Biphasic rectangular |

*The amplitude is depending on the muscles size. The values are based on own clinical experience and correspond to the existing literature.

## 1.6.3 SIGNIFICANCE OF STIMULATION PARAMETERS

The effectiveness of the different stimulation parameters should be taken into account. The applied current is characterized by three parameters namely the amplitude, the pulse duration and the frequency. Mainly the amplitude and pulse duration must be adequate to exceed the threshold of excitability of the stimulated tissue. An increasing current amplitude (mA) leads to an increased muscle torque (Nm) by the recruitment of additional motor units. This excitation of additional nerve fibres includes the smaller fibres near the electrode as well as the larger fibres farther from the stimulating electrode. The number of nerve fibres and motor units can also be manipulated by changing the pulse duration. Increasing the pulse duration has shown to increase the torque (Nm) by increasing motor unit activation. That means, that the amplitude as well as the pulse duration or both can be adjusted to control motor response. The pulse duration determine what kind of nerve fibres will be excited, whereas the rate of their firing is dependent on the frequency (Hz). Therefore, the frequency shapes the quality of the ES evoked muscle contraction. Despite a muscle contraction similar to a physiological one can be elicited with ES, it is metabolically more consuming and fatiguing. This is caused by the repeated, synchronous activity of the same nerve fibres and motor units under ES evoked muscle contraction in contrast to a physiological voluntary muscle excitation. In the latter, the activation is asynchronous and the motoneurons are excited at different times and rates and thus contract and relax at different times. Furthermore, increasing the frequency (Hz) leads to an increased evoked torque (Nm) by increasing the torque per active muscle area (72,73).

## 1.6.4 MOTOR POINTS

There are different definitions of the term motor point (MP). The first description and definition was published by Duchenne de Boulogne 1855 as the site of ES that produces the most effective muscle contraction in response to the applied stimulus (5,74). More recently motor points were described as the site of lowest electrical threshold (75) or the site producing a maximal and defined muscle response at the lowest stimulation intensity (70). A further definition describes the MP as a small region of a skeletal muscle in which motor endplates are aggregated; the muscle is most sensitive to ES at this point (76) (Figure 4). The latter definition refers to the anatomic definition of the motor entry point, which describes the location where the motor branch of the nerve enters the muscle belly (77). This has to be differentiated from the electrophysiological identified MP that should be used for the best electrode positioning to apply ES. At least the definition given by Hunter Peckham is clinically relevant, to identify a stimulation point, where an isolated muscle responds at the lowest stimulation amplitude. Beside, having the best stimulation quality by placing electrodes over MPs, two limitations of ES could be eliminated: The limited spatial recruitment and second the sensory discomfort for the patients (77-79).

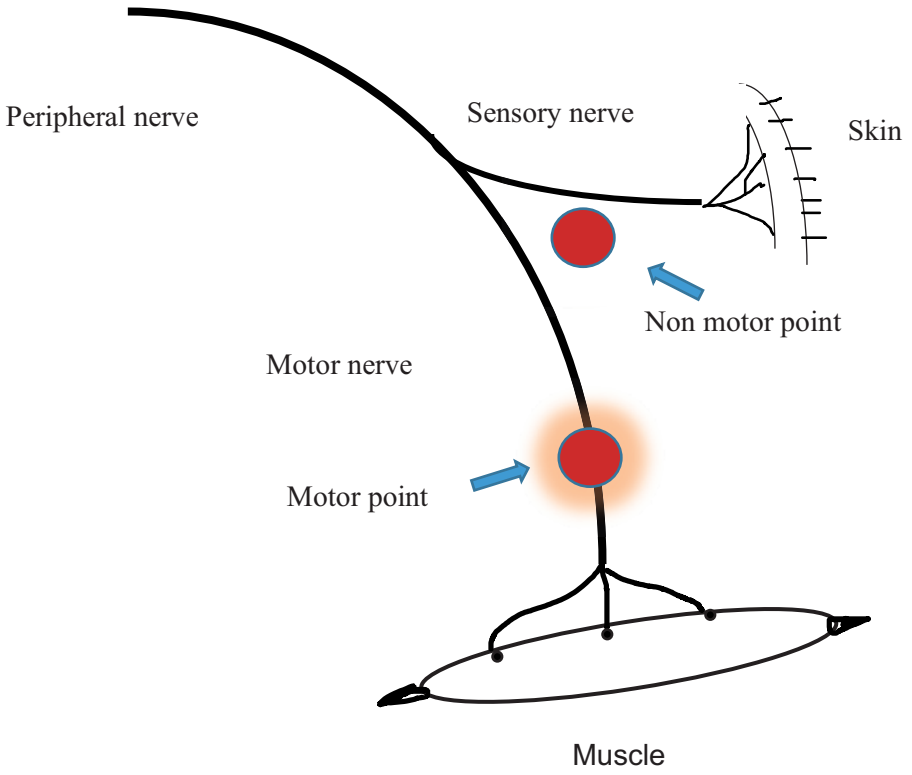


*Figure 4. Sketch of motor point localization*

The accuracy of stimulating an isolated muscle gains importance if ES is used as an assessment to differentiate between an UMNL and LMNL.

However, in clinical practice the identification of a MP before the application of FES, is normally not performed. Reasons therefore are mostly the time expenditure and the lack of knowledge about MP mapping and their identification by ES.

In addition, some other factors, as impedance and electrode size and positioning should be considered to enable a certain stimulation accuracy.

Current flows easier through substances with low impedance and high conductivity. The conductivity of tissue is correspondent to the content of ions and water (muscles 75%, fat 15%, skin and bone 5 – 15%). In addition to the relatively high conductivity of muscles, the conduction due to ES is four times better in the longitudinal direction. The density of the current is high near the interface between skin and electrode and decreases with distance. Fat and bone have higher impedance and hinder the transmission of current to deeper tissue layers. Furthermore, the density of the current under an electrode is increased as the size of the electrode is decreased. A small electrode placed as close as possible to the nerve or motor point increases the density of the current locally and makes the stimulation more precise (80,73).

## 1.6.5 ES AS A DIAGNOSTIC TOOL

Typically, ES is applied through nerves to elicit action potentials. The stimulation electrodes create an electric field that depolarizes the cell membrane of adjacent neurons. If the critical threshold is exceeded, action potentials will be transmitted by the neuromuscular junction and induce a muscle contraction. ES for motor function utilises the fact that the stimulation activates nerves rather than muscles. Thus, by stimulation via nerve to achieve an effective muscle contraction, the LMN has to be intact from the anterior horn of the spinal cord to the neuromuscular junctions in the muscle (81). Accordingly, if no muscle contraction occurs by ES the LMN must be affected. In case of partial innervation, no complete muscle contraction can be expected. Hence, ES can be used as a diagnostic tool to detect an LMNL. In case of testing muscles of the lower limbs, customized large to medium size electrodes can be applied e.g. on the hamstrings or quadriceps or calf (anterior compartment) muscles. Identifying motor points or detecting a partial or complete LMNL in the lower limbs, is quite easy because of the single layer of the muscles and their merely partial overlapping arrangement. In contrast, the muscles of the upper limbs, particularly the forearm muscles, are arranged in two layers. The anterior compartment with its superficial layer consists of the M. pronator teres, M. flexor carpi radialis, M. palmaris longus, M. flexor carpi ulnaris and the M. flexor digitorum superficialis. The deep layer of the same compartment is formed by M. pronator quadratus, M. flexor digitorum profundus and M. flexor pollicis longus. The posterior compartment that reflects the dorsal aspect of the forearm contains on the superficial layer, the M. extensor digitorum communis, M. extensor digiti minimi and the M. extensor carpi ulnaris, whereas the deep layer consists of the M. abductor pollicis longus, M. extensor pollicis brevis, M. extensor pollicis longus and M. supinator. ES testing in this environment of overlying, numerous muscles is complex and needs accuracy in order to find reliable stimulation points. Cartographies of motor points for stimulation, developed for body parts such as the forearm are helpful in clinical practice and need to be standardized in daily practice (82,67). The developed mapping system is based on a line between osseous landmarks of the forearm. The motor points for the different muscles lie in a defined setting to this line and the distances are in a fixed relation to the length of this line. Therefore, the motor points can be calculated

as a function of the line length and consequently of the forearm length. The motor points were sought by systematically testing with a pen electrode (Figure 5) to detect the most selective, efficient and powerful muscle response for each predefined muscle. The muscle response yielded as efficient by gaining the full range of motion of the requested muscle, excluding responses from neighbouring muscles. After determination of the stimulation point it was flagged and set into relationship to the landmark line. Finally, the points were set in relation to different forearm lengths and tested for their reproducibility first in able bodied people before transferred on people with cSCI (82,67).

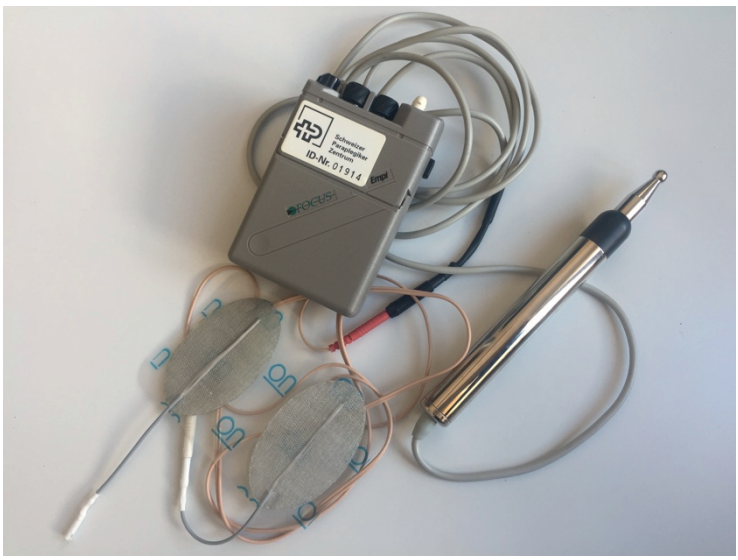


*Figure 5. EMPI 300 PV portable neuromuscular stimulator with a pen electrode*

The Medical Research Council Scale (MRC) was used to classify the answer of a stimulated muscle in innervated, partially denervated and denervated. The MRC tests the range of motion by ES. A muscle yielded as innervated in case of ≥3 MRC during ES, partially innervated/denervated in case of <3 MRC and denervated if no muscle contraction could be provoked.

## 1.6.6 STRENGTHENING OF MUSCLES BY FES

In cSCI muscle strength, endurance and a low fatigability of the upper limb muscles are important. The arms and hands are used for wheelchair propulsion, transfers, manipulating objects and multi – fold other activities of daily living. One major task in rehabilitation is to build up strength and endurance of the upper limb muscles. Classical therapy treatments are often less efficient and tedious. Strengthening of muscles or muscle groups can be successfully performed and supported by FES (63,83,84). Several studies in individuals with SCI have shown that it is possible to increase torque and power output by FES – supported exercises in the lower and upper extremities if the LMN is intact (29,85,86). Furthermore, an increase in the physiological cross-sectional area of the stimulated muscles can be achieved (87).

Mostly the training regarding strength is performed by FES – cycling, FES – rowing and arm – cranking or combined FES arm and leg – cycling.

Nevertheless, there is uncertainty about the best training protocol regarding pulse duration, frequency of FES, the time duration of the single training session and the training sessions per week. In addition, other factors should be taken into account if in SCI, training of muscle strength should be effectively combined with FES. These include the extent of the lesion (motor – complete /motor – incomplete), the type of the lesion according to the stimulated muscles (innervated, partially innervated/denervated, denervated) and the time after injury, regarding the muscle fibre shift (88,89), in form of an increase in the proportion of fast glycolytic and fatigable type IIB fibres and a decrease in the slow oxidative and fatigue resistant type I fibres. In addition, paralyzed muscles show a low oxidative capacity (90). The muscle atrophy starts in type II fibres (91). Hence, at least four different training strategies are required, for acute and subacute motor – complete, chronic motor-complete, acute and subacute motor – incomplete and chronic incomplete SCI patients.

Transferred into clinical practice it should be considered that the muscle fibre shift from type I to type II within four to six weeks post injury as well as the muscle atrophy influence the endurance and fatigability of the muscle (91). To increase the endurance, the time until fatigue needs to be extended. Consequently, more fatigue resistant type I fibres or at least the type II C fibres

need to be augmented. Atrophied muscles in chronic SCI wear out earlier and require low frequency stimulation in the beginning (72,91). Thus, chronic patients need to be trained in the beginning with low frequency and less load to reach the preconditions for a subsequent strength training with higher frequencies and load. Motor incomplete SCI could regain more muscle strength by FES cycling in the lower limbs than motor complete SCI due to the combination of partially paralyzed and voluntary innervated muscles (92).

After an ES trained muscle has regained its previous condition concerning its fibre type composition, a FES training for strengthening can be initiated. Hereby the distribution of the fibre types should be in accordance with the muscle function. Muscles mostly designed for powerful and dynamic movements have a higher percentage of type II fibres, whereas the muscles needed for endurance contain a higher number of type I fibres (89).

The most efficient training mode is 3 sessions per week for 30 minutes each (93). Petrofsky and colleagues compared different training modalities concerning the duration of the training sessions, the ratio of the work and rest time and the number of training sessions per week for isokinetic exercise training in SCI. The greatest increase in force could be achieved with a training dose of 3 times per week with a resting day in between. The differences in forces were 28.1 N (1 time a week) to 281 N (3 times a week) to 223.9 N (5 times a week). The fact that a 5 times training per week is not superior to a 3 times training per week is probably due to residual fatigue, that describes a long-term component of fatigue persisting if new exercises continue too early (93). The performance of the trained muscle will be reduced every day due to this component (94).

Based on the above-mentioned aspects i.e., the extent of the lesion, the time after lesion and thus the muscle fibre shift, a FES based training schedule for muscle strengthening was designed and is illustrated in Table 2. The classification of motor complete and incomplete is based on the American Spinal Injury Association (ASIA). The AIS (ASIA Impairment Scale) is subdivided into a scale from A – E.

AIS A describes a sensory – motor complete lesion,

AIS B a motor complete but sensory incomplete lesion and

AIS C/D a sensory – motor incomplete SCI.

The subdivision into acute/subacute and chronic refers to the time of the fibre shift occurrence after SCI.

*Table 2. Training schedule for FES cycling and FES arm cranking*

| **Training parameters** | **Acute /subacute lesion motor complete AIS A/B** | **Chronic lesion motor complete AIS A/B** | **Acute/ subacute lesion motor incomplete AIS C/D** | **Chronic lesion motor incomplete AIS C/D** |
|---|---|---|---|---|
| **Pulse duration** | 300-400 $\mu$sec | 300-400 $\mu$sec | 400 $\mu$sec | 400 $\mu$sec |
| **Frequency** | 50 Hz | 20 Hz | 35-50 Hz | 20 Hz |
| **Amplitude** | Lower extremities 80-140 mA<br><br>Upper extremities 20-80 mA | Lower extremities 80-140 mA<br><br>Upper extremities 20-80 mA | Depending on the sensibility and the tolerance to sustain the stimulation current | Depending on the sensibility and the tolerance to sustain the stimulation current |
| **Resistance** | 70% of maximal force<br>50 rpm | 20 % of maximal force<br>10-20 rpm | 70% of maximal force<br>Adaptive training* | 20 % of maximal force<br>Adaptive training* |
| **Training time and sessions per week** | 30 minutes 3 times a week | 30 minutes 3 times a week | 30 minutes 3 times a week | 30 minutes 3 times a week |

*adaptive training: if the revolutions per minutes (rpm) decrease under the defined level the stimulation current increases automatically. Abbreviation: AIS = ASIA Impairment Scale

## 1.6.7 FES AND MUSCLE FATIGUE

Muscle fatigue often limits the use of FES. It occurs after repeated contractions and appears as a decrease of torque. Similar to fatigue in voluntary contractions a reduction in excitation – contraction coupling occurs, induced by metabolic changes. The availability of ATP is compromised, the calcium release and the myofibrillar calcium sensitivity decrease (95). This fatigue can persist for hours or days. FES activates motor and sensory pathways. The predominant activation depends on the stimulation parameters and electrodes' positions either over the muscle belly or nerve trunk. Both forms of activation lead to muscle contraction. By stimulating over the muscle belly mainly superficial motor units are activated. If the amplitude is increased additional motor units located deeper in the muscle are recruited (96). Large diameter axons have a lower depolarization threshold and are faster fatigued in contrast to small diameter axons. Hence, FES recruits more the fast – fatigable motor units. The discharge rates of the motor units can be influenced by the stimulation frequency. High motor unit discharge rates is a main factor for fatigue and occurs in higher frequencies (>50 Hz) (97). This high frequency fatigue is rapid, in both onset and recovery (minutes) (72). Furthermore, the excitability of motor axons decreases over time by trains of elicited muscle contractions during unchanged frequency and amplitude (98,99).

Fatigue during FES can be reduced by imitating the physiological size recruitment principle. Therefore, motor units should be recruited via reflex pathways (Hoffmann – reflex) in the spinal cord rather than directly by the motor axons in the muscle. Hereby, the active electrode should be placed over the nerve trunk (97). Variation in the pulse duration and frequency can also be considered to reduce fatigue. Higher pulse durations in combination with higher frequencies increase the activation of sensory axons to the spinal cord. The reflex activity of the motor axons recruits a larger number of fatigue resistant muscle fibres (100).

Multi pad electrodes could also reduce fatigue. They reduce motor unit discharge rates by creating asynchronous discharge of motor units similar to voluntary contractions. The entire electrodes consist of small electrodes that are activated in an adjustable order. A similar approach is the application of interleaving ES where the stimulation alternates between the muscle belly and the nerve trunk. This method demonstrated that the stimulation of the peroneal nerve and the muscle belly of the tibialis anterior recruited different types of motor units (101). At present, it remains unclear whether this method can be applied to all muscles. Hence interleaving ES or stimulation with varying frequencies during a single treatment, appears to be the method most likely to be transferred to clinical practice.

## 1.6.8 MOTOR LEARNING BY FES

Paralyzed muscles lose their motor cortex representation within two months (102). During neurological recovery after cSCI, the maintenance of the representation of hand function, for example hand opening and closing, may support the relearning process without compensatory movement strategies. Popovic and colleagues have shown that even in subacute incomplete cSCI the combination of task – oriented grasping with FES is superior to task – oriented grasp training alone (31). Clinical observations have shown that in subacute and even in chronic stages after cSCI a FES task – oriented training could improve and maintain voluntary hand function. The following example describes a case of a patient with cSCI four years post lesion. The opposition of thumb and index finger as well as the active closure of the hand was reduced. The patients' goal was to close the buttons of his shirt. 16 weeks of stimulation, two to three times per day for 15-20 minutes, enabled him to perform his defined task. After finishing FES, the function persisted (Figure 6).

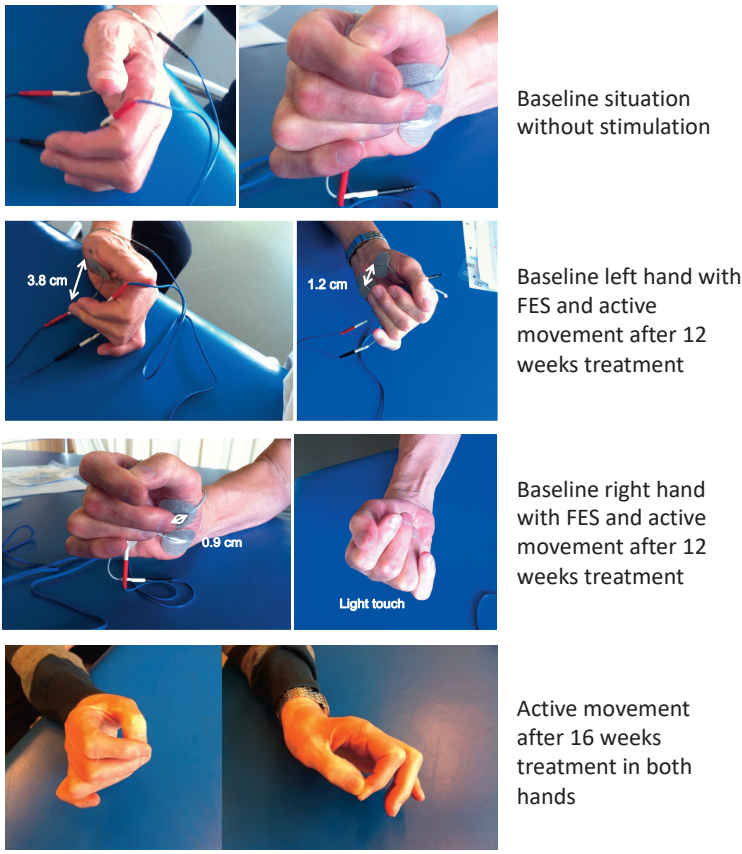


*Figure 6. Case report*

In the illustrated case FES had three benefits. First, the therapy was used as a short-term intervention. Second, the patient did not need to use his adaptive equipment any longer to fulfil special tasks and thirdly the patient regained more fine motor skills.

The EMG – triggered stimulation, cyclical stimulation, somatosensory stimulation in combination with functional task – oriented stimulation opens the field of motor learning and relearning (31,103-106). Clear definitions of the motor tasks and the movements to be learned therefore, are essential preconditions for the effectiveness of motor learning. Automatized movements that are already present or were present on the motor cortex are easier to learn then new movements (107). The muscles to be stimulated for the movement have to be tested by ES and the electrode positioning and the stimulation patterns have to be defined (108). In case of an EMG – triggered stimulation the threshold for the initiation or the support of the movement has to be defined. Finally, the movement with FES has to be performed under visual control and mental imagery of the patient. Concentration and motivation to perform the task are important to stimulate the motor cortex (109-111). FES without EMG – trigger use switchers to start the desired movement. Alternatively, cyclical FES is used for repetitive tasks. Depending on the stimulator and the available channels simple or complex movements can be executed. If once the stimulator is programmed and the motor points for the electrode positions are identified, the FES can be embedded easily into daily therapy (Table 3). It was shown that repetitive task – oriented training is essential for neuronal reorganization and recovery and thus motor learning (112). FES allows tetraplegic patients to train and use their hands in a way that would not be possible by solely voluntary function in early stages of rehabilitation. Therefore, FES can be used to retrain the neuromuscular system and should be applied already in the acute and latest in the subacute phase after cSCI.

*Table 3. Training schedule for motor learning in the upper extremities*

| **Stimulation parameters for upper extremities** | |
|---|---|
| **Pulse duration** | 250-400 $\mu$sec |
| **Frequency** | 35 Hz |
| **Amplitude** | 10-60 mA |
| **Training duration and number of sessions per week** | Daily once 30 minutes<br>Better twice to thrice a day* |

*based on the theory of repetitive task-oriented training

# 1.7 RISKS AND CAUTIONS

There are some cautions that must be respected when electrical current is applied through the skin on muscles or nerves. The skin reaction to the current under the electrodes varies. Normally, after stimulation a slight redness of the skin occurs and disappears within two to four hours. This can be considered as a physiological effect. However, if the redness is not homogenous and some singular red spots appear or only the edges of the electrodes leave a read margin, the reaction can be rated as a skin irritation. Even skin irritations disappear after several hours and do not necessarily reappear after the next treatment. However, the stimulation should not be repeated on an irritated skin area. In the unlikely event of blistering or skin burning the stimulation has to be stopped immediately and the reason for this adverse event has to be detected and documented. Most frequent reasons for skin irritations are defect electrodes, shaving of the stimulation area less than 5 hours before the treatment and the previous application of cosmetics containing alcohol. Skin burning might occur when using defect electrodes, by applying electrodes on inflamed or injured skin, as well as by the usage of self-adhesive electrodes and salt containing gel in direct muscle stimulation. When applying direct muscle stimulation, with pulse durations of ms, the user must be aware that the pulse duration is about thousand times longer compared to nerve stimulation (μs) and thus stronger.

Implants, such as osteosynthesis material or electronic devices as pacemakers should be checked regarding their position and function prior to the planned ES application.

In case of a cardiac pacemaker the application of ES via surface electrodes is possible in all parts of the body, even in the proximal parts of the upper limbs. The only procedural exception is to embed the cardiac pacemaker into the electrical field.

Osteosynthesis material does not present a general contraindication. If the electrical field embeds an implant like for example a screw the current flow is diverted and concentrated in the metal. This effect occurs mainly in direct

muscle ES. The stimulation effect is falsified (Figure 7). Hence, the usefulness of ES application should be reconsidered.

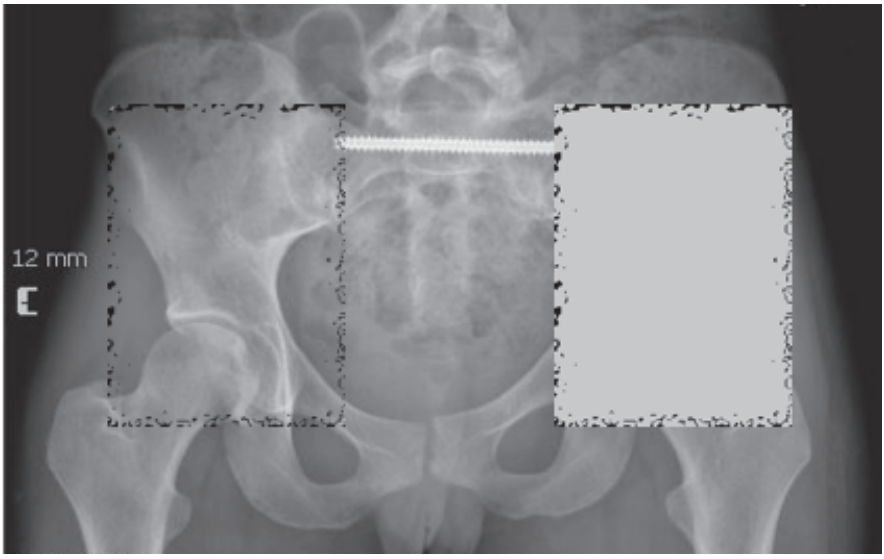


*Figure 7. Direct electrical stimulation of the glutaeal muscle with a fixation screw embedded in the electrical field*

ES can be assumed as a safe treatment method that does not cause damages if used properly. Fridén and colleagues described a myoneural necrosis and a loss of muscle strength by stimulating a cast – immobilized rabbit hindlimb (113). They used a current of 50 Hz with a duty – cycle of 4 sec stimulation on and 4 sec rest for 1 hour per day over a four weeks period. The adverse effects described, demonstrated that the application of ES with higher frequencies on atrophied muscles causes an additional decrease of muscle strength. This might be explained by the use of not modulated or stepwise increased frequencies (114) and the metabolic effect that higher frequencies cause higher ATP costs per contraction than lower frequencies (20Hz) (72). In addition, accumulation fatigue might occur by stimulating daily long periods without sufficient recovery. The myoneural necrosis, potentially caused by increased intramuscular pressure that led to ischemia under the cast during

stimulation is discussed in detail (113). With respect to the application of ES to SCI patients the particular physiological conditions of the muscles as well as the effect of the applied current on the muscle properties under various conditions have to be considered, including the time after lesion and the type of motoneuron lesion.

# 1.8 NEUROMODULATION

Restorative neurology utilizes the modification of residual nervous system function and is part of the rehabilitation in SCI. Techniques of neuromodulation belong to restorative neurology (115). One of those techniques is FES. Until now it is focused on patients with an upper motor neuron lesion. It is implemented in the acute and sub-acute stages after SCI to support the neurological recovery (116,117). Most studies focus on the lower extremities and gait activities (59,118,119). The results of our own retrospective study document the increase in FES induced as well as in voluntary force of the lower limbs in patients with complete and incomplete acute and subacute SCI. We could achieve an improvement in FES induced force for the extensor and flexor muscles of the legs as well as for the voluntary evoked force for the same muscle groups (Bersch and colleagues *Robot assisted training in combination with functional electrical stimulation for improving lower limb function after spinal cord injury,* accepted for publication in Artificial Organs).

These results encourage to transmit this method to the upper limbs. There is evidence that rhythmic and alternating locomotor output, such as leg or arm cycling is mediated by a spinal central pattern generator (CPG) (120). Forman and colleagues could demonstrate that the corticospinal excitability of the M. biceps brachii increased with the cadence of arm cycling (121,122). These findings are relevant because the corticospinal pathway that is involved in the voluntary control of motor output seems to be modulated by muscle activity. We suggest that by combining arm cycling with FES, this effect could be intensified. In addition, the effect of arm movements in modulating the corticospinal drive into the legs was investigated. In locomotor tasks the coupling of the upper and lower extremities supported by CPGs is hypothesized. Furthermore, there is evidence that there is a neural connection between the upper and lower extremities during rhythmic combined arm and leg movements, that can be performed by cycling (123). Zhou and colleagues could show that in incomplete SCI motor evoked potentials in the tibialis anterior muscle increased during simultaneous arm and leg cycling, latter supported by FES, whereas in the leg cycling alone did not (124). Bisio and colleagues demonstrated that motor training in combination with action

observation and FES could increase the excitability of motor cortical areas, mainly the primary motor cortex (59).

# 1.9 STIMULATION OF DENERVATED MUSCLES

In clinical practice the stimulation of denervated muscles gets increased attention. Not at least because of the promising results of the RISE (Research and Innovation Staff Exchange) project. In this EU project it was shown that ES of denervated muscles in SCI increased muscle mass and improved its trophic in the lower extremities (125). Furthermore, muscles structurally altered into fat and connective tissue could be rebuilt into contractile muscle tissue by ES (126,127). But it has also been shown that the increase of time extension after SCI hinders the impact of stimulation (114,115). Koh and colleagues investigated in rats the alterations in fibre cross sectional area (FCSA) and the effect of ES and its timing of application. They showed that the FCSA increased with ES by an immediate onset of stimulation after injury and that the structure could return to normal (128).

The denervation process of a muscle can be described by four chronological steps. First fibrillations appear after a few days, followed by a loss of tension during electrical evoked tetanic contraction. After months a severe disorganization of the contractile structure in the muscle occurs and finally ends after years in a transformation of muscle fibres into fat and collagen (129). The best results in terms of structural regeneration have been observed within three years after SCI (130). Nevertheless, even after five years of denervation followed by two years of daily stimulation the muscle could partly be reversed into contractile structures (131,132). Denervated muscles do not respond to short stimulation impulses (μs), that are used for innervated muscles. They require impulses of a longer pulse duration (ms) to achieve a muscle response.

The stimulation protocol started with single twitches for 12 weeks, five to seven times per week for 30 minutes, followed by a combination of single twitches and tetanic stimulation patterns until the completion of the trainings period (133). The progress in stimulation training to elicit a tetanic contraction – 40 ms pulse duration with a pulse pause of 10 ms and bursts of 2 sec for 30 minutes 5 times per week – could take some months in chronic stage after SCI (125). In most of the investigated studies the stimulation of the M. quadriceps, Mm. ischiocrurales and the M. gluteus maximus was performed to achieve

certain qualities for standing or walking. It has been shown that the CSA of denervated muscle fibres could increase by early ES and structural changes could be prevented (128). It indicates that early onset of stimulation could preserve the contractile structure in denervated muscles for potential reinnervation or further treatment options. This is of particular interest in the treatment of arm and hand function in cSCI even though until now, none has investigated the named effects on muscles of the upper extremities. Especially cSCI patients who would benefit from nerve transfers for hand and arm function, could gain time for making their decision (82). If a nerve branch is transferred into a denervated or partially denervated muscle it might be beneficial if the target muscle preserved its contractile structure. Therefore, the muscles affected should be trained daily (five times per week) by stimulation for at least 30 minutes each. This is a rather high time expenditure in consideration that only two muscles can be stimulated at the same time for technical reasons. In the acute and subacute phase after cSCI the prognosis to preserve the muscle structure by stimulation is good. Consequently, it justifies an early onset of direct muscle stimulation not least because ES could promote peripheral nerve recovery (Figure 8) (134). Provided that small muscles in the forearm and hand react in the same way concerning regeneration under direct muscle stimulation as those in the lower extremities do, the benefit of ES will justify the expenditure of time to perform this complex treatment.

# 1.10 DIFFERENCES IN STIMULATION PROTOCOLS FOR THE UPPER EXTREMITIES

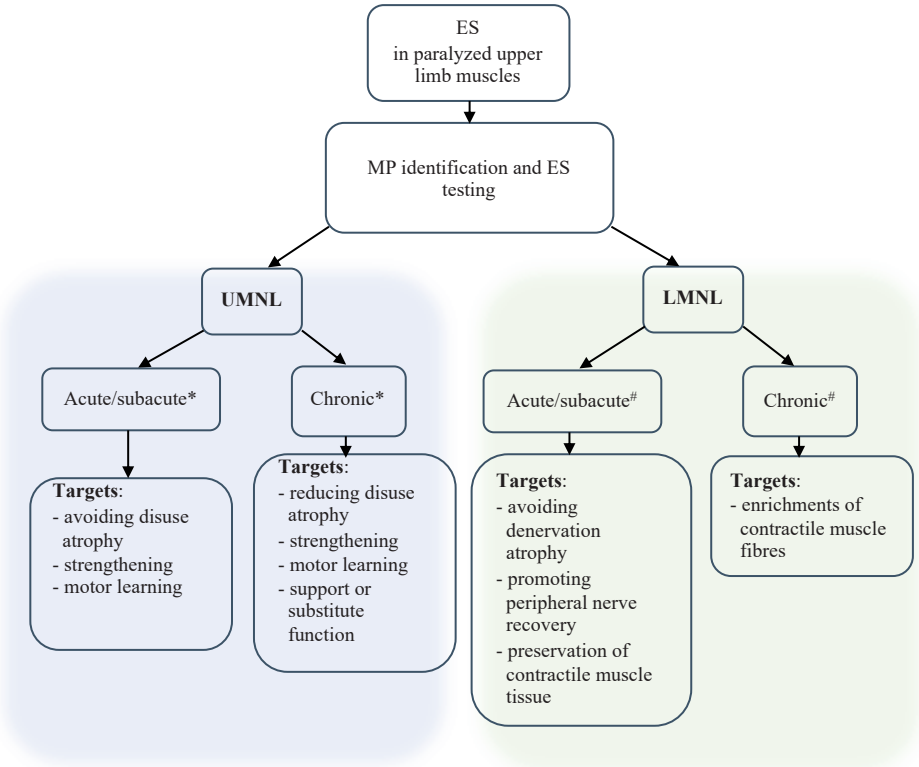


*Figure 8. Description upper extremity stimulation protocols Acute/subacute ≤ 6 months post SCI, chronic ≥ 6 months post SCI*(135), acute/subacute ≤ 2 years post LMNL, chronic ≥ 2 years post LMNL #(125)*

# 1.11 RECONSTRUCTIVE TETRAPLEGIA HAND AND ARM SURGERY (RTHAS)

The recovery of arm and hand function is one of the most important issues for patients after cSCI. Anderson reported that 49% of 347 people with cSCI would rate their quality of life decisively better if they could use their arms and hands better (136). This statement is confirmed by 77% of 565 people with cSCI in the English and Dutch populations (137).

Surgical techniques have been developed to improve hand and arm function in people with cSCI. The targets are the restoration of the elbow extension, forearm pronation, wrist movement, hand closure and opening involving the thumb. There are two therapeutic principles, tendon transfer and nerve transfer, requiring different surgical interventions. In a tendon transfer the distal tendon of an innervated and expendable muscle is detached from its original insertion, rerouted and reinserted into the tendon of a paralyzed muscle. This allows the patient to use the function of the paralyzed muscle by voluntarily activating the donor muscle. Optimally, a donor muscle should match the muscle architecture necessary for performing the new function with sufficient strength. (138,139). In addition, surrounding muscles in the adjacent joints, should provide sufficient control to ensure that the new arm or hand function can be used in ADL. Tendon transfers are mostly performed after achieving a neurological steady state, which can be expected after 6 months in complete cSCI. In incomplete cSCI it normally takes longer time until the nerve recovery is finished (140). Noteworthy, a tendon transfer remains possible even after years of cSCI.

In case of a nerve transfer, the donor nerve originates from a muscle innervation supplied by a supra – lesional segment. The recipient nerves are either located in a muscle innervated by an infra – lesional segment or by a nerve with a LMNL, mostly located in the intra – lesional segment of the spinal cord. In the latter case early surgery is required because of the proceeding neuromuscular endplate degeneration that results in a structural muscle alteration. Nerve transfers in those muscles are questionable regarding the recovery of their function.

# 1.12 COMBINATION OF ES AND RTHAS

ES has a potential to enhance hand surgery. There are five issues where ES supports rTHAS and can supplement the surgical intervention pre- as well as postoperatively.

1. ES can be used as a diagnostic tool in the planning of surgery. For that reason, a standardized mapping system for defined extensor and flexor forearm muscles, that are key actuators for wrist and grip function, was developed (67,82). It is used to detect an UMNL or a LMNL in the nerve supply of these muscles and provides assistance in the decision process for tendon and nerve transfers. The preoperative ES testing of potential donor and/or recipient muscles is a simple and reliable method to find out if the contraction of these muscles is sufficient or if the muscles show signs of denervation.

2. Preoperative selective ES of the donor muscle has a positive influence on strengthening, cross – sectional area, muscle structure and muscle fibre type adaptation. The strength of the donor muscle is crucial for a satisfying functional outcome.

3. Postoperative strengthening of the transferred muscle by ES statically or dynamically applied load may help to enhance the rehabilitation process. The strength of the arm – and hand muscles has a direct impact on functional capabilities and independence in ADL (141). Furthermore, strengthening is more effective and can be regained in a shorter time if classical therapeutic exercises are combined with FES (63,142).

4. EMG – triggered ES (voluntary – initiated, threshold – based activation) may improve the process of motor learning after rTHAS. In postsurgical treatment, EMG – triggered ES is applied to train the transferred muscle in performing its new function. It may also affect neuroplastic changes in the motor cortex to support motor learning.

5. Stimulation of denervated muscles in the acute and subacute phase after cSCI should preserve contractile muscle fibres and avoid denervation atrophy. If a nerve transfer is considered, the recipient muscle should at the best not show any denervation signs in order to achieve a good reinnervation result after surgery (143). Direct muscle stimulation could be performed to prolong the time window for the patients and surgeons' decisions for a nerve transfer in the upper extremities. Nevertheless, the influence of the direct stimulation on a denervated muscle or its related nerve and the expected functional outcome after nerve transfer remains unclear.

# 1.13 OUTCOME MEASUREMENTS

In this thesis the primary and secondary outcome measure is chosen to have a quantitative as well as a qualitative instrument to assess the impact of the interventions. In particular, the qualitative outcome measures should reflect the participants view regarding effort and benefit of ES. Force (N), torque (NM) and power output (W) represent the units of the quantitative outcome.

The voluntary and FES induced force and power output of the lower and upper extremities are measured on the MotionMaker™. This is a stationary robotic exoskeleton that combines passive and active leg movements and NMES of the lower limbs. The movements include extension and flexion in the hip, knee and ankle joints. The MotionMaker™ contains motors for each joint of the exoskeleton and sensors for position and force measurement. The device can be used with and without ES. The force sensors are located on the foot plates. The sensors to measure the positions are centred in each hip -, knee - and ankle joint of the orthosis. The position sensors record the horizontal and vertical leg movements. The described functions of the MotionMaker™ enables to measure torque and power output objectively and repetitively (Figure 9).

To measure the pushing force of the arms a special modification of the device was developed by the manufacturer. This allows to measure the power output of the arms in voluntary as well as by ES evoked pushing. For the purpose of a validation, patients perform two series of three repetitions each at maximal power output (Figure 10).


*Figure 9. MotionMaker™ in cycling mode*

*Figure 10. MotionMaker™ in the mode to measure the pushing force of the arms*

## Ultrasound (US)

US for the determination of the CSA and thickness of a muscle

US assessing muscle thickness and CSA was shown to be a valid and reliable method. The correlation coefficient between mean US measurements and mean actual measurements (in cadavers) was 0.993 ($p<0.001$) for the M. biceps brachii and M. brachialis regarding the validity. In addition, the intrarater correlation was 0.999 and the interrater correlation was 0.998 for the same muscles. The significance level was set at $p<0.001$ (144). Mohseny and colleagues investigated the reliability and validity for predicting the strength of intrinsic hand muscles by CSA on US. They showed a strong correlation between the CSA of the assessed muscles and their strength ($r=0.82$-$0.93$, $p<.01$). Furthermore, the intrarater reliability was described as excellent and as good for the interrater reliability of the method (145). Ultrasound measurements of muscle thickness serve as a valid and reliable assessment for the estimation of muscle size in the upper extremities. There is a relationship between muscle thickness measured by ultrasound and CSA and muscle volume measured by MRI. Muscle thickness might serve as a predictor for strength in the upper extremities (146).

US for the determination of the pennation angle (PA)

The PA is defined as the angle between the orientation of a fascicle and the attached tendon axis (147). For measuring the PA the US yields as a reliable and valid method that is easy to use, not invasive and cost effective (148,149). Nevertheless, this method is often underestimated. (147). The pressure of the probe that is given on the examined muscle is crucial. High pressure compresses the muscle and influences the result. The positioning of the probe must be defined precisely for repeated measurements. Bony landmarks or parallel lines to joints or other clearly reproducible marks e.g. intramuscular aponeuroses should be defined. At least it is recommended that in case of repeated measurements the same person performs the examination (Figures 11,12).

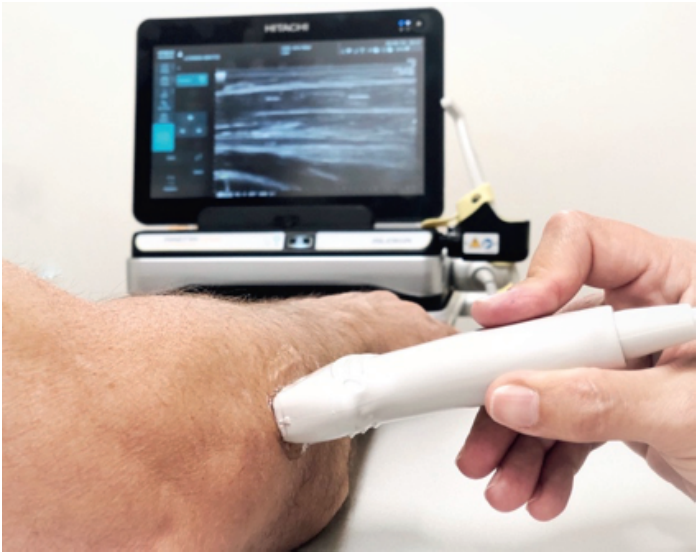

*Figure 11. Ultrasound imagination of the ECU*

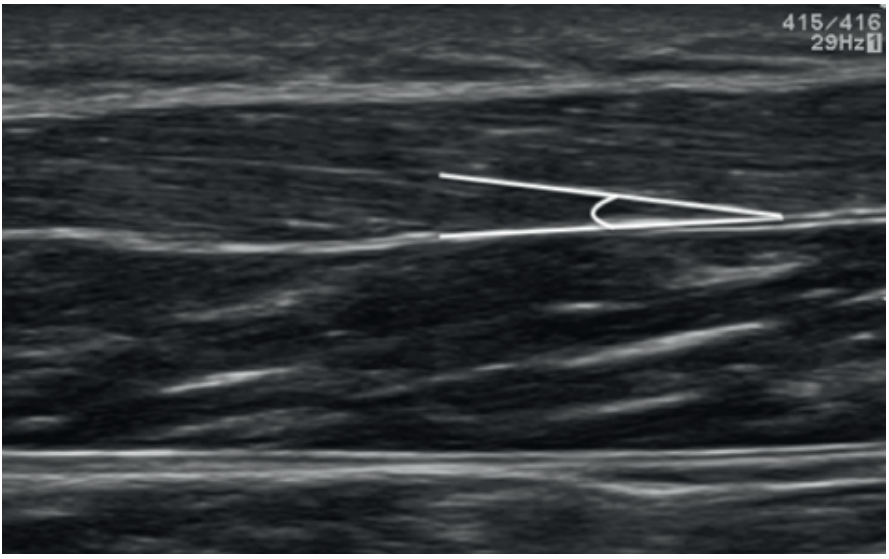


*Figure 12. Pennation angle of the ECU illustrated by ultrasound*

Questionnaire about participant perception of the treatment

A three-point questionnaire should give some evidence about the feasibility of ES regarding to a) expenditure of time, b) observed benefit, c) handling of the device.

This is intended to provide information why ES application is poorly used after rehabilitation in domestic setting (62). It may help therapists in their decision if and how ES is recommended for the individual patient and give engineers hints for further developments of devices and accessories e.g. electrodes or wireless transmission.

# 1.14 RATIONALE OF THE THESIS

In 1992 FES was introduced as a supplementary therapy method in rehabilitation of SCI at the Swiss Paraplegic Centre, Nottwil (SPZ). Over the years ES has been established as an essential part of in – and outpatient rehabilitation.

The time line illustrates the development and enhancement of the different treatment targets and their implementation into clinical practice. The constantly increasing number of treatments underline the successful approach of this method (Figure 13).

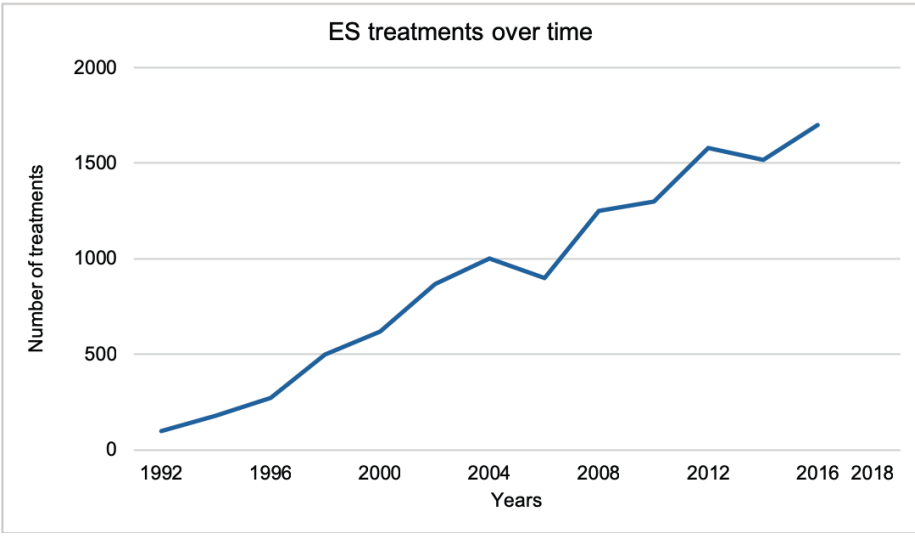


*Figure 13. Number of treatments per year in the Swiss Paraplegic Centre*

The indications for ES application extended stepwise. Every time a new indication was implemented the same process was pursued to decide when and how ES should be applied during the rehabilitation and to define the assessments that could evaluate the treatments outcome. Additionally, the treatment and the details of application as well as the expected benefit were

discussed with the patients. For 25 years a wide range of ES applications could be established as a part of the treatment in people with SCI and neuromuscular diseases.

Biomedical research is often initiated by a clinical observation or a specific clinical question. This approach is inductive. The present research project idea originated from the desire to optimize the muscle structure and function before and after rTHAS. ES had proven efficiency in the lower extremity to improve muscle contractile properties and function. Therefore, it was logical to address multiple clinical questions related to ES ability to improve and refine diagnostics and treatment options in the surgical and non – surgical upper extremity functional rehabilitation.

Beside the theoretical assumption some patients received FES before and/or after reconstructive arm- and hand surgery to strengthen the muscles that were essential for the patients transfer from bed to wheelchair as well as for wheelchair propelling. In these cases, the clinically observed outcome indicated improved muscle strength and function.

# 2 AIMS

The general aim of this thesis was to investigate how and in which cases ES can be used to support the efficiency of hand and arm surgery regarding tendon and nerve transfers in patients with tetraplegia.

Specific aims

a) to demonstrate if an ES mapping system of the forearm can be used to differentiate an UMNL and LMNL of the key extensor muscles affecting the tenodesis grasp and to analyse if a relation between the type of motoneuron lesion in the tested muscles and the final hand posture could be detected.

b) to develop a topography map for standardized stimulation points on the palmar forearm side and to detect if the M. pronator teres (PT), M. flexor digitorum profundus III (FDP III) and M. flexor pollicis longus (FPL) are affected by an UMNL or LMNL. These muscles are key actuators for grasp function. FDP and FPL are target muscles for nerve transfer to restore finger and thumb flexion.

c) to investigate if direct electrical muscle stimulation of denervated muscles has an effect on muscle structure preservation.

d) to investigate the difference between FES induced and voluntary force (Newton (N)) of the lower limbs in patients with incomplete SCI in the sub – acute phase using a stationary robotic device (MotionMaker$^{TM}$).

# 3 PATIENTS, METHODS AND RESULTS

# 3.1 RELATIONSHIP BETWEEN THE INDIVIDUAL STUDIES

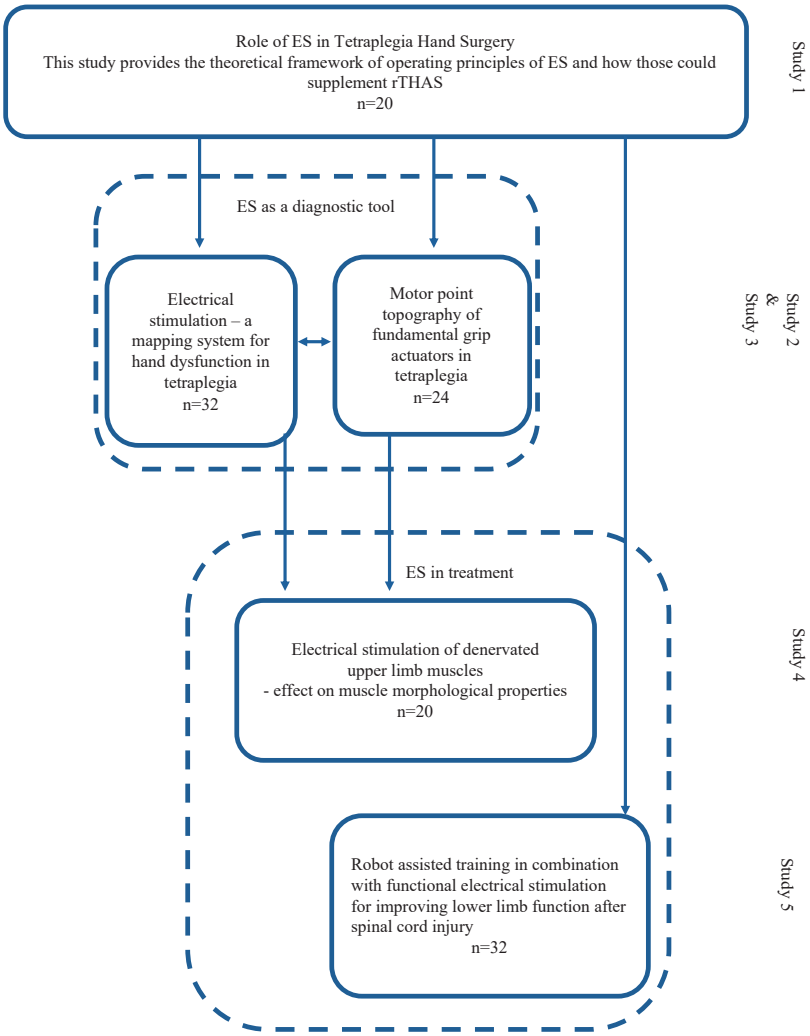


*Figure 14. Study Flow Chart*

## 3.2 ETHICAL CONSIDERATIONS AND APPROVALS

The studies comply with all applicable institutional and governmental regulations concerning the ethical use of human volunteers and were followed during the course of this research project. All studies were reviewed and approved by an internal review board (EGKF "Entscheidungsgremium für klinische Forschung") consisting of the board of directors of the Swiss Paraplegic Centre and Swiss Paraplegic Research.

**Study 1** provided a theoretical overview about the different effects and alterations of ES and the possible supplementation with rTHAS. Based on clinical evidence examples were described. No ethical approval was needed according to the internal review boards decision (see footnote).

**Studies 2 and 3** both addressed an existing clinical routine for ES testing that was optimized by the development of two standardized mapping systems. These studies were included in the project "The effect of functional electrical stimulation in tetraplegia reconstructive surgery of the upper limbs" (approved by the internal review board 08.07.2014). Because of the interventional part of this project it was also reviewed and approved by the national ethical committee of Switzerland and registered under Project ID 2016-02104. The interventional part of the project is still ongoing and detailed under chapter "Future directions".

**Study 4** was an interventional study with a treatment protocol, approved by the internal reviewer board on 05.06.2018. Thereafter, the study was approved by the national ethical committee of Switzerland and registered under Project ID 2018-01238 BASEC and in ClinicalTrials.gov NCT03698136.

**Study 5** comprised a retrospective data analysis which was based on a data collection used in clinical practice to document the treatment efficacy of a robot device. The use of data for analysis was approved by the internal review board on 09.10.2008 as a part of the study "Characterization of the changes in signaling pathways during spinal cord injury – induced skeletal muscle atrophy".

Footnote: According to the Swiss Human Research Law (2014) all data that are collected during the rehabilitation process may be used anonymized for research and publications. To guarantee the protection of data privacy, all patient received either a letter or were asked in the Swiss Paraplegic Centre if she/he agreed that their anonymous clinical data are used for research. The information about study participation and data management is handled by the Clinical Trial Unit of the Swiss Paraplegic Centre within the first 6 weeks (in case of a primary rehabilitation) after admission. If a patient neither wants to participate in a study nor wants to provide the collected data, a flag occurs in the clinical documentation system.

## 3.3 STUDY 1

### Methods

In a standardized and regularly performed consultation, all inpatients with tetraplegia are examined by a specialized interdisciplinary team within three months after injury as well as before discharge, typically nine months post – injury. The team consists of three hand surgeons, two physiotherapists and three occupational therapists. In case of eligibility for a tendon or nerve transfer the patients are informed about reconstructive arm – and hand surgery and an individual reconstruction plan for each patient is outlined.

Based on the results of the clinical screening process for reconstructive surgery the patients were therapeutically prepared for surgery, where ES was used as an integrated but not standardized treatment tool. So only few patients received FES before and/or after reconstructive surgery. According to the preconditions that are required for the donor muscle before rTHAS and the therapeutic treatment goals after surgery, a stimulation schedule was designed. This schedule is based on scientific articles and clinical evidence (29,150,151,152, 33,85). The stimulation protocol focuses on muscle strength and endurance (Table 4 – 6). To address fine motor skills and motor learning, EMG-triggered stimulation is applied after surgery 30 minutes daily for 2 weeks. The aim is to relearn a new function of a muscle that had originally another task. For example, after the transfer of the M. brachioradialis (BR) to the M. extensor carpi radialis brevis (ECRB) to gain wrist extension without concomitant elbow flexion and forearm rotation (the original functions of the BR). This motor learning process can be supported by EMG – triggered stimulation in functional task specific movements (104) (31). By executing a certain task, in this case wrist extension, the brain sends an order via the efferent pathways to the executive region (wrist). If the impulses achieve a sufficient threshold in the BR, the muscle contracts and a voluntary wrist extension occurs. As soon as the activity of the BR is detected by EMG, FES starts and supports and intensifies the contraction. Afferent nerves lead the information of BRs activity to the brain where the information is processed in terms of “activating the BR now leads to wrist extension”, which is the purpose of this exercise besides muscle strengthening.

*Table 4. Stimulation schedule*

| **Elbow extension** | | | | | | |
|---|---|---|---|---|---|---|
| **Before surgery** | Donor muscle | DEL | | | | |
| | Recipient muscle | TRI | | | | |
| | FES training | Loaded with resistance in function, 30 minutes/day, 3 times/week, 8 weeks | | | | |
| | Stimulation parameters | 300 µs | 20 – 50 Hz | 20 – 70 mA | 10 sec on time | 10 sec off time |
| **After surgery** | FES training | | | | | |
| | Onset after 4 weeks | Arm – cranking or movements without resistance, 30 minutes/day, 3 times/week, 2 weeks | | | | |
| | Stimulation parameters | 300 µs | 20 – 35 Hz | 20 – 40 mA | 10 sec on time (not arm – cranking) | 10 sec off time (not arm – cranking) |
| | Onset after 6 – 8 weeks | Arm – cranking against increasing resistance or functional movements against resistance or with load, 30 minutes/day, 3 times/week, 12 weeks | | | | |
| | Stimulation parameters | 300 µs | 20 – 50 Hz | 50 – 70 mA | 10 sec on time (not arm – cranking) | 10 sec off time (not arm – cranking) |

Abbreviations: DEL = Deltoid, TRI = Triceps

*Table 5. Stimulation schedule*

| **Wrist extension** | | | | | | |
|---|---|---|---|---|---|---|
| **Before surgery** | Donor muscle | BR | | | | |
| | Recipient muscle | ECRB | | | | |
| | FES training | With resistance in function, 30 minutes/day, 3 times/week, 8 weeks | | | | |
| | Stimulation parameters | 300 µs | 20 – 50 Hz | 15 – 50 mA | 10 sec on time | 10 sec off time |
| **After surgery** | FES training | | | | | |
| | Onset after 4 weeks | Dynamic movements without resistance, 30 minutes/day, 3 times/week, 2 weeks | | | | |
| | Stimulation parameters | 300 µs | 20 – 35 Hz | 15 – 30 mA | 10 sec on time | 10 sec off time |
| | Onset after 6 – 8 weeks | Functional movements against resistance or load, 30 minutes/day, 3 times/week, 12 weeks | | | | |
| | Stimulation parameters | 300 µs | 35 – 50 Hz | 40 – 50 mA | 10 sec on time | 10 sec off time |

Abbreviations: BR = Brachioradialis, ECRB = Extensor Carpi Radialis Brevis

*Table 6. Stimulation schedule*

| **Key pinch** | | | | | | |
|---|---|---|---|---|---|---|
| **Before surgery** | Donor muscle | BR | | | | |
| | Recipient muscle | FPL | | | | |
| | FES training | Loaded with resistance in function, 30 minutes/day, 3 times/week, 8 weeks | | | | |
| | Stimulation parameters | 300 µs | 20 – 50 Hz | 15 – 40 mA | 10 sec on time | 10 sec off time |
| **After surgery** | FES training | | | | | |
| | Onset after 4 weeks | Dynamic movement without resistance, 30 minutes/day, 3 times/week, 2 weeks | | | | |
| | Stimulation parameters | 300 µs | 20 -35 Hz | 15 – 20 mA | 10 sec on time | 10 sec off time |
| | Onset after 6 – 8 weeks | Functional movements with resistance or load, 30 minutes/day, 3 times/week, 12 weeks | | | | |
| | Stimulation parameters | 300 µs | 35 – 50 Hz | 30 – 40 mA | 10 sec on time | 10 sec off time |

Abbreviations: BR = Brachioradialis, FPL = Flexor Pollicis Longus

## Results

Twenty patients could be identified who received either pre – and/or postoperative FES (Table 7).

Two patients who received a posterior deltoid to triceps transfer were stimulated before the reconstruction. They were able to increase the strength of the donor muscle and improved the preoperative functional condition. Thus, the loss of strength of the transferred muscle during the postoperative period of immobilization was less noticeable. The preoperative muscle strength before and after 12 weeks of FES training was assessed by manual muscle testing and the self-reported stability of the arm during bed to wheelchair transfers. Three patients who received a triceps reconstruction exclusively used FES after surgery to build up muscle strength. The therapists documented a fast regaining of strength. They experienced the combined therapy of strength training supported by FES as more effective and faster than the strength training alone.

The 11 patients with grip reconstruction were trained after surgery with EMG – triggered stimulation to facilitate the transferred muscles new function. After two to three treatments, including grasping supported by FES, the patients were able to reach, grasp and manipulate an object twice as fast as observed in the same task specific training without FES.

The four patients, who had the combination of hand and triceps reconstruction received post operatively FES for strengthening but did not train regarding the recommended stimulation schedule illustrated in Table 4. Based on the reports of the clinical documentation system, FES was applied after therapy neither in function nor with resistance and additionally not regularly. Hence no comments were documented.

*Table 7. Patient characteristics*

| Patient | Gender | Diagnosis | AIS | Procedure |
|---|---|---|---|---|
| 1 | F | C5 | C | triceps reconstruction |
| 2 | M | Plexus lesion | | hand reconstruction |
| 3 | F | C6 | A | hand reconstruction |
| 4 | M | C6 | C | triceps and hand reconstruction |
| 5 | M | C4 | A | triceps reconstruction |
| 6 | M | C5 | A | triceps and hand reconstruction |
| 7 | M | C5 | C | hand reconstruction |
| 8 | M | C5 | B | triceps reconstruction |
| 9 | M | C4 | B | triceps and hand reconstruction |
| 10 | M | C5 | A | triceps reconstruction |
| 11 | M | C7 | C | hand reconstruction |
| 12 | M | C5 | A | hand reconstruction |
| 13 | M | C5 | D | hand reconstruction |
| 14 | M | C5 | B | hand reconstruction |
| 15 | M | C6 | A | triceps reconstruction |
| 16 | M | C6 | C | hand reconstruction |
| 17 | M | L3/TBI | C | hand reconstruction |
| 18 | M | C6 | B | triceps and hand reconstruction |
| 19 | M | C4 | D | hand reconstruction |
| 20 | F | LIS | | hand reconstruction |

Abbreviations: M = male, F = female, C = cervical, L = lumbar, TBI = traumatic brain injury, AIS = Asia Impairment Scale, LIS = Locked-in-syndrome

## 3.4 STUDY 2 AND STUDY 3

**Methods**

Development of a standardized ES mapping system in forearm muscles

The classification of UMNLs and LMNLs in forearm and hand muscles is crucial for the understanding for the development of hand function in tetraplegia. Furthermore, it might serve as a predictor for the expected outcome regarding hand position and function. It allows to determine the treatment effect of splinting and positioning of fingers and hand, physio – and occupational treatment strategies and finally to opt for the convenient operative method to restore grasp function either by tendon or nerve transfers. Hence, for the two elaborated forearm cartographies, the motor points of those muscles were chosen that are either key actuators for tenodesis grasp or are critical for nerve transfers.

The development of the cartography for five muscles on the dorsal side and the three muscles of the palmar side of the forearm was carried out in two steps before it was used for ES testing in patients. First, the diagonal line on the dorsal forearm from the most prominent part of the lateral epicondyle to the most prominent part of the radial styloid for the extensor muscles was determined. The other diagonal line for the muscles on the palmar side of the forearm stretched from the most prominent part of the medial epicondyle to the most prominent part of the radial styloid. Both lines served as landmarks to detect the stimulation points of the selected muscles (Figure 15 and 16). The location of the stimulation points of each muscle in relation to both lines was based on and defined after repetitive test measurements in able body population for its reproducibility. The mean forearm length in the able body test population was determined and served as the reference length for the calculation of the motor points. For the extensor mapping 20 able body (eight males and 12 females) adults and for the flexor mapping 48 (27 males and 21 females) were bilaterally tested.

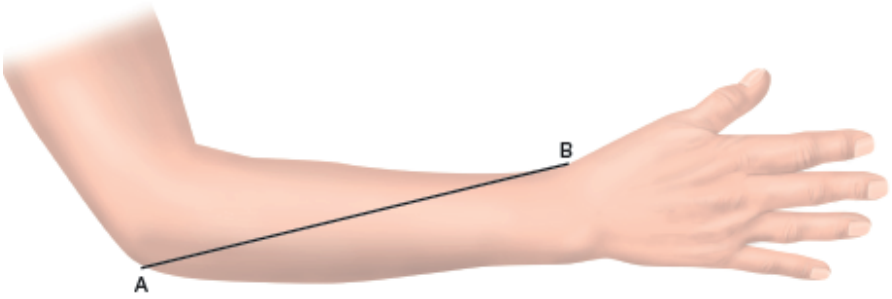


*Figure 15. Reference line for the extensor muscle motor points*

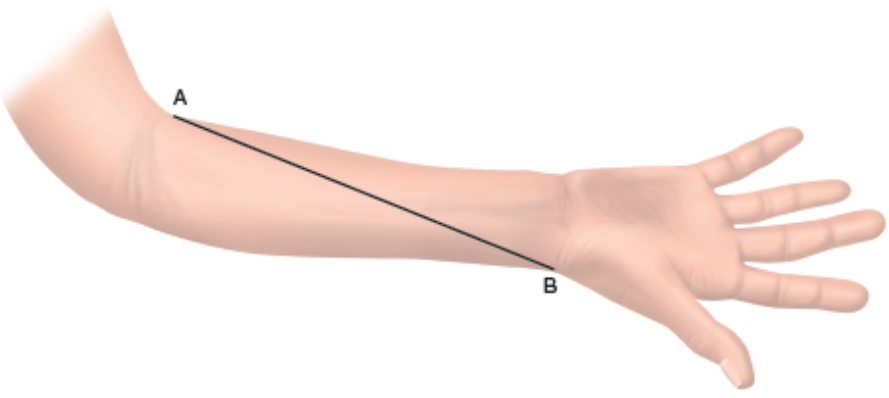


*Figure 16. Reference line for the flexor muscle motor points*

All distances of the stimulation points were generated in relation to the forearm length. The selected muscles on the dorsal forearm side were M. extensor carpi ulnaris (ECU) and radials (ECR), M. extensor digitorum communis (EDC), M. extensor pollicis longus (EPL) and abductor pollicis longus (APL) (Figure 17)

and on the palmar side M. pronator teres (PT), M. flexor digitorum profundus III (FDPIII) and M. flexor pollicis longus (FPL) (Figure 18).

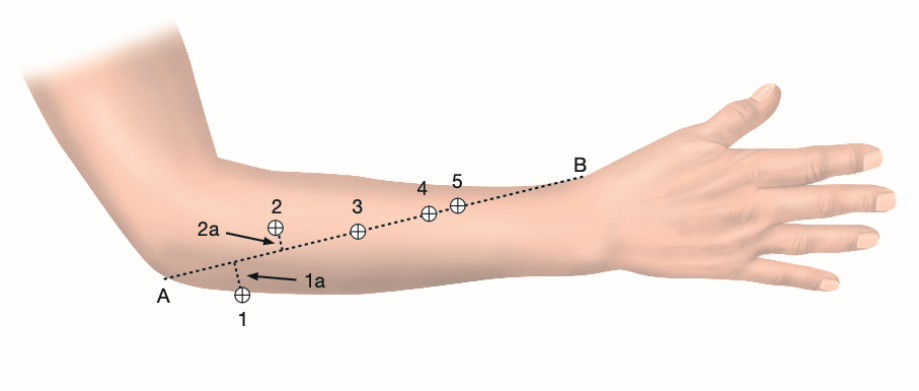


*Figure 17. Landmark line A–B lateral condyle to radial styloid including the distances A-1a, A-2a, A-3, A-4 and A-5, 1a and 2a to the stimulation points of 1 ECU, 2 ECR, 3 EDC, 4 EPL, 5 APL*

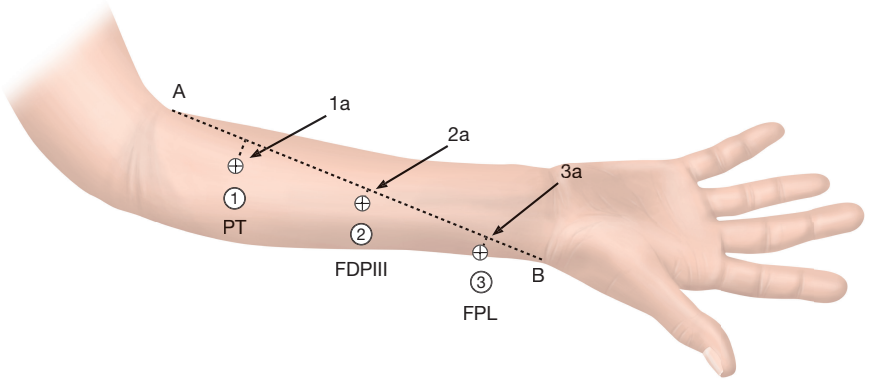


*Figure 18. Landmark line A – B medial condyle to radial styloid including the distances A-1a, A-2a, A-3a, 1a, 2a, 3a to the stimulation points of 1 PT, 2 FDPIII, 3 FPL*

One self-adhesive electrode was placed on the lateral epicondyle for the muscles innervated by the radial nerve or over the medial epicondyle for the muscles innervated by the median nerve. The corresponding electrode was a pen-electrode with a diameter of 0.5 cm. With the pen – electrode the motor points of the selected muscles were detected at the calculated stimulation points.

The testing of the able body reference group showed a reliable reproducibility.

Based on the testing results, the mapping systems were transferred to clinical routine. Up to this time the ES testing of motor points already was performed in clinical practice but not standardized so that a large variability between therapists and clinicians occurred. The most common inaccuracy arose between identifying muscles as denervated or partially denervated.

In patients, the standardized testing for the defined extensors and flexors was performed during rehabilitation and ambulatory consultation at the department of Tetraplegia Hand Surgery. The cartography was transferred by drawing the reference line either on the dorsal side and/or palmar side and the distances to the motor points were calculated. Subsequently, the ES testing could be performed easily, reliably and fast.

**Results**

In study 2 the data of 63 hands were analysed. 20 (31.7%) hands developed a tenodesis grasp. The remaining 42 hands (66.6%) showed no shortening of the finger flexors despite of consistent splinting and positioning. One hand was excluded by reason of a fracture. In all hands that developed a tenodesis grasp the EDC was not excitable by electrical nerve stimulation. One hand that had a partially denervated EDC developed no tenodesis grasp. Two patients developed unilateral tenodesis grasp and showed no tightening of the finger flexors on the contralateral hand.

A similar appearance could be seen in the position of the thumb to the index finger. 16 hands (25.4%) that showed a denervated EPL and APL could perform a passive movement of the thumb by dorsiflexion of the wrist, so that a lateral pinch could be performed. The stimulation matrix in Table 8

illustrates the distribution of the denervated, innervated and partially denervated muscles.

*Table 8. Stimulation matrix*

| | | | Voluntary activity (MRC) | | Stimulation matrix | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ID | NLI | AIS | ECRL (R) | ECRL (L) | ECU (R) | ECU (L) | EDC (R) | EDC (L) | EPL (R) | EPL (L) | APL (R) | APL (L) | TG (R) |
| 1 | C5 | A | 1 | 3 | | | | | | | | | YES |
| 2 | C6 | B | 5 | 4 | | | | | | | | | YES |
| 3 | C5 | A | 3 | 2 | | | | | | | | | NO |
| 4 | C6 | B | 5 | 4 | | | | | | | | | YES |
| 5 | C2 | C | 0 | 1 | | | | | | | | | NO |
| 6 | C5 | A | 2 | 2 | | | | | | | | | YES |
| 7 | C5 | A | 2 | 2 | | | | | | | | | YES |
| 8 | C4 | A | 1 | 0 | | | | | | | | | YES |
| 9 | C5 | A | 2 | 2 | | | | | | | | | NO |
| 10 | C4 | B | 1 | 3 | | | | | | | | | NO |
| 11 | C6 | A | 4 | 4 | | | | | | | | | YES |
| 12 | C5 | C | 2 | 1 | | | | | | | | | NO |
| 13 | C4 | C | 0 | 0 | | | | | | | | | NO |
| 14 | C3 | C | 1 | 1 | | | | | | | | | NO |
| 15 | C4 | C | 3 | 2 | | | | | | | | | NO |
| 16 | C3 | C | 0 | 0 | | | | | | | | | NO |
| 17 | C5 | C | 2 | 4 | | | | | | | | | NO |
| 18 | C5 | B | 3 | 3 | | | | | | | | | YES |
| 19 | C5 | D | 4 | 4 | | | | | | | | | NO |
| 20 | C6 | B | 4 | 4 | | | | | | | | | YES |
| 21 | C7 | A | 5 | 5 | | | | | | | | | NO |
| 22 | C3 | C | 3 | 1 | | | | | | | | | NO |
| 23 | C6 | D | 1 | 1 | | | | | | | | | NO |
| 24 | C4 | D | 4 | 5 | | | | | | | | | NO |
| 25 | C2 | D | 4 | 4 | | | | | | | | | NO |
| 26 | C5 | B | 2 | 1 | | | | | | | | | NO |
| 27 | C4 | A | 2 | nt | | nt | | nt | | nt | | nt | YES |
| 28 | C5 | B | 5 | 5 | | | | | | | | | NO |
| 29 | C4 | C | 1 | 1 | | | | | | | | | NO |
| 30 | C2 | D | 4 | 4 | | | | | | | | | NO |
| 31 | C6 | C | 4 | 4 | | | | | | | | | NO |
| 32 | C5 | A | 1 | 1 | | | | | | | | | YES |

Abbreviations: NLI = neurological level of injury, AIS = ASIA impairment scale, MRC = British medical research council scale, ECRL = M. extensor carpi radialis longus, ECU = M. extensor carpi ulnaris, EDC = M. extensor digitorum communis, EPL = M. extensor pollicis longus, APL = M. abductor pollicis longus, TG = tenodesis grasp, YES = tenodesis grasp, NO = no tenodesis grasp. Upper motor neuron lesion, partially denervated, lower motor neuron lesion.

Furthermore, the frequency of the tenodesis grasp differed significantly between the groups with an UMNL and LMNL ($p < 0.0001$). In Figure 19 the distribution of an LMNL (0) and an UMNL (1) in dependency on the tenodesis grasp of the tested muscles is illustrated. Hereby, the number 2 indicates “yes” for the presence of a tenodesis grasp. In contrast number 3 elucidates “no” for the absence of a tenodesis grasp. To illustrate the combination of the presence or absence of a tenodesis grasp, respectively, a LMNL or UMNL a numerical

code was chosen. The characters 0 and 1 refer to the type of lesion, whereas 2 and 3 relate to the tenodesis grasp. For example, 0:2 means a LMNL with the presence of a tenodesis grasp. The results highlight that there was none of the tested patients who had neither LMNL on the EDC and developed no tenodesis grasp nor an UMNL on the EDC and developed a tenodesis grasp.

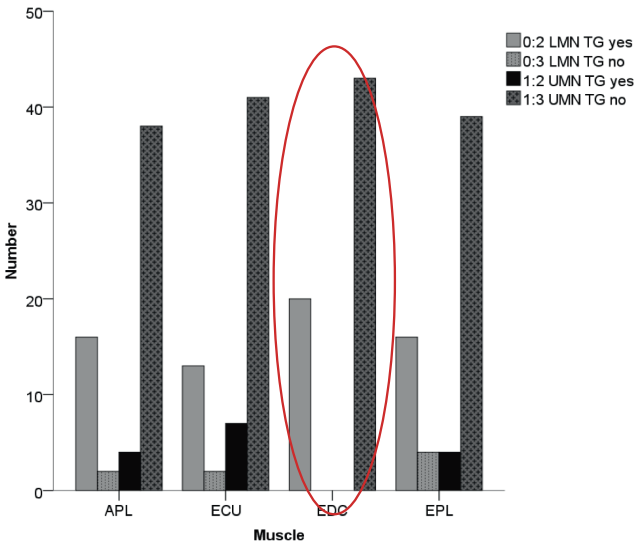


*Figure 19. Distribution of LMNL and UMNL in combination with the presence of a tenodesis grasp*

*Abbreviations: APL = M. abductor pollicis longus, ECU = M. extensor carpi ulnaris, EDC = M. extensor digitorum communis, EPL = M. extensor pollicis longus, 0:2 LMN TG yes = lower motor neuron lesion and tenodesis grasp, 0:3 LMN TG no = lower motor neuron lesion no tenodesis grasp, 1:2 UMN TG yes = upper motor neuron lesion and tenodesis grasp, 1:3 UMN TG no = upper motor neuron lesion no tenodesis grasp*

In study 3 the data of 44 arms were analysed. The muscles on the palmar side, innervated by the median nerve presented a higher number of partially denervated muscles than those on the dorsal aspect. In 16% the PT, in 23% the FDPIII and in 27% the FPL was partially denervated (Table 9). In contrast only 11.1% of the muscles, innervated by the radial nerve were partially denervated. The distribution was 1.6% each ECU and EDC and 8.0% the APL (Figure 20).

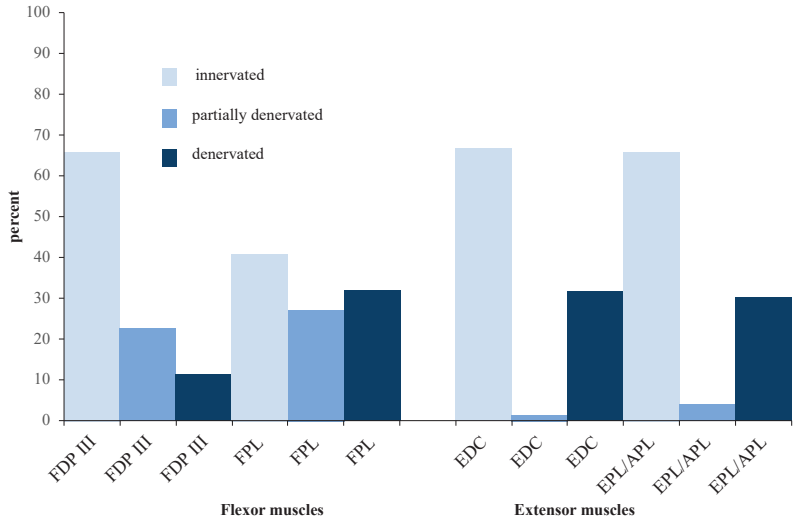


*Figure 20. Proportions of partially denervated and denervated muscles*

*Abbreviations: FDPIII = M. flexor digitorum profundus III, FPL = M. flexor pollicis longus, EDC = M. extensor digitorum communis, EPL = M. extensor pollicis longus, APL = M. abductor pollicis longus*

Most denervated muscles were found in the group with lesions at the levels C6 to C8. The denervated muscles corresponded to the level of lesion and their segmental spinal innervation (Table 10). Still, there were 4 patients where an unexpected denervation or partial denervation in at least one muscle occurred. In one C3 patient the PT was partially denervated. In another C3 tetraplegic patient the FDPIII was partially denervated and the FPL denervated. Both bilaterally. In two other C4 patients unilaterally once the FPL was denervated and once partially denervated (Table 9).

*Table 9. Stimulation matrix*

| Stimulation matrix | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ID | NLI | AIS | PT left | PT right | FDP III left | FDP III right | FPL left | FPL right |
| 1 | C2 | C | | | | | | |
| 2 | C3 | D | | | | | | |
| 3 | C3 | D | | | | | | |
| 4 | C3 | A | | | | | | |
| 5 | C4 | A | | | | | | |
| 6 | C4 | C | | | | | | |
| 7 | C5 | D | | | | | | |
| 8 | C5 | D | | | | | | |
| 9 | C5 | C | | | | | | |
| 10 | C5 | A | | | | | | |
| 11 | C5 | A | | | | | | |
| 12 | C6 | B | | | | | | |
| 13 | C6 | A | | | | | | |
| 14 | C6 | C | | | | | | |
| 15 | C6 | A | | | | | | |
| 16 | C6 | B | | | | | | |
| 17 | C6 | A | | | | | | |
| 18 | C6 | B | | | | | | |
| 19 | C7 | B | | | | | | |
| 20 | C7 | C | | | | | | |
| 21 | C7 | A | | | | | | |
| 22 | C7 | B | | | | | | |
| 23 | C8 | A | | | | | | |
| 24 | CMT | nt | | | | | | |

Abbreviations: NLI = neurological level of injury, AIS = ASIA impairment scale, PT = M. pronator teres, FDPIII = M. flexor digitorum profundus III, FPL = M. flexor pollicis longus, innervated, partially denervated, denervated, white = not tested, CMT = Charcot Marie Tooth

*Table 10. Innervation schedule*

| Spinal innervation segment | | | | |
|---|---|---|---|---|
| Muscle / Nerve | C6 | C7 | C8 | TH1 |
| PT / median nerve | | | | |
| FDPIII / median nerve | | | | |
| FPL / median nerve | | | | |

Abbreviations: PT = M. pronator teres, FDPIII = M. flexor digitorum profundus III, FPL = M. flexor pollicis longus

## 3.5 STUDY 4

### Methods

Stimulation of denervated muscles in the upper extremities and especially in forearm and hand muscles in people with SCI is rarely applied in practice and less investigated scientifically. The present investigation intended to monitor the effect of direct muscle ES on the muscle structure expressed by the pennation angle and the muscle thickness from baseline to the end of the stimulation period. The overall hypothesis was that direct muscle ES can preserve the function of the motor endplates and muscle excitability over the denervation process. The chosen two outcome parameters are combined to each other and can be imaged and measured by ultrasound (Figure 21) in clinical practice (153-155).

*Figure 21. Ultrasound performed on the IOD1 and ECU*

*Abbreviations: IOD1 = first dorsal interosseus muscle, ECU = M. extensor carpi ulnaris*

The study protocol was set up as illustrated in Figure 22.

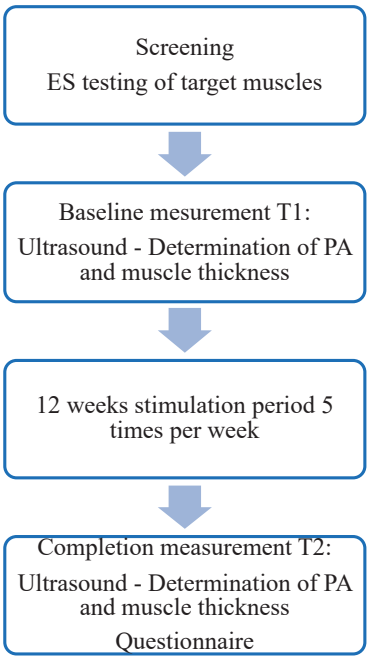


*Figure 22. Schematic study plan*

The patients were tested for eligibility during a standardized ES testing (described in Study 2 and 3). If an in – or outpatient fulfilled the inclusion criteria, he/she was informed about the study. After the defined time for consideration of 24 h the patient signed the informed consent.

No stimulation protocols exist regarding the intensity (mA) of stimulation of denervated muscles in the upper limbs. To elicit a contraction in a denervated muscle a long pulse duration is required. To induce a tetanic contraction the frequency should be at least 20 Hz. Pulse duration and frequency can be compared to the stimulation parameters for the large denervated muscles in the lower limbs, whereas the amplitude for small muscles has lower values. Based on the stimulation protocols that were used in the RISE project (125,133,156) the stimulation protocol was defined in the following way:

Depending on the number of muscles to be studied, 45 to 75 minutes of stimulation per session were required over a 12 weeks period. Two muscles could be stimulated simultaneously by using the Stimulette 2den, a two-channel device. For inpatients daily ES was embedded in the rehabilitation program and performed by the study staff (Figure 23).

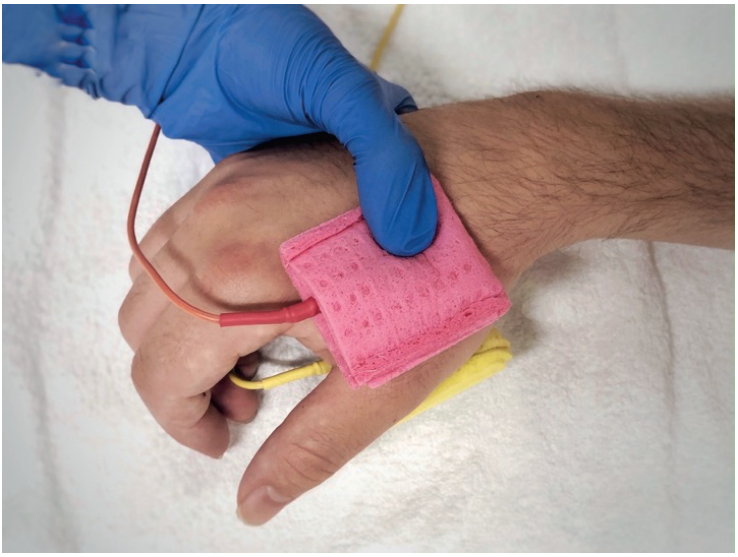

*Figure 23. Stimulation of the IOD1*

*Abbreviation: IOD1 = first dorsal interosseus muscle*

Outpatients performed the stimulation independently at home or with the help of their relatives or caregivers. The latter were supported by weekly telephone calls and had the possibility to call at any time if extra support was necessary.

A questionnaire about the perception and the effectiveness of the treatment was used as a secondary outcome.

## Results

The data of six male and one female patients with a median age of 46 (25/72) (min/max), AIS A, B and D with a median time since lesion of 0.5 (0.5/42) years could be analysed (Table 11). Seven EDC muscles and nine IOD1 muscles were stimulated.

*Table 11. Patient characteristics*

| ID | Gender | Age | Ethiology | Level of lesion | AIS | Time since injury (years) |
|---|---|---|---|---|---|---|
| 1 | m | 46 | traumatic | C7 | A | 1.5 |
| 2 | m | 47 | traumatic | C7 | B | 0.5 |
| 3 | m | 42 | non traumatic | CMT | nt | since birth |
| 4 | m | 71 | non traumatic | C7 | D | 2 |
| 5 | m | 25 | traumatic | C6 | A | 0.5 |
| 6 | m | 34 | traumatic | C6 | A | 0.5 |
| 7 | f | 72 | traumatic | C6 | D | 0.5 |

Abbreviations: AIS = ASIA impairment scale, m = male, f = female, nt = not tested, CMT = Charcot-Marie-Tooth disease, C = cervical

There was only a statistically significant increase in the median muscle thickness of 6 mm (1.4 mm/10 mm) to 10.7 mm (6 mm/12.3 mm) (p=0.016) and in the PA 6° (2°/8°) to 11.4° (9°/17°) (p=0.022) of the IOD1 (Figure 24). In contrast, there was neither a statistically significant change in the median muscle thickness of the ECU 10 mm (8.4 mm/12 mm) to 9 mm (4.4 mm/11.3mm) (p=0.469) nor in the PA 8.8° (1°/12°) to 11.5° (7.5°/18°) (p=0.125) (Figure 25).

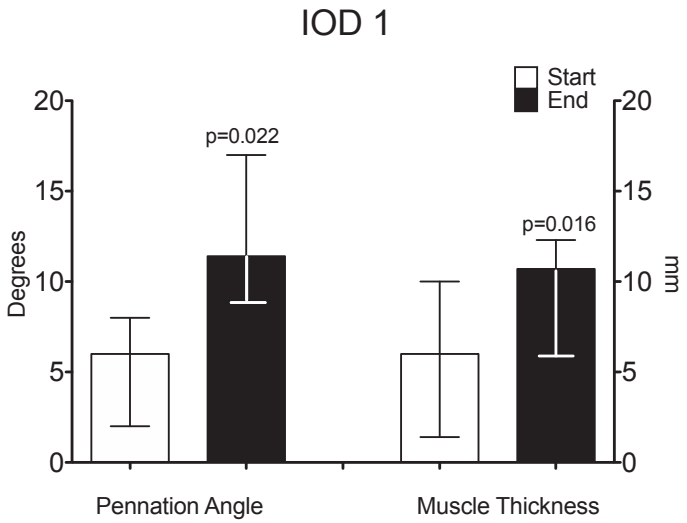


*Figure 24. Differences in PA and muscle thickness from baseline to completion after 12 weeks of ES in the IOD1, Abbreviations: IOD1 = first dorsal interosseus muscle*

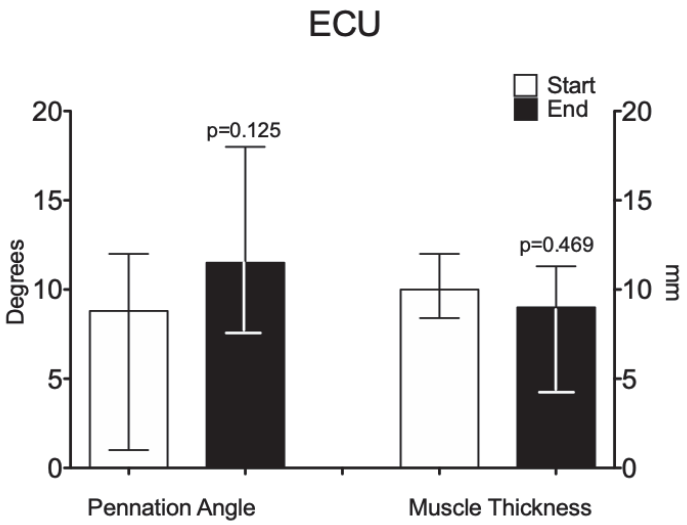


*Figure 25. Differences in PA and muscle thickness from baseline to completion after 12 weeks of ES, Abbreviations: ECU = M. extensor carpi ulnaris*

The results of the questionnaire showed that the users' convenience regarding the device as well as the time expenditure was assessed positively. Four of the seven patients could imagine using the ES as a long – term treatment (Figure 26).

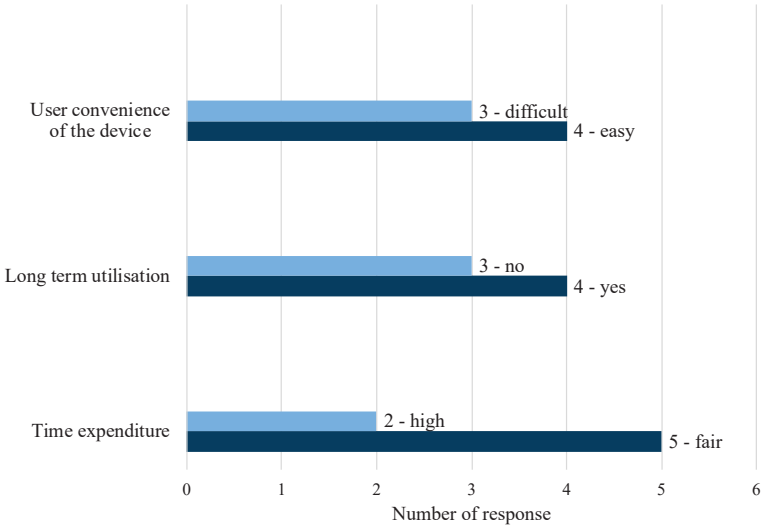


*Figure 26. Questionnaire about participant perception of treatment*

# 3.6 STUDY 5

**Methods**

In this retrospective study, data of inpatients with acute and sub – acute SCI who actively trained limb mobilization by using a stationary robotic system (MotionMaker$^{TM}$) were analysed. Each training session consisted of repetitive voluntary and FES induced flexion and extension of the lower limbs. First the voluntary movements were performed followed by the FES induced movements. During extension and flexion of the lower limbs, the following muscles were stimulated bilaterally: M. glutaeus maximus, M. rectus femoris, Mm. vastus medialis and lateralis (with separate electrodes on each part), Mm. ischiocrurales, M. gastrocnemius, M. tibialis anterior (Figure 27). First the voluntary movements without FES were performed and the integrated power sensors measured the voluntary force of the extensor and flexor muscles of the right and left leg separately.

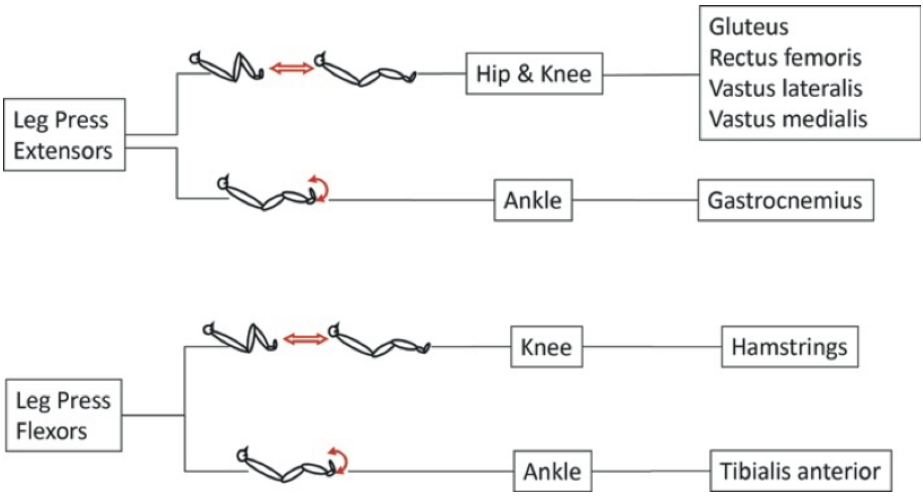


*Figure 27. Movements of the lower limbs and stimulated muscles during extension and flexion performed on a stationary robotic system. In the left box the movement is named, followed by the illustration of the movement and the corresponding joint. In the right box the stimulated muscles are listed.*

Subsequently the FES-supported force is measured as described before. The pulse duration was 300 μsec and the frequency 35 Hz whereas the amplitude was individually determined for each patient. These parameters remained unchanged throughout the training period.

The primary outcome was the improvement in force (N) of the legs from the first to the last training session during FES – induced as well as voluntarily induced flexion and extension. The secondary outcome was the sum score of active muscle function of seven lower limb muscles before and after the training period.

**Results**

Data of 32 patients with acute and subacute SCI were analysed. The median lesion time was 67 days. The number of the completed training sessions ranges from 3 to 25, with a median of 13 sessions.

There was a significant increase in median force from 2.38 to 3.48 N for FES induced extension ($p<0.001$) and from 1.29 to 3.03 N for voluntary extension ($p<0.001$). The FES induced flexion force increased significantly from 1.96 to 2.62 N ($p<0.018$) as well as the voluntary flexion force from 0.91 to 1.89 N ($p<0.001$). No significant correlations were found between FES induced and voluntary flexion ($r=0.275$, $p=0.128$). In contrast, the extension demonstrated significant correlations between FES induced and voluntary movements ($r=0.592$, $p=0.00$) (Table12). The median muscle sum score was 17 points at baseline and 24 points at the last session.

*Table 12. Correlation of FES – induced force and voluntary muscle force for leg extension and flexion*

| **Correlation between FES – induced and voluntary muscle force** | | |
|---|---|---|
| Extension | r = 0.592 | p < 0.001 |
| Flexion | r = 0.275 | p < 0.128 |

# 4 DISCUSSION

# 4.1 STUDY 1

The aim of this first overview article was to clarify wherein FES could support and supplement rTHAS. Therefore, principles of FES within the meaning of stimulation parameters regarding muscular physiology, activation and recruitment of muscle fibres, fatigue effects and principles regarding the improvement of muscle strength were explained. These criteria were contrasted with the prerequisites for rTHAS. Concurrently, existing data of patients that already received FES in combination with rTHAS were collected and analysed. Before surgery the muscle strength of the donor muscle could be improved by FES. Despite only two patients reported a subjective increase in strength, there is evidence that a combination of resistance training and FES is superior to training alone (63). Muscles which are not powerful enough to fulfil the criteria of becoming a potential donor could be strengthened with FES to make them suitable.

Moreover, the strengthening effect can be used after surgery when the therapy focuses on building up muscle strength to perform activities of daily living such as wheelchair to bed transfers and lifting and manipulating objects. If the FES strengthening is planned pre- or post-surgery the settings have to be considered carefully. If the training should be performed as an in- or outpatient setting, devices as stimulators and strengthening equipment as well as assistance must be available. If the patient is on her/his own or has only a caregiver to provide some help, stimulation and exercise protocols have to be adapted individually to make the training feasible. In addition, stimulation devices should be easy to handle.

The EMG – triggered stimulation showed a surprising effect in learning how to use the transferred muscle in the new function. To execute the demanded task by activating the muscle without compensatory movement strategies succeeded after two to three trials. In comparison, patients exercising without stimulation trained almost one week to achieve a satisfying result. The ES acts as an additional stimulus to the voluntary movement. As soon as some activity is detected in the muscle by the surface EMG the ES starts to intensify the contraction and thus the movement is enhanced. The initiation of the desired movement can be supported by visual and auditive feedback. Furthermore, the

device allows to place a second pair of EMG electrodes over the region where the donor muscle had its previous function. There the activity can be measured, and the device can be programmed to stimulate only if the activity of the previous function is lower than that of the actual desired one. A too strong activity of the donor muscle may lead to an unwanted movement according to its previous function. Hence the stimulation provides two targets, first the motor learning process of the new function of the transferred muscle and second the inhibition of the previous function. The effect of EMG – controlled stimulation on upper limb function and the activation of the sensory – motor cortex has been well investigated in stroke patients. Hara and colleagues could show a significant increase in brain cortical perfusion in the sensory – motor cortex of the damaged hemisphere by training with EMG – triggered stimulation in comparison to voluntary initiated movements alone (104). The increase of cortical perfusion is associated with an increase in activation. The clinical results in the cited study were a significant increase in the Fugl – Meyer score and in grip strength.

All the reported results have a limitation because they are based on clinical observations. These results served as a base and motivated to formulate the research plan for the studies II and IV as well as for a still ongoing study.

## 4.2 STUDY 2 AND STUDY 3

Both studies showed that the developed ES mapping systems could help to detect an LMNL and UMNL in forearm muscles of the dorsal and palmar aspects. In all tested muscles the localization of the stimulation points was reproducible in the tested able – bodied population and in the tetraplegic persons. In addition, the described mapping of function of defined muscles by ES on the forearm can be applied easily in clinical practice by therapists and clinicians. This clinical implementation can be supported by providing measuring panels, that can be used directly on bedside. The presence of an UMNL or LMNL of the key actuators affecting the tenodesis grasp or fine motor grasping influences further treatment strategies. First the development of a tenodesis grasp, second surgical interventions as tendon and/or nerve transfer. The formation of the tenodesis grasp is considered as the classical treatment to achieve a grasp and release function of the tetraplegic hand by active or passive extension of the wrist. The patients' group who can benefit from the tenodesis grasp are C5 – C7 tetraplegic persons. However, clinical experiences reported that despite of splinting, positioning and functional exercises the development of a tenodesis grasp is not guaranteed (157-159). One determining factor might be the innervation pattern of the EDC. As Study 2 (82) could emphasize, an UMNL of the EDC is one factor that influences the lack in tightening of the finger flexors and hence the closure of the fingers in active or passive extension of the wrist. Out of the 63 tested arms, the frequency of the tenodesis grasp significantly differed between the UMNL and LMNL groups ($p<0.0001$).

For therapeutic interventions, this finding indicates a need to modify the treatment schedule that most frequently uses splinting and positioning of the hand. The fingers are either taped at the palmar side of the hand (ECR < 3 MRC) or kept in position by using a glove or taping a lope (ECR ≥ 3 MRC) during day time. The splints or tapes can be taken off during therapeutic treatment. During night, an "intrinsic plus" splint is applied.

If the innervation pattern of the EDC is mainly responsible for developing an usable tenodesis grasp it would be reasonable to assume that in case of an UMNL of the EDC taping the fingers could be even counterproductive. Thomas and colleagues investigated the motoneuron excitability after cSCI. They showed that intrinsic motoneuron excitability could change the generation and strength of involuntary muscle contractions. In addition, it is mentioned that the excitability is less in the centre of lesion and one to two level below but increases further away from the lesion centre (160,161). These findings could match with ours that around the centre of lesion the LMN is damaged and therefore the motoneuron excitability is reduced. Another study investigated the firing rates in muscle spindles in static stretched muscles in SCI (162). Muscle spindles are sensitive length – tension receptors in the skeletal muscles. A stretch induced activation leads to an excitation of the Ia and II afferents in the spindle (163). The discharge of muscle spindle afferents is dependent on the resting length of the muscle and can be increased by pressure on the muscle belly or tendon or by moving the joint in the direction that increases the muscle stretch (164). One can hypothesize that by splinting or taping the fingers into a flexed position the stretch onto the finger extensors will excite the mentioned afferents, at least transiently. This occurs if the EDC has an UMNL. The actual intension to shorten the flexor muscle might be hampered by an increased activation of EDC. The result is a missing or inefficient tenodesis grasp. In contrast, if the EDC has a LMNL it could be useful to tape and splint the hand and fingers in a position to support the development of the tenodesis grasp if desired.

The distribution of innervated, partially denervated and denervated muscles differed from the dorsal aspect to the palmar aspect of the forearms in the tested cSCI patients. Whereas, the muscles in the coverage area of the radial nerve were mainly either innervated or denervated the number of partially denervated muscles of those in the coverage area of the median nerve was striking. The reasons for this finding remain unclear.

The type of motoneuron lesions affecting the key flexor muscles influence the early decision – making in nerve transfers. Accordingly, the three muscles PT, FDPIII and FPL were selected for the study. The FDP for instance is the key muscle to restore finger flexion and thus grasping. A suggested method to restore finger flexion is the nerve transfer from nerve branches of the brachialis muscle to the anterior interosseous nerve (AIN). The stimulability of the

recipient nerves influences if and when a nerve transfer is considered after injury. Nerve transfers are performed early even if the recipient nerves do not respond to ES. Several studies discuss the unpredictable outcomes and the controversial patient selection for this treatment (165-168). However, if a nerve transfer is considered it should be performed before the complete structural change of the muscle properties from contractile to connective tissue occurs. Neuromuscular endplates in denervated muscles degenerate over a period of two years (167). The fibre diameter reduction results in an averaged 30% decrease of CSA of the muscle. The remaining part of the CSA transforms into connective and adipose tissue (70,169).

If the LMN is intact, nerve transfers can be successful a long time after the lesion. Until now two methods have been used to test the integrity of the LMN. The electrodiagnostic testing consisting of nerve conduction and electromyography and intraoperative stimulation. Nerve conduction as well as electromyography will show abnormalities in case of denervation, the latter not immediately but in state of Wallerian degeneration. Both diagnostic assessments provide information about a LMN damage but less about its extent. Another method is the intraoperative nerve stimulation that triggers muscle contractions by nerves with an intact motoneuron. For this purpose, a biphasic current allows repetitive stimulations with low fatigue, Normally, those stimulators provide defined amplitudes with a variable pulse duration. This intraoperative stimulation is the most reliable assessment, but it is performed after the decision for nerve transfer. The electromyographic testing gives solid information but is invasive, requires time, equipment and usually neurologists to interpret the data. Nevertheless, the unpredictable outcome in flexor reinnervation suggests the investigation of clinical and electrodiagnostic predictors for the postoperative results (170).

ES as a diagnostic tool with a feasible, applicable mapping system to reliably find the stimulation points serves to determine the innervation pattern of the extensor and flexor forearm and hand muscles. It supplements the existing methods and is recommended to become standard in clinical rehabilitation.

## 4.3 STUDY 4

The case report of the seven patients shows that direct muscle ES could increase the muscle thickness and the PA over 12 weeks of daily stimulation (5 times a week, 33 minutes). The small sample size consisted of a mixed population of two chronic, one subacute and three acute patients after lesion. The data encourage to include a larger sample size to verify if a statistical significance can be found in both intrinsic (IOD1) and extrinsic (ECU) muscles. Moreover, a correlation between the increase of muscle thickness and the PA should be proven as it is described in other studies (171,148,154). In addition, the baseline muscle thickness and the PA should be analysed in relation to the time after lesion. The latter could provide evidence about the denervation and degeneration process in traumatic and non-traumatic SCI and illness causing tetraparesis. It might give information about the beginning of changes in muscle structure and whether they depend on other factors as age, gender or reason for lesion (traumatic, non – traumatic). The results could influence the onset of ES according to the time after lesion.

The results have an impact on treatment strategies. Thus, the clinical relevance to start early with direct muscle ES should be taken into account. This applies to the upper as well as to the lower extremities. In the upper extremities, direct muscle ES should also be focused on the proximal muscle groups, mainly the deltoid muscle and the rotator cuff muscles which stabilize the shoulder joint. In addition, the M. triceps brachii is a recipient muscle for tendon and nerve transfers to regain active elbow extension in people with tetraplegia. For a potential nerve transfer the muscle should have preserved contractile elements and degeneration should be avoided. Hence an immediate stimulation onset should be targeted. An effective direct muscle ES of the upper extremities requires current of high amplitudes and pulse durations, that has to be applied by relatively small electrodes (3x3cm, 5x5cm or 5x7cm). This elicits often an uncomfortable sensation during stimulation. The change of the wave form from rectangular to triangular can reduce the painful sensation but spreads out the electrical field to the neighbouring muscles (172). The current tolerance is individual and might be a limitation in performing an effective stimulation. Till now no empirical values for stimulation parameters are available due to the lack of studies on denervated muscles with ES in the upper limbs. The

applied current, mainly the amplitudes are based on clinical experience in ES of denervated muscle of the lower limbs and are adapted to the smaller muscles by reducing the intensities required for eliciting a muscle contraction.

In clinical practice it was difficult to implement the treatment into the rehabilitation process. In case of stimulating 4 muscles (both IOD1 and ECU) the patient was occupied for 75 minutes including setting up the device, 5 times per week. It has to be proven if the benefit of the ES justifies the time intensive treatment during primary rehabilitation.

# 4.4 STUDY 5

The results of this retrospective study demonstrate the increase in FES induced as well as in voluntary force of the lower limbs in patients with complete and incomplete SCI after a period of FES. The fact that FES can increase force and power output in persons with motor complete and incomplete SCI has been described in previous studies (84,63,47,92,173). The present results highlight some additional observations. The MotionMaker™ allows to differentiate between the increase of the FES induced force of the legs' extensor muscle group and the flexor muscle group. The extensor muscle group gained more strength than the flexor muscle group. The FES induced extension increased 1.1 N while the FES induced flexion increased 0.6 N. Similar turned out regarding the voluntary induced strength that increased 1.7 N for extension and 0.9 N for flexion. One explanation for this discrepancy could be the difference in the number of stimulated muscles. The stimulation in extension included M. glutaeus, M. rectus femoris, M. vastus medialis and lateralis and M. gastrocnemius. In contrast, the stimulated flexor muscle group contained only the hamstrings and the dorsiflexors of the foot.

It should also be taken into account that based on clinical observations, mostly the flexor muscles, namely the hamstrings, show slower and less neurological recovery than the extensor muscles during primary rehabilitation. To date, there is no neurological explanation for this observation. The correlation between FES induced and voluntarily induced movements for extension was significant but not for the flexion. This result could affirm the above – mentioned suggestion regarding slower and less powerful neurological recovery in flexor muscles. The patients could possibly not transfer the gain of the FES induced force into their voluntary leg movements in flexion. That led to another clinical observation that patients, training with FES on the MotionMaker™ reported difficulties to coordinate their voluntary muscle activity with the FES triggered activity, especially during flexion movements. One possible explanation that ES of the extensors is better transferred into voluntary activity could be found in a study by Gerasimenko and colleagues. They described a neuromodulatory effect by plantar pressure stimulation and the excitatory effects on locomotor activity (118). By stimulating the extensors during the MotionMaker™ training, the activation of the M.

gastrocnemius is included. Plantar flexion pressure stimulation was shown to activate the primary sensorimotor cortex that is associated with load – bearing stepping (118). This observation might explain the lack of correlation of the FES induced force and the voluntary force for the leg flexors.

The results of the study justify the application of this method to the upper limbs too. There is evidence that rhythmic and alternating locomotor output, such as leg or arm cycling is mediated by spinal central pattern generators (CPG) (120).

Forman and colleagues could demonstrate that the corticospinal excitability of the M. biceps brachii increased in dependence of the arm cycling cadence (122). This underlines the importance of the corticospinal pathway as a descending motor pathway involved in the voluntary control of motor output. It is suggested that by combining arm cycling with FES, the effect could be intensified. Bisio and colleagues demonstrated that motor training in combination with action observation and peripheral nerve stimulation could increase the excitability of motor cortical areas, mainly the primary motor cortex (59). Based on clinical experience FES supported arm cycling under action observation in the acute and subacute phase after SCI might enhance motor learning and thus motor recovery. Systematic clinical trials are required.

# 5 GENERAL CONCLUSION

The current studies have shown that two well established methods in SCI rehabilitation – rTHAS and ES – can supplement each other. ES can be applied as a diagnostic tool as well as for improving of functionality and muscle structure. In diagnostics, ES serves to differentiate between LMN lesions and UMN lesions by testing the motor points of selected muscles. The tested muscles are key actuators for further treatment options as nerve and tendon transfers and serve either as recipient or donor muscles. The early knowledge about the type of lesion might help physio – and occupational therapists to optimize their treatment like positioning and splinting of fingers and hand regarding the expected outcome of the hand shape and its functionality in tetraplegic patients. The early knowledge about a LMNL enables the early start of direct muscle ES to avoid the transformation from contractile muscle tissue into connective tissue and fat. This in turn prolongs the time axis for nerve transfers without impairment of the outcome. The positive results of the neuromodulatory effect in the lower limbs by increasing the voluntary as well as the FES induced force with a robot – assisted training may facilitate the recruitment of motor units and support the motor learning process in the upper limbs as well.

# 6 FUTURE PESPECTIVES

## 6.1 ES IN DENERVATED MUSCLES OF THE UPPER LIMBS

The results of the case series showed the effect on muscle thickness and PA in the IOD1 but less in the ECU. To verify a possible different effect of direct ES in long fibered extrinsic muscles to short fibered intrinsic hand muscles a higher number of participants is required. Furthermore, the influence of direct muscle ES on other muscle properties need to be addressed. Under ES, the muscle contracts and a mechanical tension occurs in the muscle fibres. If this is activated more by the structural fibre parts (e.g. molecule titin) the fibres increase under training in volume mainly by gaining length because the sarcomeres are added in series. If the tension in the muscle fibres is produced more by active actin – myosin – crossbridges, the fibres increase in diameter by adding the sarcomeres in parallel (162,163). Both alternatives lead to a muscle hypertrophy. How a muscle gains hypertrophy depends amongst other factors on its length and the lengthening velocity. If the applied stimulation releases a small range of motion, it is comparable to a strength training and results in increases of CSA, hence muscle thickness. In contrast, a full range of motion training regains more fascicle length (174). In the present study the ECU performed a full range of motion training during ES whereas the IOD1 executed only a partial range of motion under stimulation, caused by the patients' inability to extend their fingers and the thumbs. This might be an explanation for the differences between the increase in muscle thickness between the ECU and IOD1.

The recruitment of patients for this study will be continued until 20 patients are included.

## 6.2 ES AFTER NERVE TRANSFER TO PROMOTE NERVE REGENERATION

The early stimulation of denervated forearm muscles that might be eligible as recipient muscles for a nerve transfer showed a positive impact on muscle properties. It should be considered if a continuing stimulation might promote the nerve regeneration after nerve transfer as well. There is some evidence for a positive effect on motor and sensory function by applying ES in combination with exercise after peripheral nerve injury and surgical repair (134,175-178). To date all studies were performed in animals, except one, that investigated the effect of ES immediately after carpal tunnel release surgery in 21 persons (179). Only patients with distinct axonal loss of the median nerve were included. The participants were randomized in a stimulation and control group. The ES was performed with 4 – 6 V, 0.1 – 0.8 ms and 20 Hz on the median nerve as a single treatment for one hour after decompression surgery. All patients in the stimulation group showed an earlier and complete reinnervation of the thenar muscles in comparison to the control group. It was shown that the delay in regeneration of axons crossing the repair site was reduced so that a greater number of axons could reinnervate the target muscle. The positive effect of ES is explained by the increase of the expression of neurotrophic factors and their receptors in chronic and acute axotomized neurons (134). The latter findings and those of the stimulation effects on denervated muscles and their properties (129,180) might emphasize an additional treatment strategy after nerve transfers in the upper limbs of patients with cSCI. This implies the early start of the direct muscle stimulation of denervated muscle that may be considered for a nerve transfer and the immediate stimulation of the transferred nerve after surgery for one hour. Three to four weeks later when the nerve suture is resistant to mechanical traction, EMG – triggered stimulation can be applied to train the target muscle in its new function (181). In addition, it is of interest to determine if the representation of the regained function activates the corresponding area in the motor cortex that was reduced because of disuse.

## 6.3 TRANSCUTANEOUS CERVICAL SPINAL CORD STIMULATION

Transcutaneous spinal cord stimulation (tSCS) moves into the focus of clinical application since improvements regarding lower limbs functions in persons with chronic SCI have been reported (182,118,183). The influence at different levels of the lumbo – sacral spine by tSCS was shown (184). The activation of sensory and motor roots by tSCS triggered leg movements and improved muscle strength and function beyond the treatment session (185). Consequently, tSCS was applied on the cervical spine to investigate similar effects regarding upper limb function. Two case series reports on chronic SCI showed improvements in motor and sensory function mainly in the hand and forearm (186,187). These effects remained as well after the treatment period.

Interestingly, those patients who initially had a higher motor score could achieve better results regarding grip strength than those starting with a lower motor score (186). There is some evidence for reorganization of supraspinal networks and hence the recruitment of motor units. However the whole mechanism is poorly understood to date and it remains unclear if tSCS activates more the sensory afferent system at the level of the dorsal roots or the post – synaptic motor fibres belonging to the upper limbs (188). The latter would reflect a similar mechanism as in FES but less specific for function. Nevertheless, the development of this method should be followed. The future rehabilitation of SCI might combine the cervical tSCS to stimulate the residual functions by neuromodulation and promote neuroplasticity, followed by ES via nerve or muscle to regain more specificity. In addition, both techniques should be accompanied by task specific exercises whether manually or robot supported to regain known and automatized motor functions.

# 6.4 THE EFFECT OF FES IN RTHAS

Information about a current study

The current study *"The effect of functional electrical stimulation in tetraplegia reconstructive surgery of the upper limbs"* will provide information if FES before and after reconstructive tetraplegia hand and arm surgery combined with traditional physio – and occupational therapy supports the improvement of functional outcome after surgery. The primary objective is to investigate the effect of FES in terms of force and power output in innervated and transferred muscles before and after surgery. Both force and power output are measured as a surrogate for muscle strength. The secondary objectives are the performance and satisfaction of the participants measured by the COPM and grasp release test (GRT) before and after surgery. The muscle volume measured by US and the EMG should provide information about the activation of the transferred muscle in its new function during the motor learning process. Eligible are patients who will receive a tendon transfer either at the arm (elbow extension) or at the hand (e.g. wrist extension). 30 patients will be included in this randomised control trial. A block randomisation ensures that to each tendon transfer in the intervention group a counterpart in the control group exists.
FES is supposed as an add on therapy embedded in the standard therapy. The control group receives the standardized treatment after surgery. The flow chart illustrates the study process (Figure 28).

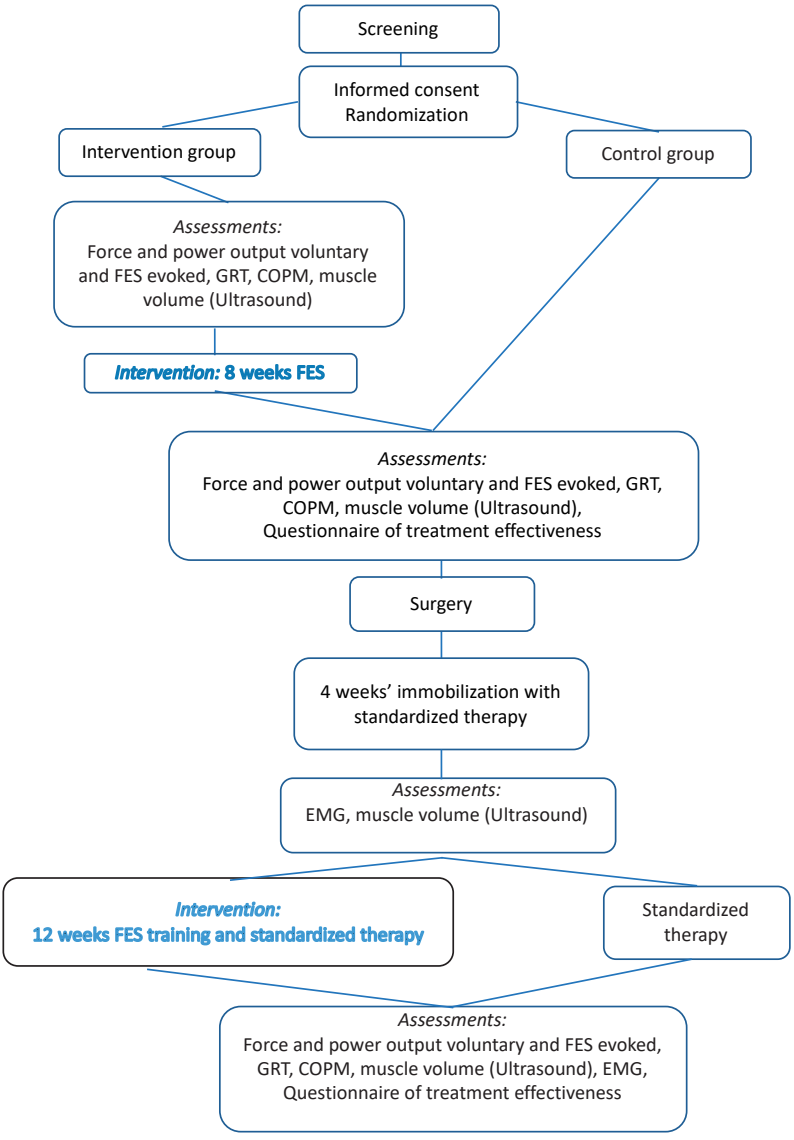


*Figure 28. Flow chart of the study*

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# APPENDICES

Paper I

Paper II

Paper III

Manuscript (IV)

Paper V