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DISSERTATION

Functional Electrical Stimulation of
Human Denervated Muscle:
Technical Equipment and Patient Study

ausgeführt zum Zwecke der Erlangung des akademischen Grades
eines Doktors der technischen Wissenschaften unter der Leitung von

Ao. Univ. Prof. Dipl.-Ing. DDDr. Frank Rattay

eingereicht an der Technischen Universität Wien
bei der Fakultät für Elektrotechnik

von

Dipl.-Ing. Christian Hofer
Matrikelnummer: 8825083
Schanzstraße 18/1501
1150 Wien

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Für Uschi, Fabian, Amelie und meine Eltern!

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Abbreviations

ACh	acetylcholine
AP	action potential
CAT	computed axial tomography
CT	computed tomography
DC	direct current
DDM	denervated degenerated muscle
DICOM	digital imaging and communications in medicine
EMG	electromyography
ES	electrical stimulation
FES	functional electrical stimulation
HU	Hounsfield unit
ISI	inter-stimulus interval
MFCV	muscle fibre conduction velocity
MFRP	muscle fibre refractory period
MU	motor unit
MUAP	motor unit action potential
NiMH	nickel-metal hydride
PDA	personal digital assistant
PC	personal computer
pixel	picture element
ROI	region of interest
SCI	spinal cord injury
SEM	standard error of the mean
SNEMG	stimulation needle electromyography
SR	sarcoplasmic reticulum
T system	transverse tubule system
T tubule system	transverse tubule system
TTX	tetrodotoxin
voxel	volume element

Kurzfassung

In Europa erleiden jährlich ungefähr 20 Personen pro Million Einwohner eine Querschnittslähmung. Ein Viertel der Verletzungen liegt im Bereich Conus Cauda oder Cauda Equina und führt zu Denervation und schlaffer Lähmung der unteren Extremitäten. Als Folge treten extreme Atrophie und später Degeneration bei gleichzeitiger Vermehrung von Fett- und Bindegewebe im und um den Muskel auf. Die Funktionelle Elektrostimulation (FES) ist derzeit die einzige Möglichkeit, die degenerativen Veränderungen in der denervierten Muskulatur zu verzögern oder sogar rückgängig zu machen.

Da die technische Ausrüstung für die FES denervierter Muskulatur bisher nicht als Medizinprodukt für die Therapie verfügbar ist – nicht zuletzt aufgrund einschränkender Vorgaben der EU-Normen für Reizstromgeräte - war ein wichtiges Ziel der gegenständlichen Arbeit die Entwicklung eines sicheren für eigenverantwortliche Heimanwendung geeigneten Stimulationsgerätes für Patienten mit schlaffer Querschnittslähmung.

Neue nicht- bzw. minimal invasive Methoden, welche den Muskel einerseits hinsichtlich seiner morphologischen Zusammensetzung und andererseits seiner elektrophysiologischen Eigenschaften beschreiben, waren ebenfalls Entwicklungsziele im Rahmen dieser Arbeit und erlauben eine quantitative Erfassung des aktuellen Abbau- bzw. Trainingszustandes der denervierten Muskulatur. Eine dieser Methoden basiert auf der erweiterten Auswertung von CT-Querschnittsbildern des Oberschenkels, eine zweite auf einer auf Nadelelektroden basierenden Technik, die Reizweiterleitung (M-Welle) einzelner Muskelfasern bzw. -fasergruppen zu vermessen.

Im Rahmen der klinischen Studie des europäischen Forschungsprojektes „RISE“ wurden die neu entwickelten Geräte und Methoden an Patienten erprobt. Nach zwei Jahren FES-Training zeigten die Patienten abhängig von der individuellen Denervationszeit vor Beginn der Studie verschiedengradige Verbesserungen hinsichtlich Muskelquerschnittsfläche und -gewebeverteilung sowie Leitgeschwindigkeit und Refraktärverhalten der Muskelfasern. Die Ergebnisse korrelieren mit anderen klinischen Untersuchungen und Auswertungen von Muskelbiopsien.

Die vorliegende Arbeit liefert den Nachweis, dass denervierte Muskulatur mittels Anwendung entsprechender Stimulationsparameter und Protokolle trainierbar ist und erhalten werden kann. Damit können in der betroffenen Patientengruppe häufig auftretende Sekundärerkrankungen mit schwerwiegenden Folgen wie Druckgeschwüre weitgehend verhindert werden.

Abstract

In Europe the rate of occurrence of spinal cord injury is approximately 20 per million citizens. About 25% of the patients have an injury in conus cauda or cauda equine which leads to denervation and flaccid paralysis of their lower extremities. This causes a severe loss of muscle mass (atrophy) and later degeneration accompanied by an increase in fat and connective tissue within and around the muscle. Functional electrical stimulation (FES) is currently the only way to slow down or even reverse the degenerative changes of denervated muscle.

Since technical equipment for FES of denervated muscle as a medical product is not available for therapy – not at least due to limitations by actual EU standards for stimulation equipment – one of the goals of this work was development of a suitable and safe stimulator for home based training.

Novel non- or minimal-invasive methods for assessment of muscle morphology and fibre specific electrophysiology were developed allowing a quantitative description of the muscle's tissue composition and electrophysiological properties. One method is based on CT scans of the patients thigh, a second is a special electrode needle based M-wave recording technique allowing to measure conduction velocity and refractory behaviour of single or small groups of muscle fibres.

Within the scope of a clinical study carried out in the context of EU research project "RISE" the developed equipment and methods were applied to patients. ES therapy with the developed stimulator was conducted over a period of two years. Depending on their denervation period before start of therapy the patients showed individual amounts of improvements of their muscle cross-sectional area and tissue composition and of their fibre conduction properties. The findings are in agreement with results from other clinical tests and biopsy analyses performed in the study.

The study showed the feasibility of training and maintenance of denervated muscles by application of long-duration impulses and appropriate protocols and a clear benefit in avoidance of secondary diseases like pressure sores - a frequent problem with severe consequences - in the target patient group.

Abbreviations	iv
Kurzfassung	v
Abstract	vi
1 Introduction	1
1.1 Aim of the study	3
2 The denervated muscle	4
2.1 Anatomy, Physiology (neuromuscular system)	4
2.2 Changes induced by denervation	12
2.2.1 Morphological, structural changes.....	13
2.3 Electrophysiological changes.....	15
2.3.1 Biomechanical changes	17
3 Stimulation equipment	18
3.1 Biophysical principles of the extracellular activation of nerve and muscle fibres.....	18
3.2 Basic principles of electrical stimulation	24
3.2.1 Electrical parameters	24
3.2.2 Stimulator technology.....	28
3.2.3 Electrode technology	29
3.3 Differences between “spastic, innervated” and “flaccid, denervated” muscles regarding electrical stimulation	30
3.4 Special design criteria for stimulators for long-term denervated muscles	31
3.5 Commercially available equipment, stimulators	33
3.6 A stimulator for functional activation of denervated muscles.....	34
3.6.1 Summary.....	34
3.6.2 Introduction	35
3.6.3 Concept of a suitable stimulator	35
3.6.4 Research prototype	36
3.6.5 Discussion.....	38

3.6.6	Additional details on the developed stimulator.....	40
3.7	Solution for experimental use (Experimental stimulator).....	45
4	Functional assessment of the denervated muscle.....	48
4.1	Stimulation Needle EMG / M-Wave.....	48
4.1.1	Muscle fibre conduction velocity	50
4.1.2	Muscle fibre refractory period	51
4.2	In vivo assessment of conduction velocity and refractory period of denervated muscle fibres	53
4.2.1	Abstract.....	53
4.2.2	Introduction	53
4.2.3	Materials and methods.....	54
4.2.4	Results	57
4.2.5	Discussion.....	59
4.2.6	Conclusions.....	60
4.3	Computed tomography	61
4.3.1	Muscle cross-sectional area measured by computed tomography	63
4.3.2	Quantification of tissue components, thigh and muscle composition (Distribution of density of tissue)	67
4.4	Isometric strength testing, knee extension torque	71
5	Human application (patient study)	73
5.1	Patients	73
5.1.1	Inclusion criteria	75
5.1.2	Neurophysiologic assessment	75
5.2	Stimulation training protocols, execution of training and time expenditure.....	76
5.3	Results	78
5.3.1	Required pulse duration for activation of denervated muscles .	78
5.3.2	Increase of knee extension torque.....	81

5.3.3	Change in size of muscle (muscle cross-sectional area)	83
5.3.4	Change in tissue composition	87
5.3.5	Electrophysiological changes (MFCV, ISI)	91
5.3.6	Functional outcome	95
6	Discussion	97
	Literature	108
	Appendix	118
A	Stimulation device programme listing	119
B	Matlab scripts for CT analysis and MFCV & MFRP	134
C	Operating and programming manual for the developed stimulation equipment (in German)	142
	Curriculum vitae	154
	• Personal data	154
	• Education, academic and professional background	154
	• Scientific publications	155

1 Introduction

Electrical stimulation (ES) is a method where a certain amount of current is applied to electrically excitable tissue like nerves and muscles in order to activate these structures in most cases. The first known, documented application of electrical stimulation for therapy dates back to approximately 400 years before Christ. Hippocrates treated asthma and various other diseases by means of electrical shocks produced by torpedo fish. In the 18th and 19th century a multitude of electrical stimulation devices for therapeutic application were developed. Most of them were based on electrostatic generators (Mc Neal 1977).

Functional electrical stimulation (FES) is the application of electrical stimulation to restore or improve lost or impaired function of the body due to neurological disorders caused by spinal cord injury, stroke, traumatic brain injury or neurological disease. The key experiment for functional electrical stimulation was the frog's leg experiment described by Luigi Galvani 1791 (Mc Neal 1977). He connected nerve and muscle of a frog's leg with an arc consisting of two different metals. The contact voltage elicited by this setup depolarised the contacted nerve and consequentially caused a contraction of the muscles. With this experiment Galvani could show the connection between electrical stimulation of the nerve and the contraction of muscles innervated by it.

Clinical applications of this principle were always closely connected to the technological progress. The first functional application of electrical stimulation is the pacemaker for the heart. Paul M. Zoll was able to maintain heart action by a pacemaker with surface electrodes for the first time in 1952 (Zoll 1952). Furman and Schwedel treated a patient 96 days with a pacemaker in 1958 (1959). Because of the size of this pacemaker, it had to be carried on a trolley in front of the patient. The stimuli were applied through percutaneous electrodes. A few months later the first fully implantable pacemaker was introduced. Nowadays far more than 500.000 patients per year are treated with cardiac pacemakers (Møller et al. 2002).

Other applications of functional electrical stimulation are restoring the function of the respiratory system (Judson and Glenn 1968, Talonen et al. 1990, Mayr et al. 1993), bladder and bowel (Ingersoll 1957, Brindley 1977, 1986), lower and upper extremity (Liberson 1962, Peckham et al. 1981, Marsolais et al. 1983, Holle et al. 1984, Kern et al. 1985, Keith et al. 1988),

the cochlear (Brackmann 1976, Banfai 1978, Hochmair et al. 1979), and the retina (Greenberg 1998, Uhlig et al. 2001).

All above mentioned applications, with the exception of the cardiac pacemaker, are based on the excitation of neural structures. The denervated muscle, however, has to be activated directly by electrical stimulation. That means that due to the absence of the nerve and thus the missing neuromuscular junction the cellular membrane of each muscle fibre has to be depolarised to elicit a contraction. This direct stimulation requires more energy and it is more difficult to achieve a contraction of the whole muscle since there is no branching nerve distributing the action potential to multiple parts of the muscle.

The use of electrical stimulation for denervated muscles is still considered to be controversial by many rehabilitation facilities and medical professionals. This is largely because current teaching and training for therapists is still based on the scientific and technological knowledge of the fifties and sixties. The literature contains a limited number of animal studies investigating the effects of long-term stimulation on denervated muscles, especially in the rat and rabbit. These have been designed mainly to address basic scientific issues (Mokrusch et al. 1990, Gunderson 1998). In virtually every case the muscles were denervated only for a short time before stimulation is commenced, and the results therefore have limited relevance to the human condition, where long-standing denervation has already resulted in severe atrophy and degeneration of muscle fibres. Other experimental work was mainly focused on strategies for reinnervation.

A clinical study on denervated muscles has, however, shown that degeneration after denervation could be at least slowed down, even with less than optimal equipment (Eichhorn et al. 1984).

An animal study demonstrated that FES delivered via implanted electrodes could maintain the action of the denervated sheep cricoarytenoid muscle for up to 18 months (Carraro et al. 1988, Zrunek et al. 1991). So far only two functional clinical studies have been published. One group from Slovenia has demonstrated correction of dropped foot by FES of the denervated tibialis anterior muscle (Valencic et al. 1986). The other study showed that the problems of muscle training and restoration of basic lower extremity movements in cases of flaccid paraplegia could be solved in principle, but also highlighted some of the problems that must be overcome before the technique could be introduced in clinical practice (Kern et al. 1999, 2002).

The target group for this study are spinal cord injured patients with denervated muscles. In Europe the incidence of spinal cord injury is approximately 20 per million inhabitants per year (Wyndaele and Wyndaele 2006) and about 25 % of the SCI patients have an injury also affecting the conus cauda or cauda equine leading to partial or full denervation of their lower extremities.

1.1 Aim of the study

- Design of appropriate stimulation equipment (stimulators).
- Development of novel assessment methods and the associated devices for evaluating the stimulation induced changes in the denervated muscles.
- Testing of the new developed equipment and methods within a clinical study.

2 The denervated muscle

2.1 Anatomy, Physiology (neuromuscular system)

In the human body two types of electrically excitable cells can be found: the nerve cell and the muscle cell. The excitability of these cells is the basis for the application of functional electrical stimulation. This chapter will give an overview about the anatomical and physiological fundamentals.

Structure and function of the nerve cell

The basic unit of nervous tissue is the nerve cell. The human nervous system consists of more than 10^{10} nerve cells (Silbernagl and Despopolous 1991). Typically a neuron consists of the soma (cell body), the axon and the dendrites which are emerging from the soma. In general the axon originating from the axon hillock of the soma transmits the action potential to other nerve or muscle cells. Axons are terminated by synapses which are connected to the soma or dendrite of a following neuron or to muscle cells (Figure 2.1).

In many neurons the axon is isolated by concentric layers of the Schwann's cells building up the myelin sheath. This myelin sheath is interrupted at certain distances by Ranvier's nodes. The so called myelinated nerve fibres with a rather high conduction velocity of 3 – 120 m/s are opposed by non-myelinated fibres with a conduction velocity of 0.5 – 2 m/s.

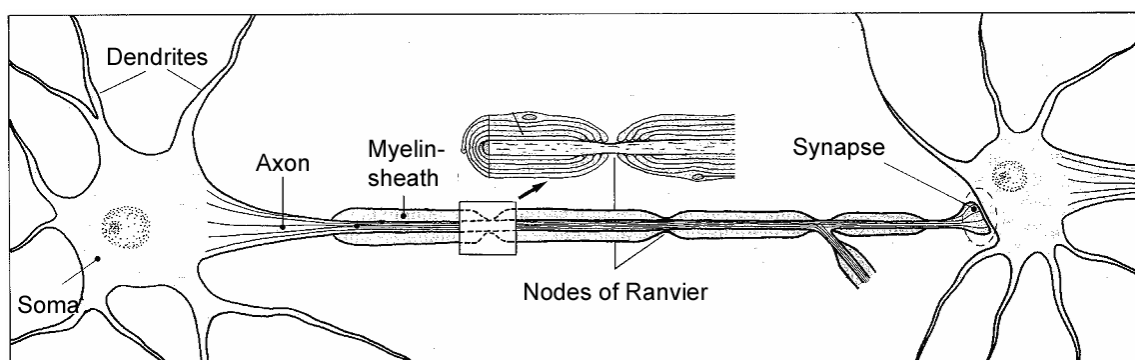


Figure 2.1: Composition of a nerve cell (adapted from Silbernagl and Despopolous 1991)

The nerve action potential is the fundamental unit used by the nervous system for transmitting information, it has a similar shape in all nerve fibres, with duration of about 1 ms and amplitude of approximately 100 mV. Electrical excitability of the nerve membrane is closely related to the voltage dependent permeability of the membrane. Active ion transport through the cell membrane maintains a precise internal concentration of several important ions, including Na^+ , K^+ , Cl^- and Ca^{2+} (Figure 2.2).

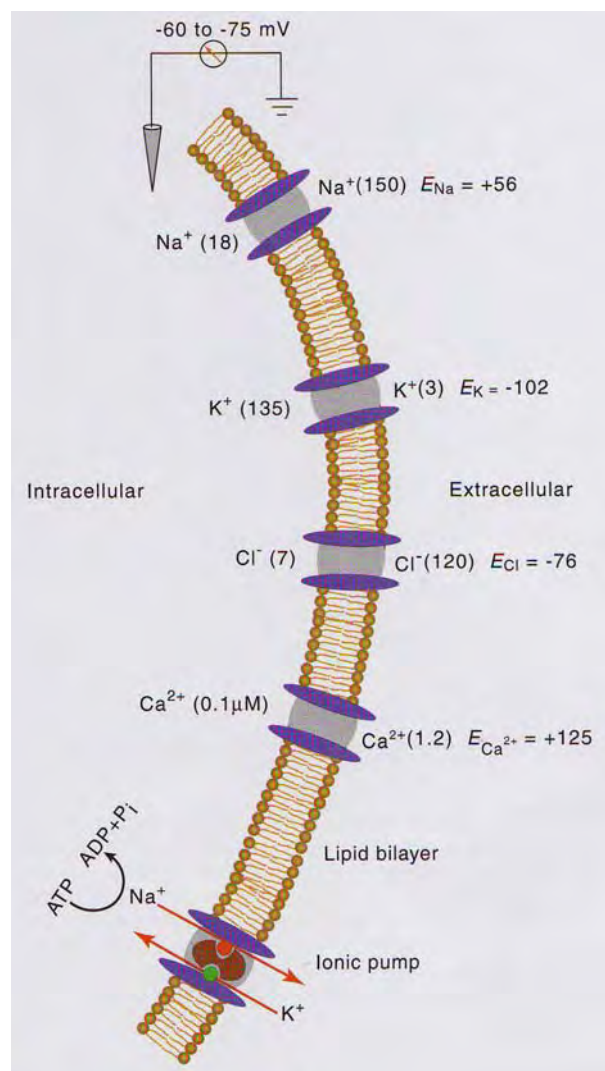


Figure 2.2: Resting membrane potential caused by differential distribution of ions inside and outside the cell membrane. Concentrations (in millimol/L except that for intracellular Ca^{2+}) of the ions are given in parentheses; their equilibrium potentials (E) for a typical mammalian neuron are indicated. (from McCormick 1999).

There is a big difference of the intracellular and extracellular concentrations of Na^+ , K^+ , Cl^- and Ca^{2+} . The ions have a tendency to diffuse according to their difference in concentration through the cell membrane but at rest the permeability of the membrane is very limited for these ions. This limited permeability and the operation of ionic pumps (e.g. $\text{Na}^+ - \text{K}^+$ ionic pump) are maintaining the difference in concentration of ions inside and outside the cell. Due to this unequal intra- and extracellular distribution of the ions a resting membrane potential of 70 – 90 mV is built up. The intracellular space carries a negative charge with respect to the extracellular space.

By application of an electrical stimulus to a nerve cell the voltage across the membrane changes and affects the ion conductance of voltage dependent ion channels within its membrane. If this stimulus exceeds a certain threshold, the ion current across the membrane rises suddenly and an action potential is generated. In a motor neuron this action potential propagates along the axon and finally causes a muscle twitch.

At the site of excitation following happens: The stimulus increases the membrane potential from about -70 mV towards 0 mV. When the threshold voltage is reached (typically -55 mV), the Na^+ -channels of the membrane are activated, causing a transient increase of the membrane sodium conductance. Due to the influx of sodium into the cell the membrane potential is breaking down – depolarisation phase. This depolarisation activates the K^+ -channels increasing the potassium conductance of the membrane whereas the sodium conductance already decreases and the membrane potential repolarises – repolarisation phase. The persisting activation of the K^+ -channels (and other membrane properties) causes the membrane potential to fall below the resting membrane potential – hyperpolarisation phase (Figure 2.3).

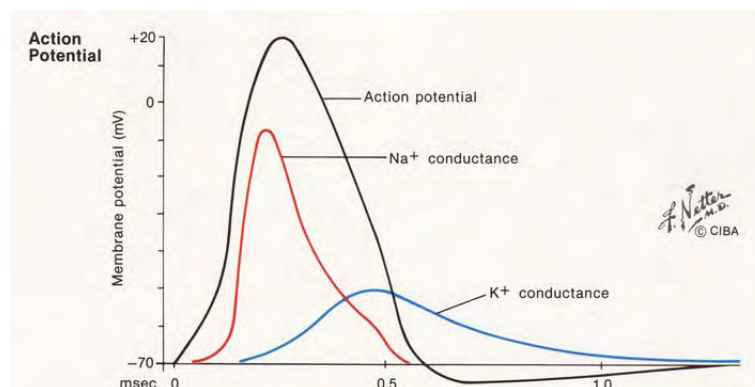


Figure 2.3: The generation of an action potential (from Netter 1983)

A stimulus eliciting an action potential does not have to be of electrical nature, it could be also a chemical, thermal or mechanical one. To cause a depolarisation certain conditions have to be met. The intensity has to be high enough and last long enough to reach the threshold level. This level depends on the tissue stimulated. Nerve cells can be activated with stimuli of much lower intensity than muscle fibres. Geometric factors are also influencing the threshold level. Nerve fibres with different diameter are showing different thresholds. The relation between intensity and duration of a sufficient stimulus is displayed by the strength-duration curve (Figure 2.4). This curve shows how long a current with given amplitude has to flow to elicit an action potential. The maximum current intensity not able to trigger an action potential even at infinite duration is called rheobase. The minimum pulse duration sufficient to depolarise the nerve or muscle fibre when the stimulus amplitude is twice the rheobase is called chronaxie.

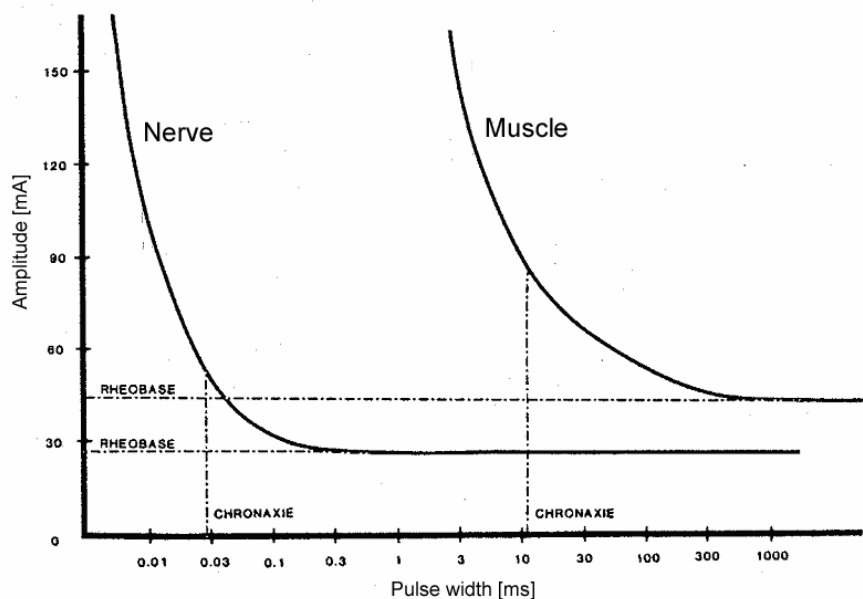


Figure 2.4: strength-duration curve (adapted from Benton 1981)

The shape of the action potential itself is independent from duration and intensity of the stimulus triggering it.

The structure of the skeletal muscle

The skeletal muscle cell has a diameter of 10 – 100 μm and a length of up to 20 cm. These muscle cells or fibres are bundled together to fibre bundles called the fascicles which are covered by the perimysium. The muscle on the other hand consists of a bundle of the fascicles covered by the epimysium. Contrary to most tissues in the human body the muscle fibre does not consist of a large number of cells. Instead the cell membranes have fused together to produce one large cell or syncytium containing multiple nuclei. The cell membrane of the muscle fibre is called the sarcolemma and the contents are called sarcoplasm. Within the fibre individual contractile units are called myofibrils which are divided into 2 μm long sarcomeres (Figure 2.5).

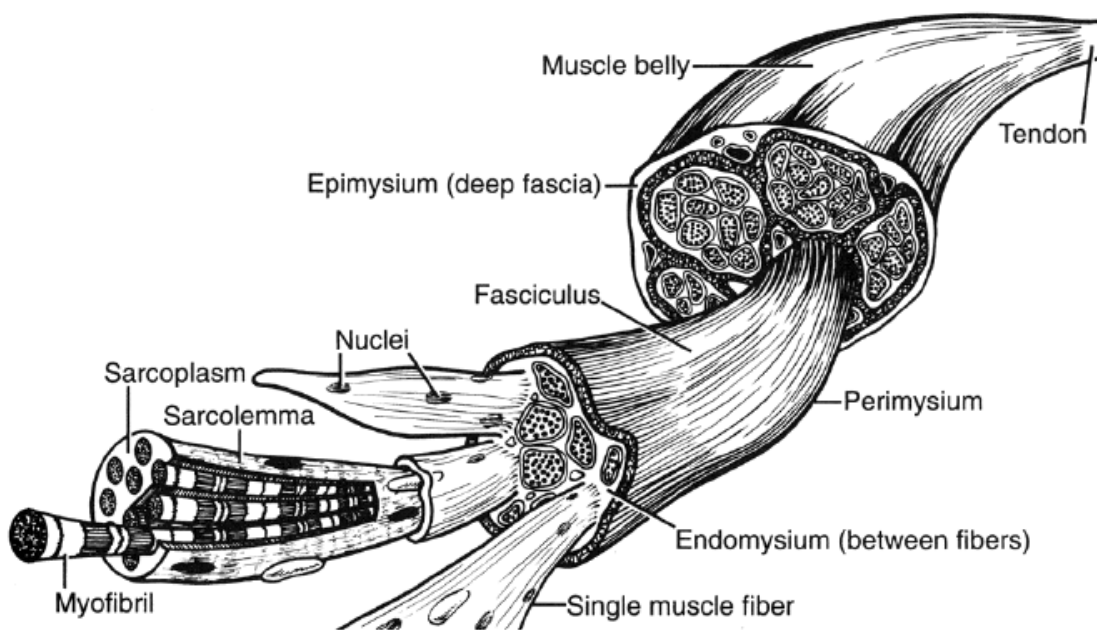


Figure 2.5: Composition of skeletal muscle. (McGinnis 1999)

The smallest functional unit of the muscle is the motor unit (MU), a combination of a single motor neuron and the muscle fibres innervated by it. According to the size and function of the muscle the number of muscle fibres building a motor unit is varying. Large muscles with high force output like the gastrocnemius muscle have MU's with a few hundred or thousand

muscle fibres. Whereas muscles for precise movements have MU's composed of very few fibres e.g. inferior and superior oblique muscles for control of eye movement have 2 – 3 fibres per motor unit.

The connection between the nerve and the muscle is called the motor end plate. It is effectively a synapse with acetylcholine acting as neurotransmitter (Figure 2.6). An action potential coming from the axon causes a release of acetylcholine from the nerve endings into the synaptic gap. The acetylcholine diffuses through the gap and activates specific ion channels on the sarcolemma. This causes a small change in the resting potential just sufficient to trigger the voltage gated sodium channels and to start the required action potential.



Figure 2.6: Motor end plates (from Wheater et al. 1979)

The action potential propagates along the sarcolemma and is distributed by the transverse tubule system (T tubule system) into the muscle fibre. T tubules come into close contact with the sarcoplasmic reticulum (SR), a form of the endoplasmic reticulum specialised for the release and reuptake of calcium in muscle fibres. The junction between the T tubules and the SR, called triads, are essential in the coupling between muscle excitation and contraction (Figure 2.7).

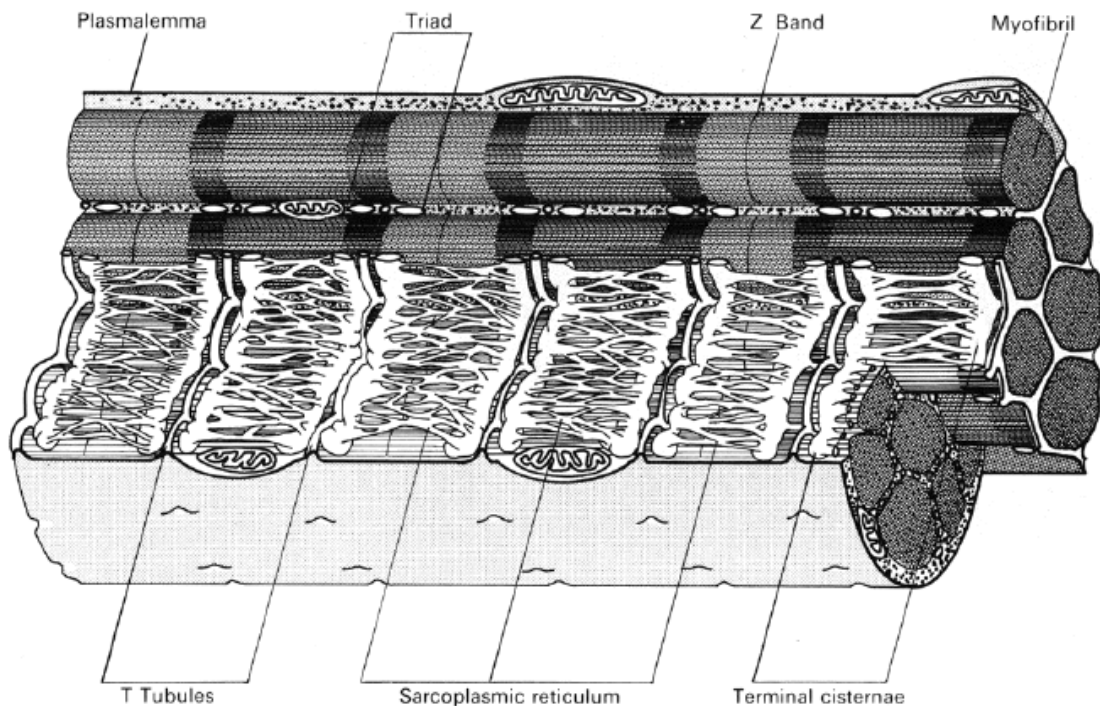


Figure 2.7: Structure of a skeletal muscle fibre (from Wheater et al. 1979)

The action potential transmitted into the fibre by the transverse tubule system causes a release of Ca^{2+} ions from the SR into the sarcoplasm leading to a contraction of the muscle fibre.

To a stimulus, with a strength exceeding the threshold for eliciting an AP, the muscle fibre always reacts with a contraction. Force generation of the muscle is controlled by two other parameters, the frequency of the stimuli and the number of motor units activated.

A single impulse elicits a muscle twitch, with increasing frequency the single muscle twitches are overlapping increasing the muscle tension. Above the twitch fusion frequency the muscle generates a steady level of force, or tetanus (Figure 2.8).

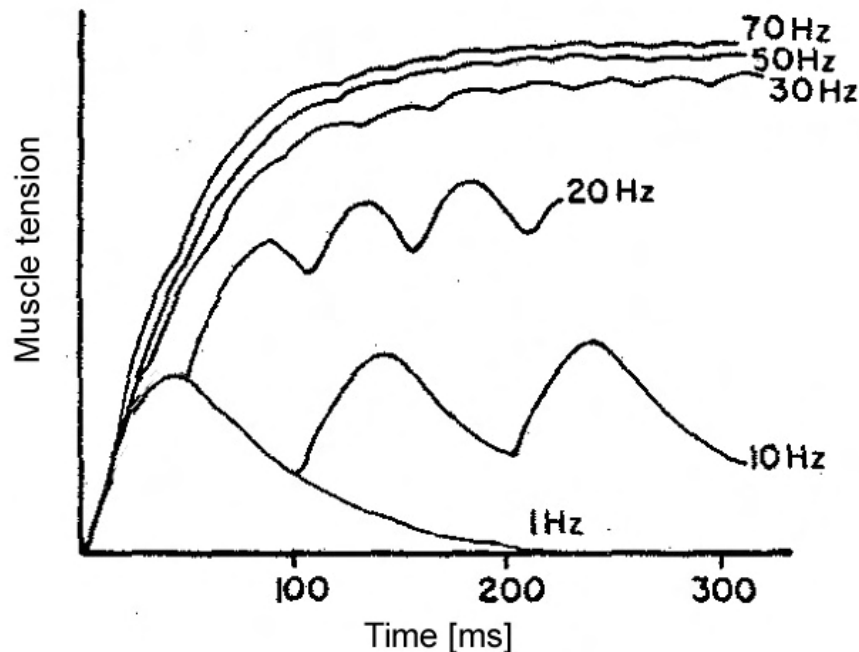


Figure 2.8: Superposition of muscle twitches with increasing stimulation frequency (from Benton et al. 1981)

The other way to control muscle force is to vary the number of simultaneously activated motor units. During a voluntary physiological contraction the motor neurons activated change continuously and also the frequency of the stimuli is varying. The advantage of this mechanism is that the muscle fatigues slower because the load is distributed over the whole muscle.

In contrast to this mechanism all motor neurons are firing simultaneously when excited by electrical stimuli. Additionally always the same area of the muscle is activated. This leads to faster fatigue of the muscle compared to normal voluntary activation. Further differences are caused by the recruitment order between physiologically and artificially excited muscles. Under physiological condition for generating low levels of force first thinner motor neurons are elicited, which are connected to slow fatigue resistant muscle fibres – type I fibres. If higher forces are demanded also the larger, faster motor units – type II fibres – are activated. Electrical stimulation activates the muscle in reverse order due to geometrical reasons. Thick fibres of motor neurons activating fast muscle fibres are more sensitive to an electrical stimulus than thinner fibres. That is why electrical stimulation causes faster muscle fatigue. In long-term stimulated muscles this reversed

recruitment induces a transformation of muscle fibre phenotype from the fast and fatigable glycolytic type II fibres to the slow and fatigue resistant aerobic type I fibres.

2.2 Changes induced by denervation

Denervation denotes the state that a muscle is deprived of the nerve normally activating it. The nerve influences the muscle by two different mechanisms: (1) by activating the muscle via electrical impulses (action potentials) causing the muscle to contract – neuromotor control and (2) potentially by delivering chemical substances via the axonal flow to the muscle – neurotrophic factors. The absence of these two different mechanisms is responsible for the changes in the muscle after denervation.

In literature the importance of the neuromotor control and neurotrophic factors is heavily discussed. At the beginning of studying the denervated muscle researchers were convinced that neurotrophic factors have a big influence on muscle properties but until today there are only a few studies providing evidence for changes in the denervated muscle caused by the missing neurotrophic factors of the nerve (Ramirez 1984, Behrens and Vergara 1992, Vergara et al. 1993, Ramirez et al. 1996 and 2003, Huang et al. 2002, Roy et al. 2002, Talon et al. 2005, Hyatt et al. 2006).

On the other hand almost all of the alterations of the muscle caused by short-term denervation can be reversed by electrical stimulation of the muscle as shown in animal experiments (Hník et al. 1962, Salmons and Vrbová 1969, Lømo and Westgaard 1975, Pette and Vrbová 1992, Awad et al. 2001, Salmons et al. 2005, Ashley et al. 2007). This indicates that activity is the major factor influencing muscle properties.

Causes for denervation can be of different nature. Denervation may be due to a disease where the death of motor neurons causes the denervation of muscle fibres (e.g. poliomyelitis), due to a chemical substance blocking the synaptic transmission of the action potential (such as botulinum toxin) or physical injury damaging peripheral nerves (as by accident).

This work is focused on spinal cord injured subjects with lesion in the conus cauda or the cauda equine. Depending on the completeness of the lesion this leads to full or partial denervation of both lower limbs. Contrary to paraplegic patients with spastic paralysis where the peripheral nerve (motor neuron) is preserved these patients do not show any muscle activity –

flaccid paralysis. The anatomical level of the spinal cord injury determines if the paralysed muscles are denervated or innervated (Figure 2.9).

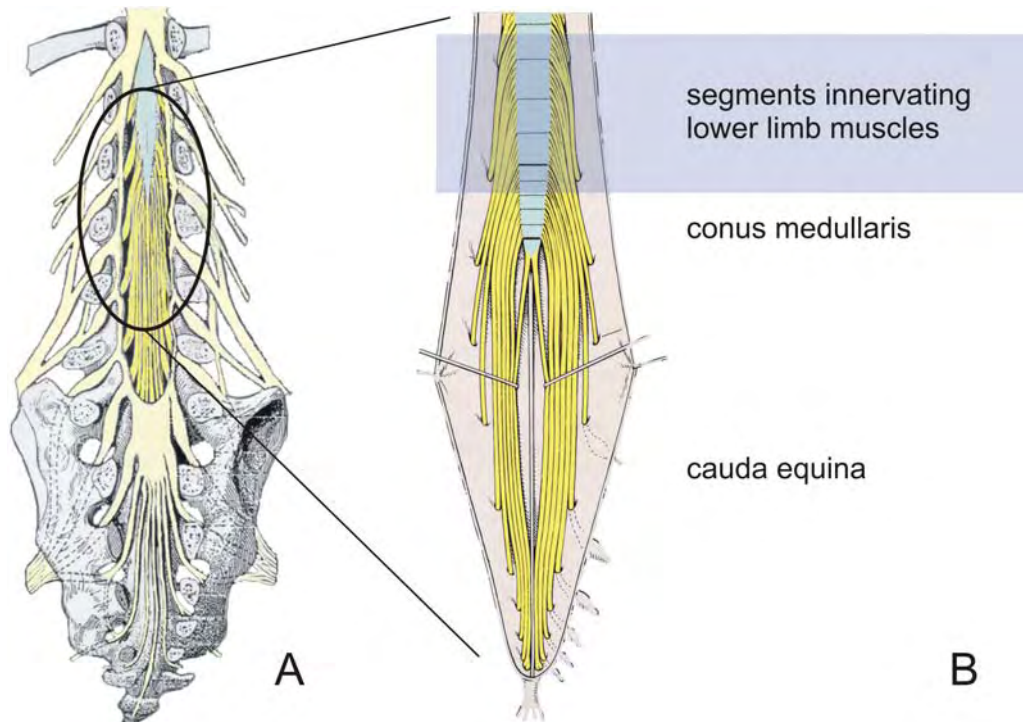


Figure 2.9: The spinal cord within the lumbar part of the spinal column. (A) The spinal cord (blue) extends only to L1 – L2 vertebral level, but the nerve rootlets (yellow) originating from the corresponding segments continue down to the appropriate vertebral column exit point. (B) Grey shaded are the spinal cord segments innervating the lower limb muscles. The tapering lower part at the terminal end of the spinal cord at the vertebral level of the first or second lumbar segment is the conus medullaris. After the spinal cord terminates, the spinal nerve rootlets continue forming the cauda equina. Lesions at the level of the conus medullaris or the cauda equina are leading to full or partial denervation of the lower limb muscles. (adapted from Duus 2001 p. 82 (B))

2.2.1 Morphological, structural changes

A severe loss of muscle mass (atrophy) represents the first obvious change after denervation. One of the first clinical observations reporting this were made by Oppenheim (1894). He described that the muscle fibres appeared smaller in diameter and their content disintegrated into granulated and lipid particles, which were resorbed, so that only sarcolemmal tubes containing the nuclei were left. The first experimental studies investigating denervation induced changes after section of the nerve were made at the end of the nineteenth and the beginning of the twentieth century as described by Gutmann and Zelená (1962). These studies were mostly restricted to short

term denervation periods. Sarah Tower (1935) studied in the cat the course of atrophy in denervated muscles for up to one year. She distinguished three stages of denervation induced muscle damage: atrophy, degeneration and fibrotic dedifferentiation.

Initial research on denervation atrophy in human muscle was carried out mostly in poliomyelitis or other forms of locomotor diseases like amyotrophies, progressive muscle atrophy, amyotrophic lateral sclerosis, etc. (Darkewitsch 1905, Kopits 1929, Adams et al. 1954). The drawback of these studies was that the onset and the extent of the denervation were seldom known. More accurate information concerning the changes in denervated muscle could be obtained in peripheral nerve lesions. In these cases the time of lesion and the nerves and muscles involved were usually known. Following nerve trauma the muscle fibre diameter is considerably reduced within the first year, some cases showing a great variation in diameter. Degenerative changes were not observed until three years after nerve interruption (Bowden and Gutmann 1944). At final stages (up to 25 years) of denervation the muscle is substituted by fibrous and adipose tissue. The findings, obtained from biopsies of denervated muscle, were also confirmed by recent studies (Kern et al. 2004, Boncompagni et al. 2007) see Figure 2.10.

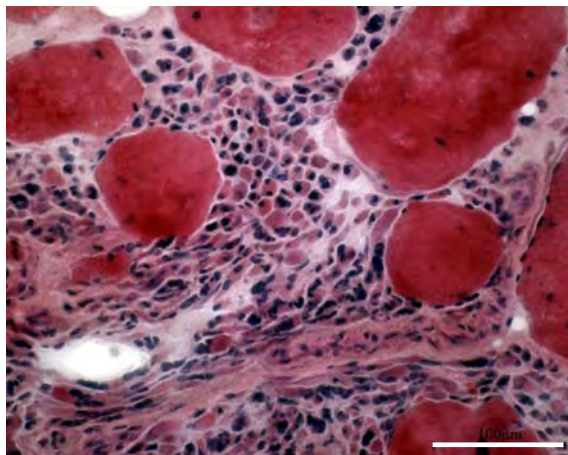


Figure 2.10: Cryosection stained with haematoxylin and eosin of a biopsy from vastus lateralis muscle of a subject 7.5 years denervated. Showing preserved large fibres surrounded by severely atrophic fibres. Bar: 100 μm (Biopsy harvested in the course of the RISE study, prepared by U. Carraro)

Alternative non-invasive methods to demonstrate changes in the size or structure of denervated muscle are measuring the thickness of the muscle

belly by ultrasound (Taylor 1993) or to determine muscle cross-sectional area by computed tomography (Termote 1980, Kern 1995). In the example of a computed tomography scan from the thigh cross-section of a denervated thigh shown below (Figure 2.11) the decrease of muscle is evident. The remaining muscle is surrounded by a thick layer of subcutaneous fat and also within the muscle the amount of non contractile tissue (intramuscular fat, connective tissue and collagen) is increased.

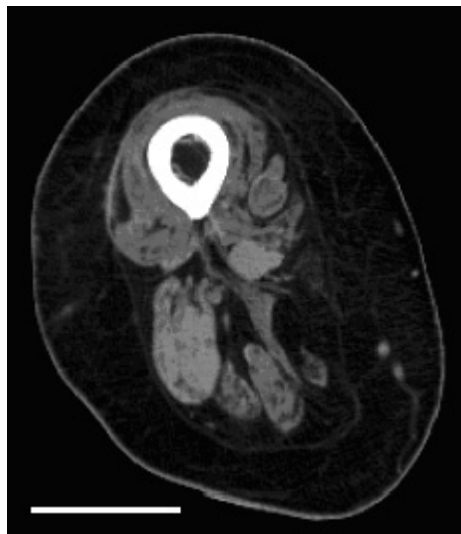


Figure 2.11: CT scan showing a cross-section of the right thigh 20cm below the top of the greater trochanter of a patient denervated for 8.7 years. Bar: 5 cm.

Changes in fibre diameter are more reliable than muscle weight, area or other macroscopic parameters since fibre size is not distorted by connective tissue, fat and collagen.

2.3 Electrophysiological changes

The reduction of resting membrane potential of the muscle fibre is the earliest sign of muscle denervation. Albuquerque and Thesleff (1968) found in the rat that 7-10 days after denervation the resting membrane potential was reduced by 10-15 mV. They also noticed an increase of threshold for generation of an action potential. This is in accordance with results of other research groups showing an increase of chronaxie in denervated muscles (Robert and Oester 1970, Midrio et al. 1997, Ashley et al. 2005), confirming a lower excitability.

Spontaneous activity is another characteristic electrophysiological feature of the denervated muscle. There are two different types of activity fibrillation potentials and positive sharp waves. A fibrillation potential which is the spontaneous depolarisation of a single muscle fibre has a duration less than 5 ms and a bi- or triphasic shape depending on the recording site (Figure 2.12 A) . If the needle is placed in the endplate region of the muscle the potential will be biphasic. When recorded outside the endplate region the potential will have a triphasic shape (Buchthal and Rosenfalck 1966). The positive sharp wave has a characteristic shape with an initial positive¹ deflection of short duration followed by a rather slow return, often with a negative phase of low amplitude, to baseline (Figure 2.12 B). The duration of the positive sharp wave ranges from several ms up to 100ms. Typical the spontaneous activity arises within one to three weeks after denervation of the muscle, concurrent with the reduction in membrane resting potential (Buchthal 1982).

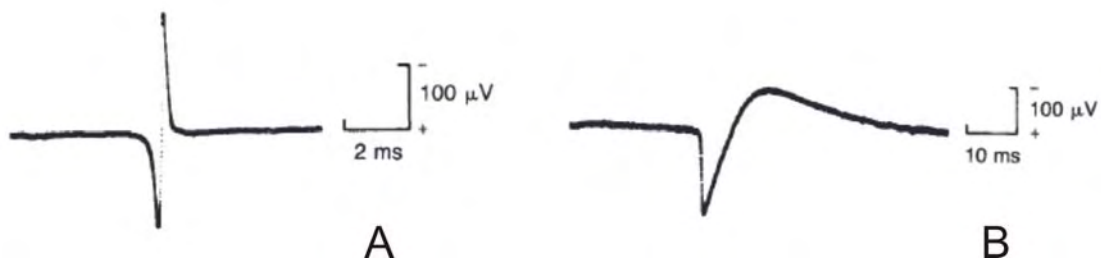


Figure 2.12: Fibrillation potential and positive sharp wave recorded with an intramuscular needle electrode. (A) Waveform of a single fibrillation potential which is the electric activity associated with a spontaneously contracting (fibrillating) muscle fibre. The potentials are bi- or triphasic spikes of short duration (less than 5 ms) with an initial positive phase and a peak-to-peak amplitude of less than 1 mV. (B) Positive sharp wave characterised by an initial positive deflection (<1 ms), its duration is usually less than 5 ms, and the amplitude is up to 1 mV. The negative phase is of low amplitude, with a duration of 10 to 100 ms. (adapted from AAEM Nomenclature Committee 2001)

¹ Note: The membrane potential is defined as the voltage across the membrane measured as the potential of the cell interior with respect to the extracellular space. Due to the fact, that the needle EMG is the extracellular recording of volume conducted APs of single or multiple muscle fibres, the measured voltage is going to be more negative if the membrane potential becomes more positive.

Other findings are an increase in the sensitivity of the membrane to acetylcholine (ACh) outside of the endplate region (Lømo and Westgaard 1975) and the appearance of a new type of sodium (Na^+) channels which are tetrodotoxin(TTX)-resistant in the membrane (Pappone 1980).

2.3.1 Biomechanical changes

The above described morphological and electrophysiological changes induced by denervation are accompanied by changes in functional properties of the muscle.

In general the denervated muscle exhibits a slower dynamic behaviour than a normal, innervated muscle (Carraro et al. 1982, Dulhunty 1985, Kotsias and Muchnik 1987, Al-Amood and Lewis 1989). The muscle twitch elicited by a single stimulus presents an increase of time to peak and half-relaxation time. Thus the total twitch contraction time is lengthened. This on the other hand reduces the minimum frequency necessary for producing tetanic contractions (fusion frequency). It appears that the reduction in shortening velocity is more pronounced in fast than in slow muscle (Gundersen 1985, Al-Amood and Lewis 1989).

The developed tension of the denervated muscle activated by electrical stimulation is markedly reduced. This reduction can be observed for twitch and for tetanic contractions where this reduction is even more pronounced. Following denervation the reduction in twitch force is progressive with a close relationship between the loss of force and the loss of contractile tissue due to muscle atrophy.

If maximal specific tension developed by the electrically activated muscle is measured the denervated muscle shows no difference or even a slight increase of tension compared to normal innervated muscle (Finol et al. 1981, Midrio et al. 1997, Germinario et al. 2002, Ashley et al. 2007)

3 Stimulation equipment

3.1 Biophysical principles of the extracellular activation of nerve and muscle fibres

The shape of a nerve axon or a muscle fibre is described by a cylindrical tube with the surface representing the fibre membrane separating the intracellular space from the outside. In order to examine the conditions for extracellular activation of such a fibre by electrical stimulation, an equivalent circuit of the fibre membrane is considered (Figure 3.1).

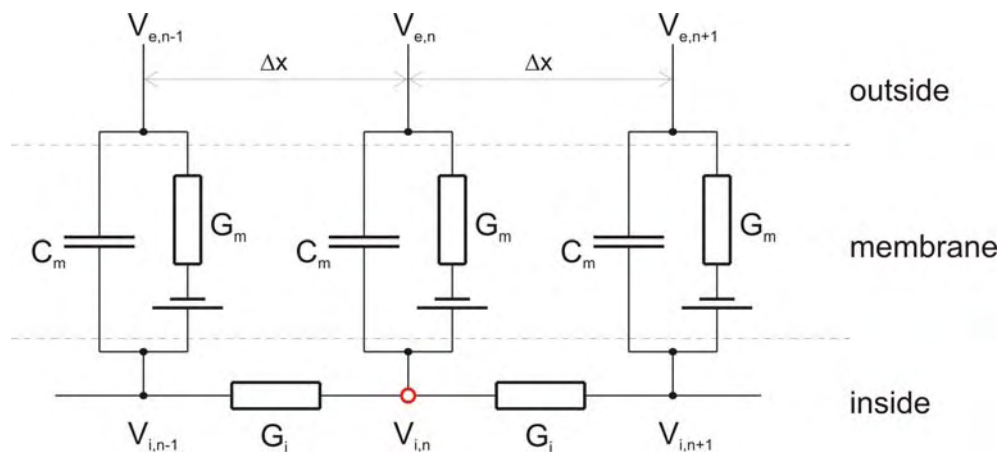


Figure 3.1: Network to simulate the currents in a nerve or muscle fibre. The fibre is segmented into cylinders with a length of Δx . The membrane of each segment is simulated by the highly nonlinear membrane conductance G_m , which depends on the activation state of the ion channels in the membrane, an ionic voltage source and the membrane capacity C_m . G_i is the intracellular conductance of the fibre and $V_{e,n}$ and $V_{i,n}$ are the external and internal potential of the n^{th} segment (after Rattay 1988).

Applying stimulation pulses to a nerve or muscle fibre with electrodes, either surface or intramuscular, the potential in the medium where the fibre is embedded changes in time as well as in spatial distribution. The current flow across the n^{th} segment (red ring in Figure 3.1) of the membrane can be described by:

$$0 = C_m \frac{d(V_{i,n} - V_{e,n})}{dt} + I_{ionic,n} + G_i(V_{i,n} - V_{i,n-1}) + G_i(V_{i,n} - V_{i,n+1}). \quad (1)$$

With the reduced voltage

$$V_n = V_{i,n} - V_{e,n} - V_{rest} \quad (2)$$

and inserting for the intracellular conductance

$$G_i = \frac{\pi d^2}{4\rho_i \Delta x} \quad (3)$$

as well as the membrane capacity

$$C_m = \pi d L c_m \quad (4)$$

equation (1) is transformed to

$$\frac{dV_n}{dt} = \left[\frac{d\Delta x}{4\rho_i L} \left(\frac{V_{n-1} - 2V_n + V_{n+1}}{\Delta x^2} + \frac{V_{e,n-1} - 2V_{e,n} + V_{e,n+1}}{\Delta x^2} \right) - i_{ionic,n} \right] \frac{1}{c_m}. \quad (5)$$

In equation (5) d designates the fibre diameter, ρ_i the intra-cellular resistivity, c_m the capacity of the membrane per area and L the active length of the membrane within the compartment. For an unmyelinated nerve or a muscle fibre $L = \Delta x$. The ionic currents across the fibre membrane are described by further differential equations e.g. the Hodgkin-Huxley equations for the unmyelinated or the Frankenhaeuser-Huxley equations for myelinated fibre (Hodgkin and Huxley 1952, Frankenhaeuser and Huxley 1964). In the case of the muscle fibre the current flow into the transverse tubular system has to be considered too, therefore the Hodgkin-Huxley-type model was extended by a passive element (Adrian and Peachey 1973, Henneberg and Roberge 1997). A detailed analysis of the different models regarding the activation of the denervated muscle fibre and the influence of the t system was carried out by Reichel (1999). For analysing the subthreshold response of the fibre the above introduced model is adequate.

In equation (5) the term

$$f_n(t) = \frac{V_{e,n-1} - 2V_{e,n} + V_{e,n+1}}{\Delta x^2} \quad (6)$$

describes the influence of the stimulation current applied with extracellular electrodes. It is the second difference quotient of the extracellular potential along the fibre. With $\Delta x \rightarrow 0$ the difference quotient becomes the second derivative of the extracellular potential with respect to x

$$f(x,t) = \frac{\partial^2 V_e(x,t)}{\partial x^2}. \quad (7)$$

$f(x,t)$ is called the activating function which explains the influence of an external applied electrical field on a muscle or nerve fibre. This concept was introduced by Rattay (1986).

For stimulating a muscle fibre the reduced voltage (2) has to become positive that is equivalent to a depolarisation of the fibre. This means that an action potential can be elicited in fibre segments where the activating function f_n is positive, in regions with negative f_n hyperpolarisation is produced (Rattay 1989).

The considerations made above are applicable for fibres which are activated by external current source in central parts of the fibre. In this case the activating function at the beginning or end of the fibre is assumed to be zero $f_n = 0$. If the fibre is stimulated near an ending the electrical network simulating currents in a fibre has to be adapted (Figure 3.2).

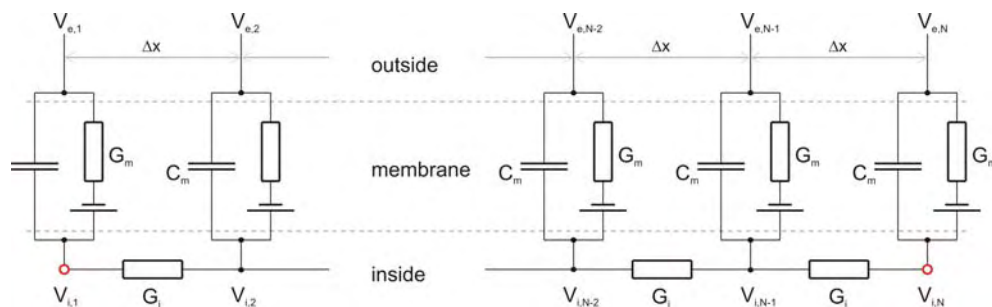


Figure 3.2: Network to simulate the currents at the fibre endings. The first and the last compartments of a fibre with a length of $N \cdot \Delta x$ are shown. $V_{e,1}$, $V_{e,N}$, $V_{i,1}$ and $V_{i,N}$ are the internal and external potential of the first and last fibre segment. G_m is the nonlinear membrane conductance, C_m is the membrane capacity and G_i is the intracellular conductance of the fibre.

The current flow at the fibre endings, node 1 and N (red rings in Figure 3.2), is described by

$$\frac{dV_1}{dt} = \left[\frac{d}{4\rho_i\Delta x} \left(\frac{V_2 - V_1}{\Delta x} + \frac{V_{e,2} + V_{e,1}}{\Delta x} \right) - i_{ionic,n} \right] \frac{1}{c_m} \quad (8)$$

$$\frac{dV_N}{dt} = \left[\frac{d}{4\rho_i\Delta x} \left(\frac{V_{N-1} - V_N}{\Delta x} + \frac{V_{e,N-1} - V_{e,N}}{\Delta x} \right) - i_{ionic,n} \right] \frac{1}{c_m} \quad (9)$$

and the terminal activating function for the endings is

$$f_1(t) = \frac{d}{4c_m\Delta x\rho_i} \frac{V_{e,2} - V_{e,1}}{\Delta x} \quad (10)$$

$$f_N(t) = \frac{d}{4c_m\Delta x\rho_i} \frac{V_{e,N-1} - V_{e,N}}{\Delta x}. \quad (11)$$

In contrast to the activating function for central parts of the fibre this function depends from the first difference quotient of the extracellular potential and is weighted by the compartment length Δx .

In the case of a fibre stimulated by a point source embedded in an infinite homogeneous isotropic medium, the external potential is

$$V_e = \frac{\rho_e I_{el}}{4\pi r} = \frac{\rho_e I_{el}}{4\pi \sqrt{\left((x - x_{el})^2 + z_{el}^2 \right)}} \quad (12)$$

where the fibre axis is the x axis of the coordinate system, x_{el} and z_{el} the coordinates of the point source, ρ_e the resistivity of the external medium and I_{el} the electrode current. The central and terminal activating function for this fibre with different position of the point source regarding to the fibre end are shown by in Figure 3.3 (Rattay 2008).

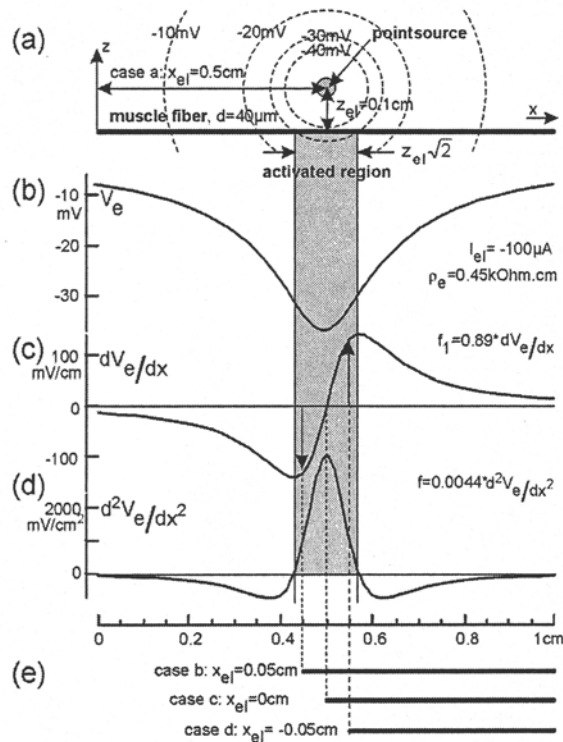


Figure 3.3: Stimulation of a fibre by a point source: geometry, electrical field, and activating functions. (a) Position of the electrode with regard to the fibre. (b) External potential along the fibre. (c) & (d) Terminal and central activating function. Grey marked is the area where the central activating function f_n is positive indicating the activated region. (e) Cutting the front part of the fibre results in a change of the terminal activating function in the first compartment of the fibre indicated by the arrows in (c). All other compartments get the same input as before cutting. Fiber parameters $d = 0.004 \text{ cm}$, $\rho_i = 0.173 \text{ k}\Omega\cdot\text{cm}$, $c_m = 1.3 \mu\text{F}/\text{cm}^2$, $\Delta x = 0.005 \text{ cm}$ (from Rattay 1989).

For a position as shown in Figure 3.3 (a) the central activating function f_n is the main input for fibre activation since the terminal activating function f_1 , driving just one single compartment, only induces a slight hyperpolarisation at the fibre end. When moving the electrode from a central position to a position near the fibre end f_1 has an even increased hyperpolarisation effect, indicated by the left arrow in Figure 3.3 (c), and therefore the threshold for activation of the fibres rises (Figure 3.3 (e) case b). At an electrode position just over the fibre end the threshold level is the same as for activation in a central position since $f_1 = 0$ (Figure 3.3 (e) case c). Moving the electrode to a position beyond the fibre end, causes positive values for f_1 , indicated by the right arrow in Figure 3.3 (c), thus activation is facilitated (Figure 3.3 (e) case d). The above described findings are leading to the conclusion that the fibre is most excitable for an electrode

position which is beyond the fibre end, because for this position both f_l and f_n have large positive values (Rattay 2008).

In the same publication the author examined also the relation of the radial distance of the point source to the fibre in respect to the influence of the central and terminal activating function. He concluded that for a placement of the electrode close (near field) to the fibre the central activating function f_n is the main driving effect for excitation and for an rather distant placed electrode (far field) the terminal activation function becomes main driving input (Rattay 2008).

For the stimulation technology and method applied for training of denervated muscles in this work (see chapters 3.6 and 5.2) the above results should also apply. But since the quadriceps muscle consists of four muscles with different orientation of their fibres and spatial distribution of the fibre ends an optimal placement of the large surface electrodes can not be found. Nevertheless for fibres lying within more profound regions of the muscles the supporting effect of the terminal activating function has a large impact on fibre activation (Martinek et al. 2005). The influence of inhomogeneous tissue composition of the denervated muscle with intramuscular fat cells (Figure 2.10) on the fibre activation was studied by Stickler et al. (2008). It was demonstrated that by placing fat cells near the muscle fibre the electrical field was changed. This led to activation of the fibre not only at the end but also at the site of the inhomogeneity.

The above presented point source simulation model resembles the situation of the stimulation needle EMG (chapters 4.1 and 4.2). This technique is based on activating a few fibres with a monopolar stimulation needle and measuring the latency of the action potential recorded by a second needle electrode placed a few centimetres away along the muscle fibres. In this case the central activating function is the main driving input since only fibres in immediate vicinity of the needles tip are activated. Moreover, the region where the fibres are excited remains constant at $x_{el} \pm z_{el} / \sqrt{2}$ (Figure 3.3) regardless of the intensity of the stimulation pulses, as long as the position of the needle is kept constant with regard to the fibre (Rattay 1986). This is crucial for estimating the muscle fibre conduction velocity by measurement of the latency of the response and the distance between the needle electrodes for stimulation and recording.

3.2 Basic principles of electrical stimulation

An electrical field applied to nerve or muscle tissue evokes an ion transport through the membrane of the tissue and consequentially activates the cell. At the junction between the electrode and the tissue - in surface stimulation the skin - the electron current is converted into an ion current. The ion current is flowing from the positive electrode (anode) to the negative electrode (cathode). In bypassing this direction of the current leads to hyperpolarisation of the membrane under the anode and to depolarisation under the cathode. When the ion current density in the tissue is sufficient to shift the membrane potential above the threshold level an action potential is elicited.

A set of factors determines the efficiency of electrical stimulation the most important of them will be discussed below.

3.2.1 Electrical parameters

Impulse duration and amplitude

For eliciting an action potential these two parameters have to exceed a certain threshold level specified by the strength-duration curve. By increasing the stimulation amplitude beyond the threshold more distant or fibres with a smaller diameter are depolarised. This enables to control the number of activated motor units and thus the strength of the muscle contraction (Figure 3.4). Above a maximum level of stimulation a further increase of amplitude does not lead to higher force output of the stimulated muscle since all fibres within the nerve innervating it are already depolarised (saturation amplitude).

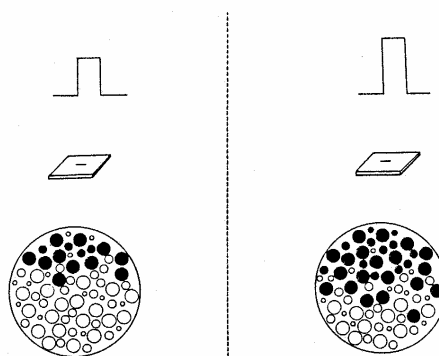


Figure 3.4: Recruitment of nerve fibres within a nerve depending on the stimulation amplitude (from Benton et al. 1981).

Analogue the contraction force of the stimulated muscle can be controlled by variation of the impulse duration. In this case the force output of the muscle is controlled only by changes in the stimulation pulse width between threshold and saturation level at constant stimulation amplitude (Figure 3.5).

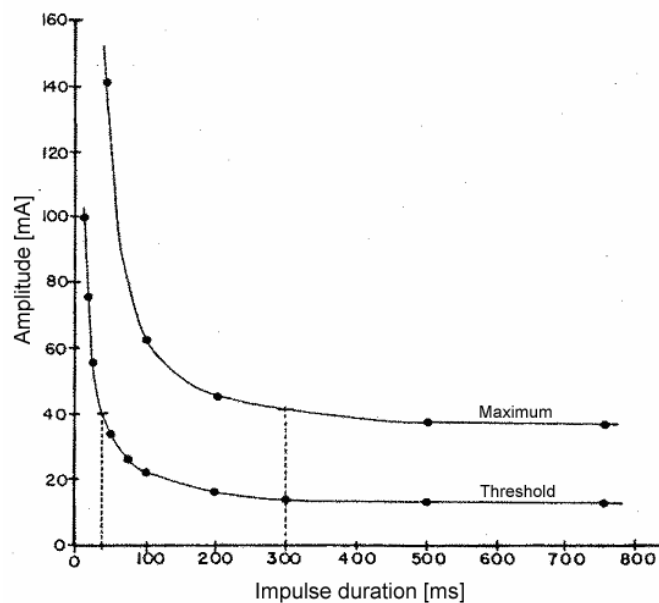


Figure 3.5: Control of muscle force by adjusting the stimulation pulse width while the amplitude is held constant at 40 mA (adapted from Benton et al. 1981).

Electrode position and size

The current density in the tissue is crucial for depolarising the membrane. Apart from the stimulus amplitude the current density is influenced by the size of the electrode, the distance between the electrodes, the distance between the electrode and the nerve or muscle fibre and the tissue composition. Small electrodes applied to the skin close to each other are activating primarily superficial tissue layers, whereas electrodes placed far apart are also activating deeper laying structures (Figure 3.6).

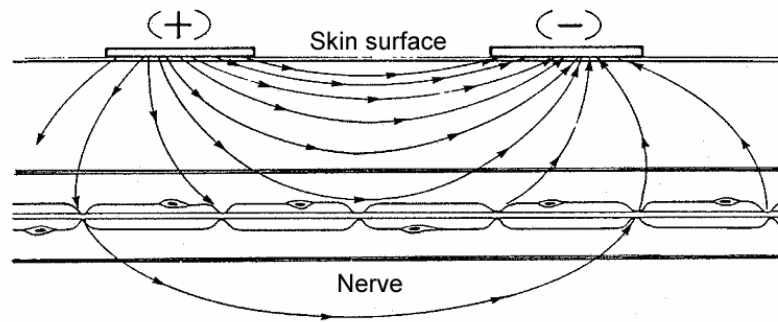


Figure 3.6: Illustration showing typical distribution of current evoked by electrical stimulation with surface electrodes (adapted from Benton et al. 1981).

Electrode size is another parameter which can be used to control the stimulation. For highly selective activation the size of the cathode could be reduced in order to increase current density under the electrode – different electrode. On the other hand the size of the anode or indifferent electrode can be increased to avoid activation.

The position of the active electrode with regard to the nerve is of importance since there are locations with low threshold for activation. It is of advantage to place the electrodes above those motor points (Figure 3.7).

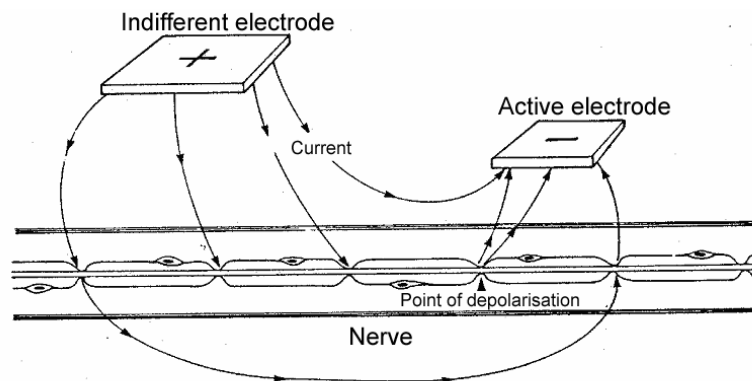


Figure 3.7: Illustration showing the influence of electrode size and location with regard to the nerve on the stimulation (adapted from Benton et al. 1981).

Impulse frequency

Muscle contraction elicited by electrical stimulation is different to normal physiologic activation. Fast fatigue is caused by the nature of electrical

stimulation to activate always the same fibres synchronously. Whereas under physiological conditions the nerve fibres activated within the nerve are changing during a contraction and they are firing asynchronously. This generates a smooth contraction of the muscle even at low stimulus frequency. A neuromuscular component of fatigue is supposed at stimulation frequencies above 40 Hz caused by depletion of the transmitter at the synapses. Additionally the blood supply of the activated fibres is reduced during the contraction leading to an impairment of the metabolism.

Impulse shape

Stimulators generating rectangular impulses are the most common used today. The pulses could be monophasic, biphasic or monophasic with alternating polarity. Since monophasic impulses without any compensation phase have an average different from zero they cause a direct current (DC) in the tissue. This can induce skin irritation and corrosion of the electrodes, especially in long-term application. In order to prevent charge accumulation the output stages of most commercially available stimulators deliver only charge balanced pulses and are generally not DC coupled. Capacitive or inductive coupling is used to deliver the impulses instead (Figure 3.8).

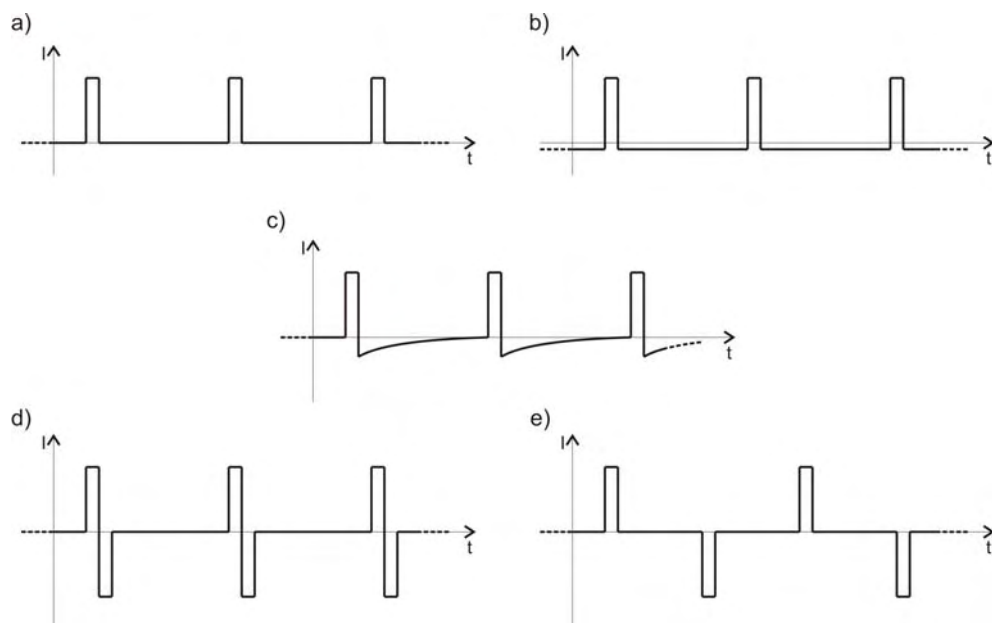


Figure 3.8: Different rectangular pulse shapes used for electrical stimulation: a) monophasic, b+c) monophasic with load compensation, d) biphasic symmetric and e) monophasic with alternating polarity.

3.2.2 Stimulator technology

Devices for electrical stimulation and the associated technology can be divided into different categories e.g. implantable stimulators and devices for surface stimulation or according to the application in devices for therapeutic and for functional electrical stimulation.

The most frequent implanted stimulation devices are the cardiac pacemaker with an incidence of above 500,000 implantations per year and the cochlear implant for stimulation of the auditory nerve in patients with hearing loss. In the last decades the field of application for implantable devices widened to deep brain stimulation for treatment of patients with Parkinson's disease and epidural spinal cord stimulation for treatment of pain or spasticity in neurological disorders. One of the most current developments is a micro miniature electrical stimulator that can be implanted by injection through a needle. It is intended to be used for drop foot stimulation, treatment of post-stroke shoulder subluxation, obstructive sleep apnoea and cough assist. The output stages of implantable devices are able to generate impulses with duration in the range of 10-450 μ s, amplitudes of up to 10 V for constant voltage and 16 mA for constant current stimulators. Depending of the application the devices are able to generate pulse trains with frequencies of up to 200 Hz (deep brain stimulation, epidural stimulation) and several kilohertz (auditory nerve stimulation) respectively.

Commercially available surface stimulators are divided into small portable devices for home based use by the patients like devices for transcutaneous electrical nerve stimulation (TENS) or tabletop devices which are mainly used at rehabilitation centres. Usually the stimulators are providing two output channels for simultaneous stimulation at two different sites. The small portable devices are primarily applied in treatment of pain, reduction of spasticity after stroke, traumatic brain injury and spinal cord injury and reversing muscle weakness. Stimulation parameters are limited to pulse widths of 50-300 μ s with amplitudes up to 70 mA and a stimulation frequency between 10 and 150 Hz.

The tabletop devices are capable of generating a broader range of stimulation parameters including so called exponential currents with pulse duration of 100, 200 or even 500ms and intensities up to 130 mA. Most of these stimulators feature different programmes for eliciting tetanic contractions with different on and off time, a programme with frequency

modulated stimulation pulses, medium frequency stimulation and galvanic current. The last-named current is a direct current often used to transport drugs through the skin into the body (iontophoresis). Moreover it is possible to change the pulse shape (rectangular, triangular) and polarity (positive, negative, biphasic) in some of the devices. In order to prevent skin irritation and electrolysis charge balanced stimulation pulses are mandatory except for galvanic currents. In case of biphasic stimulation pulses this is achieved automatically, for the monophasic pulses a compensation phase after each stimulation pulse for charge balance is required (Figure 3.8 b and 3.8 c).

All the above described stimulators for surface stimulation are used for therapeutic applications. For FES with surface electrodes only few devices are available on the market for applications like correction of dropped foot in patients with stroke, FES assisted cycling and walking in paraplegic patients (Parastep[®] System, MotionStim 8, ODFS Drop Foot Stimulator).

3.2.3 Electrode technology

There are three types of electrodes used for electrical stimulation depending on the application, each of them features advantages and disadvantages.

Surface electrodes:

This electrode type is the most often used since they are applied for functional as well as therapeutic electrical stimulation. They can be easily applied and removed. The main disadvantages are that their selectivity for activation of discrete muscles is poor and stimulation of deep muscles is not easy to achieve. For daily stimulation the time needed for donning and doffing and the difficulty to position the electrodes exactly the same way are additional drawbacks. To overcome this disadvantages attempts have been made to develop special garments with the electrodes incorporated to ensure proper electrode placement and reduce time for donning and doffing (Rafolt 1999). Two different types of surface electrodes are most widely used: electrodes made of silicone rubber applied to the skin with a wet sponge cloth or only with gel; and self adhesive electrodes composed of a conductive backing layer made of carbon film or knit metal fabric and a layer of self adhesive gel. Electrical stimulation via surface electrodes activates also sensory nerves thus, if the subject has intact or partial sensation, it is possible that the stimulation becomes uncomfortable. If surface electrodes are not properly applied to the skin (e.g. electrode peeling,

in homogeneous contact pressure, etc.), there is also the possibility of skin burns.

Implanted electrodes:

These electrodes are suited for long term application. They have a high selectivity and also stimulation of deep muscles is possible without activation of more superficial laying muscles. Further advantages are that no time is needed for donning and doffing, and their characteristics remain the same in long-term use. The main disadvantage of course is that they require surgery to be positioned. State of the art materials for implantable electrodes and leads are platinum, platinum-iridium and medical grade stainless steel.

Percutaneous electrodes:

These electrodes made of thin stainless steel require a minimal invasive procedure with a hypodermic needle to be placed intramuscular. The selectivity is improved with respect to surface electrodes and also stimulation of deep laying nerves or even direct stimulation of muscles is possible. In long-term application the main drawbacks are electrode breakage (they have to be replaced periodically) and problems with infections at the insertion site. One of their main applications is temporary use to evaluate feasibility of electrical stimulation before permanent implantation (e.g. spinal cord stimulation for controlling spasticity or pain).

3.3 Differences between “spastic, innervated” and “flaccid, denervated” muscles regarding electrical stimulation

The stimulation parameters applied for eliciting muscle contractions are depending on physiological conditions. Of particular importance for electrical stimulation is whether the connection between the muscle and the nerve innervating it is preserved or the muscle is denervated. In the latter case the muscle fibre membrane has to be depolarised by the applied electrical field directly, whereas in the first case the muscle is activated by the nerve innervating it. This phenomenological difference is essential for developing stimulation protocols since functional activation of denervated muscles requires electrical stimulation with long impulse duration in the range of 10 – 150 ms. For excitation of the nerve however impulse durations of 50 μ s – 300 μ s are sufficient. In special cases even longer pulse durations of up to 1

ms for functional activation of the thigh muscles are used. By lengthening the pulse width a more homogenous activation of the different thigh muscles is achieved (Bijak et al. 2005). Another effect of the longer pulses is the reduction of discomfort if the patient has preserved sensory function in the stimulated area.

In innervated muscle the nerve distributes the action potential over the whole muscle. This mechanism of distributing the stimulus is missing in the denervated muscle, thus it has to be replaced by an electrical field distribution capable of depolarising the fibres in every part of the muscle. Therefore a completely different approach from technical aspect is necessary to successfully activate the denervated muscle.

3.4 Special design criteria for stimulators for long-term denervated muscles

The studies related to denervated muscles carried out by several research groups (Eichhorn et al. 1984, Valencic et al. 1986, Kern et al. 1995, 1999 & 2002, Mayr et al. 2002) served as basis for establishing the properties for a stimulation device suited for therapy of the human denervated muscle.

A device suited for activation of the denervated muscle should be able to produce stimulation pulses with durations in the range between 1 and at least 100 ms, since the pulse width is the most important electrical parameter.

Another requirement for the output-stage of the stimulator is to generate high intensity impulses because of the low excitability of denervated and degenerated muscle fibres. The second reason for the necessity of high intensity stimulation is the fact that in long-term denervated patients the muscle is covered by a thick subcutaneous fat layer and also within the muscle itself fat and connective tissue is increased. This fat layer and the changed intramuscular tissue composition act as a parallel path for the stimulation current, thus only a part of the applied pulse energy is delivered to the muscle.

For treatment of incomplete denervated patients with preserved sensory nerve fibres, stimulation with triangular or trapezoidal impulses reduces the pain caused by electrical stimulation. Compared to rectangular pulses the above mentioned pulse shapes take advantage of the lost ability of the denervated muscle fibres to accommodate to a stimulus causing a relatively

slow increasing depolarising current (Figure 3.9). This provides selective activation of the denervated muscle fibres without stimulating intact sensory nerves or innervated muscle fibres (Hník et al. 1962, Edel 1991). A device especially designed for treatment of denervated muscle should therefore be able to generate different biphasic pulse shapes.

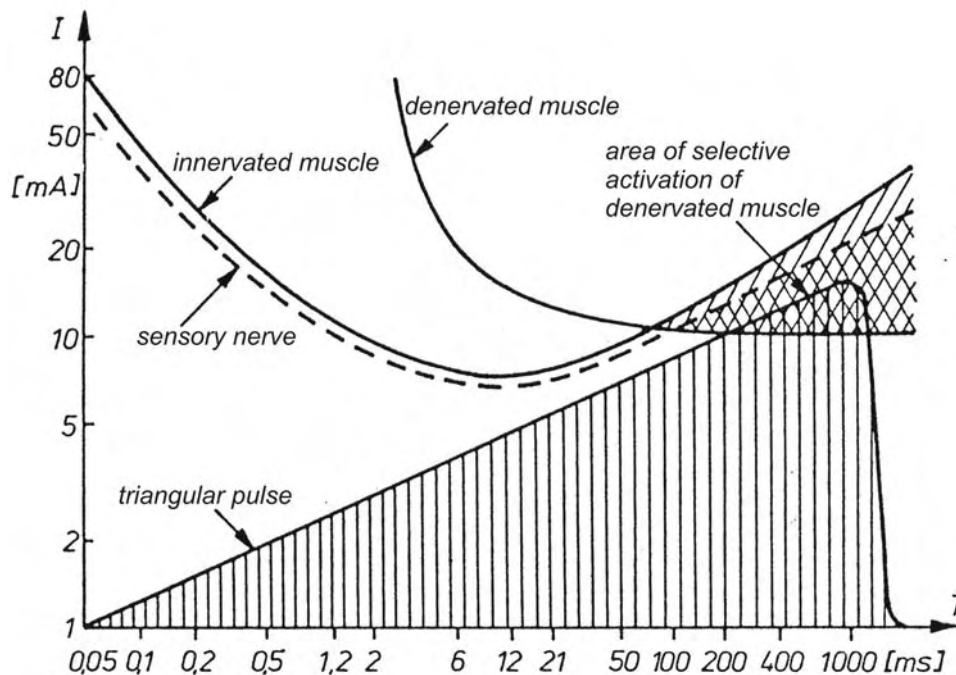


Figure 3.9: Strength duration curve of different excitable tissues for triangular pulses. (adapted from Edel 1991)

A two or more stimulation channel output stage is of advantage since this allows simultaneous therapy of different muscle groups and therefore reduces the patient's time expenditure for electrical stimulation training.

Additional desired features of the stimulation device are a user friendly interface for operating and programming, a built in memory for recording of the training activities and storing different stimulation programs especially adapted for home-based training.

For safety the stimulator should be battery powered to avoid direct line connection and during recharging the battery the unit has to be inactivated.

Since there are no nerves distributing the stimulation impulse, the use of large size electrodes generating an electrical field eliciting the whole muscle is essential. To distribute the applied stimulation current safely the

electrodes should be highly flexible in order to provide an even skin contact over the whole electrode area. This is of greatest importance because inhomogeneous current flow under the electrode easily leads to skin burns due to the high intensive stimulation protocols used.

3.5 Commercially available equipment, stimulators

Since electrical therapy for chronic denervated muscle is discussed controversial by physicians up to now there is no market for electrical stimulation devices especially designed for the needs of the denervated musculature.

Of limited use are the commercial available desktop stimulators able of generating so called exponential current with pulse duration of 100 or 200 ms. Stimulation with these parameters is suited only for slowing down atrophy in temporarily denervated muscles, because the amount of stimulation pulses (0.5 – 2 Hz) and the intensity applied with this setting is low. There is also a gap in the range of selectable pulse widths since these stimulators are only providing programmes with pulse duration up to 1 ms and the exponential current with 100 ms or longer pulse duration but nothing in between.

In Austria new stimulation devices emerged on the market in the last years with user programmable stimulation parameters allowing a continuous selection of stimulation parameters regarding pulse width, burst duration and pause. These devices are better suited for therapy of denervated muscles but nevertheless the devices have to meet the standards which are limiting the output parameters to maximal 300 mJ per pulse. This means that the maximum stimulation current is limited according the stimulation parameters chosen. Another drawback is that they have only one stimulation channel, calling for considerable commitment from the patients due to the fact that each muscle or muscle groups has to be treated individually. The resulting time span allocated for therapy of the patient's lower limbs is therefore two hours or more per day.

To increase the acceptance by physicians and to ease the application of the therapy for the patient new devices for surface stimulation of the denervated muscles are required. Special attention has to be paid to safe and easy handling of such devices since operating errors could cause severe skin burns or other problems.

3.6 A stimulator for functional activation of denervated muscles

This work was published in *Artificial Organs* 2002; 26(3):276-9.

3.6.1 Summary

In the last years various studies proved that electrical stimulation can improve contractile capability and restore muscle function in long-term denervated degenerated muscles. The low excitability of the muscle cells at the initial stage of training and surrounding connective tissue - acting as an electrical shunt - requires special stimulation parameters. Until now no appropriate devices (stimulators) are commercially available, therefore we were forced to design our own stimulators.

The control unit of the stimulators is based on a microprocessor for maximum flexibility regarding the generation of the parameters such as pulse amplitudes, pulse width, frequency, stimulation times, ramps etc. In addition the microprocessor design allows recording of training data such as stimulation date, time, duration and used programs.

The voltage constant output stage of the stimulator is able to generate biphasic charge balanced stimulation pulse with pulse width of 1-300 ms, stimulation voltages up to ± 80 V ($160 V_{ss}$) and ± 250 mA maximum stimulation current. To prevent direct current due to inexact charge compensation, the stimulation pulses are coupled capacitively. Simultaneous two-channel stimulation with independent intensity is possible.

The stimulators are programmed with notebook or personal digital assistants (PDA's) via infrared serial interface. This concept avoids stimulation with wrong parameters because the patient can only use the stimulation parameters pre-programmed for him in the outpatient clinic. For training at home only changes in stimulation intensity within given limits are possible. The portable units are powered by a internal rechargeable battery ensuring mains isolation. Highly efficient switched voltage regulators are used for power supply of all circuits to increase operating time of the stimulator.

3.6.2 Introduction

Direct electrical muscle stimulation with long pulse width – up to 300ms – has been the common treatment for denervated muscle. But this therapy is still being considered to be controversial by many rehabilitation centres and medical professionals. This is largely because current teaching and training for therapists is still based on scientific and technological knowledge of the fifties and sixties. Other sources of criticism are the contradictory statements regarding its effect on nerve growth and reinnervation (Boonstra et al. 1987, Eberstein A. and Eberstein B. 1996). Commercially available stimulation devices are only able to slow down atrophy or maintain the muscle during recovery after non permanent denervation. The stimulation parameters cannot be changed in the scope necessary for efficient therapy of permanent denervated muscles. Most of the stimulators are only able to generate pulse widths of 300, 200 or 100ms and much shorter pulses with about 1 ms pulse width but nothing between. Another limitation is induced by current EU standards for medical devices which are limiting the single pulse energy to 300 mJ per impulse. This is not sufficient for stimulating denervated degenerated muscles (DDM) because of the connective tissue surrounding the muscle acting as an electrical shunt and the long pulse duration needed for excitation of the denervated muscle fibres.

In more recent studies investigating the effects of electrical stimulation on denervated muscles especially build research prototypes or inappropriate commercially available devices adapted to the specific requirements were applied. (Eichhorn et al. 1984, Mokrusch and Neundorfer 1994, Kern 1995, Hofer et al. 1997, Kern et al. 1999, Woodcock et al. 1999).

3.6.3 Concept of a suitable stimulator

Based on experiences from previous experiments in the past years, the following concept for the design of the stimulator was made (Kern 1999).

Stimulation pulse width should be changeable continuously in a range between 1 and 300ms depending on the excitability of the muscle fibres. The output stage of the stimulator has to be capable of generating pulse energies high enough for effective treatment of long-time denervated and degenerated muscles at an initial stage of training where extremely long pulse durations and high pulse intensities are required for training.

The necessity of different biphasic pulse shapes for treatment of patients with incomplete denervation has two main reasons. First for specific

treatment of the denervated muscle fibres without eliciting contractions in the innervated parts of the muscle – altered accommodation in the denervated fibres. Second in case there are any sensory nerve fibres in the denervated area intact the use of triangular or trapezoidal shaped stimulation pulses is less distressing for the patient.

Multi channel simultaneous stimulation of different muscle groups should be possible in order to reduce daily training time.

The device should be controlled by a microprocessor for:

highest flexibility regarding the generation of stimulation parameters, storing different stimulation programs that are pre-programmed at the outpatient clinic,

easy handling of the stimulator by the patient (only a few control elements: start/stop, therapy program, intensity) and

permanent recording of stimulation activities.

For safety the stimulator should be battery powered to avoid direct line connection and during recharging the battery the unit has to be inactivated.

Since there are no nerves distributing the stimulation impulse the use of large size electrodes is essential for ensuring a contraction of the whole muscle (Kern et al. 1999). Electrodes made of soft flexible conducting rubber that are applied with a wet sponge cloth or gel directly to the skin, already used in our previous trials, proved to be best suited for stimulation of denervated muscles.

3.6.4 Research prototype

Based on the above concept a stimulation system specially adapted to the needs of patients with degenerated denervated muscles was designed (Figure 3.10). Main parts of the stimulator are the control unit for generating pulse parameters, storing stimulation programs and training records, the power supply with the rechargeable battery supplying all components and generating the necessary high voltages for stimulation and the output stage with two independent channels for simultaneous stimulation of two different muscle groups.

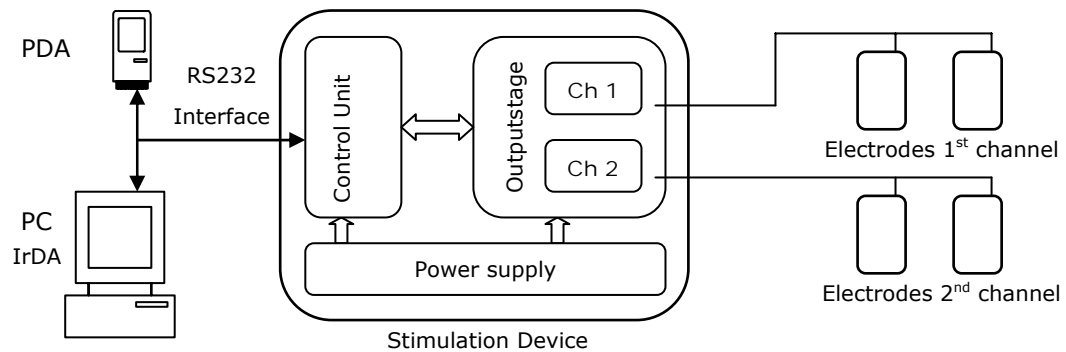


Figure 3.10: Stimulation system overview

Power supply:

For powering the stimulation device special NiMH battery packs made from single high capacity cells with additional thermistors monitoring the temperature were chosen. All circuits in the control unit and the output stage as well as the stimulation circuits are supplied by switching regulators in order to increase efficiency. This allows long training sessions without the necessity of recharging the stimulator. When running the stimulator with both stimulation channels driven at maximum power the overall power consumption is about 35W. To prevent failure of the stimulator due to battery under voltage an acoustic signal is warning the patient if battery low voltage occurs.

Output stage:

The output stage delivers current limited constant voltage impulses to avoid damage of tissue in case of electrode peeling or in case of electrode short circuits damage of the stimulator. Two separate stimulation channels with independent adjustable stimulation amplitude are realized. This allows simultaneous stimulation of two different muscle groups reducing the overall training time for the patient and thus increasing the compliance. To prevent direct current the stimulation pulses are capacitively coupled.

Control unit:

Based on a 80C517 microprocessor the control unit is generating all stimulation parameters such as pulse width, pulse shapes (4 different), stimulation frequency, stimulation on- and off-time, ramps, amplitude, program duration etc. Via infrared serial interface the stimulator is programmed at the outpatient clinic according to actual status of the patient. This interface is activated by a magnetic switch to prevent



Fig. 3.11: A personal digital assistant showing the graphical user interface for programming the stimulator is shown.

unintentionally programming of the stimulator. The control unit records training program, date and time of activation and stores this information in an onboard memory. This information is kept till the next visit to the outpatient clinic where the data is downloaded to the personal computer (PC) and added to the patient record for evaluation.

A software for personal digital assistants (PDA) comprising all features of the PC based application was developed (Fig. 3.11). These small and cheap devices are a comfortable solution for on site programming instead of the need to carry around a notebook PC. The control panel of the stimulator consists of 2 panel coders and 4 push buttons. For safe handling of

the device the user access is restricted to selecting different programs and varying the intensity within a preset range.

3.6.5 Discussion

With the developed stimulator training of DDM is possible increasing contractile capability and muscle bulk. Prolonged treatment of denervated degenerated muscle with electrical stimulation specially adapted to the current state of the muscle tissue improves the metabolism of the muscle cells and decreases the pulse width to get a muscle contraction. Shorter

stimulation pulse widths sufficient for training due to the increasing excitability of the muscle fibres are allowing higher stimulation frequencies eliciting tetanic contractions that are necessary to achieve the desired muscle fibre tension, constituting a hypertrophic stimulus.

For further reduction of daily training time and functional training like standing up with electrical stimulation the development of devices with 4 stimulation channels is necessary. This requires new high capacity accumulators and a very efficient power supply for the devices to ensure a sufficient long operating time.

Electrode garments with integrated electrodes and cables to simplify donning and doffing will also reduce training time and improve safety preventing inappropriate connections and electrode placement.

3.6.6 Additional details on the developed stimulator

The modular architecture of the stimulator allows easy repair and adaptation of the different parts of the device. Main parts are the power supply unit with the battery pack mounted at the back panel of the stimulator, the output stage generating the required stimulation pulses and the control unit for controlling the operation of the device (Figure 3.12).

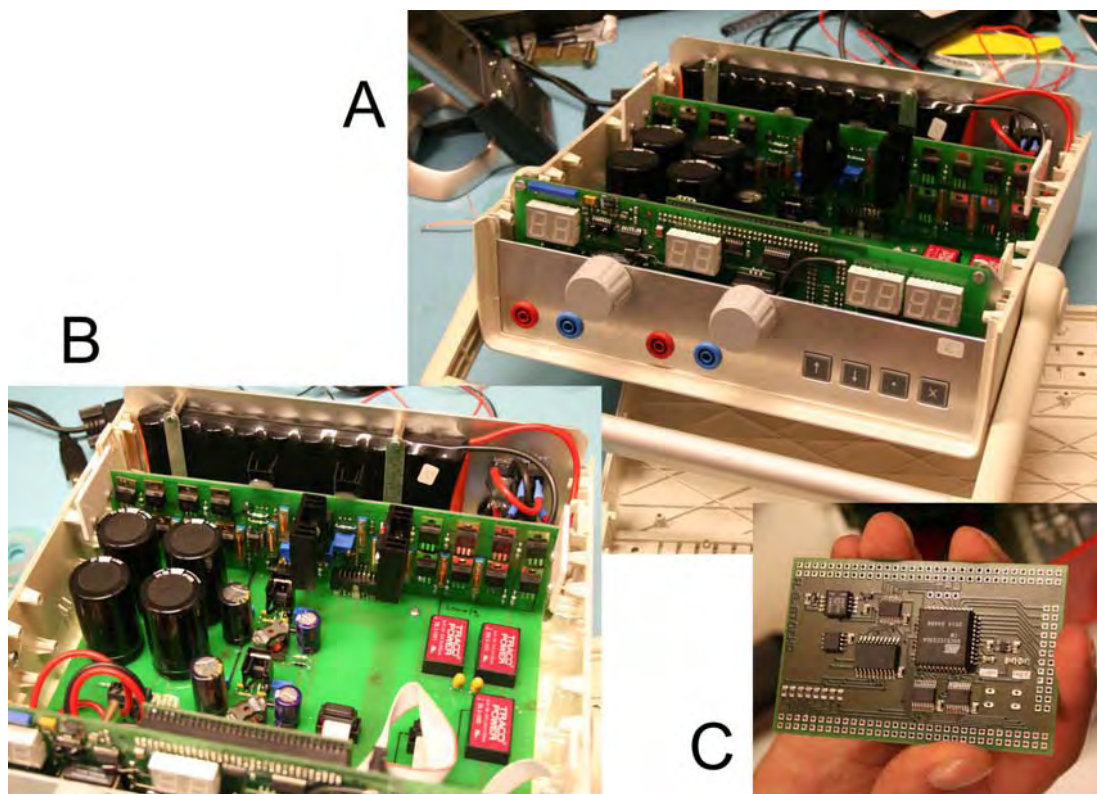


Figure 3.12: Pictures showing the inside of the developed two channel stimulation device. (A) View at the front of the stimulator - with the display filter removed - showing the control panel and the printed circuit print of the control unit with the 7-segment LED display. (B) Top view showing the power supply board of the stimulator and the output stage just in front of the battery pack mounted on the back panel. (C) Second generation main-processor board with extended memory (1GB EEPROM).

Power supply:

Special attention was paid to the efficiency of this stage in order to provide longer battery life and therefore extended training sessions without the need to recharge the stimulator. All different voltage levels needed are generated by switching regulators. The supply for the control circuits is built of commercially available regulator modules whereas the supply for the two stimulation circuits is provided by an especially designed regulator generating a constant output voltage of 80 V, providing up to 300 mA output current. For enhancing safety the unit is inactivated during charging of the battery. The printed circuit board also provides also the connections from the control unit to the output stage and the capacitors for coupling of the stimulation pulses (Figures 3.13).

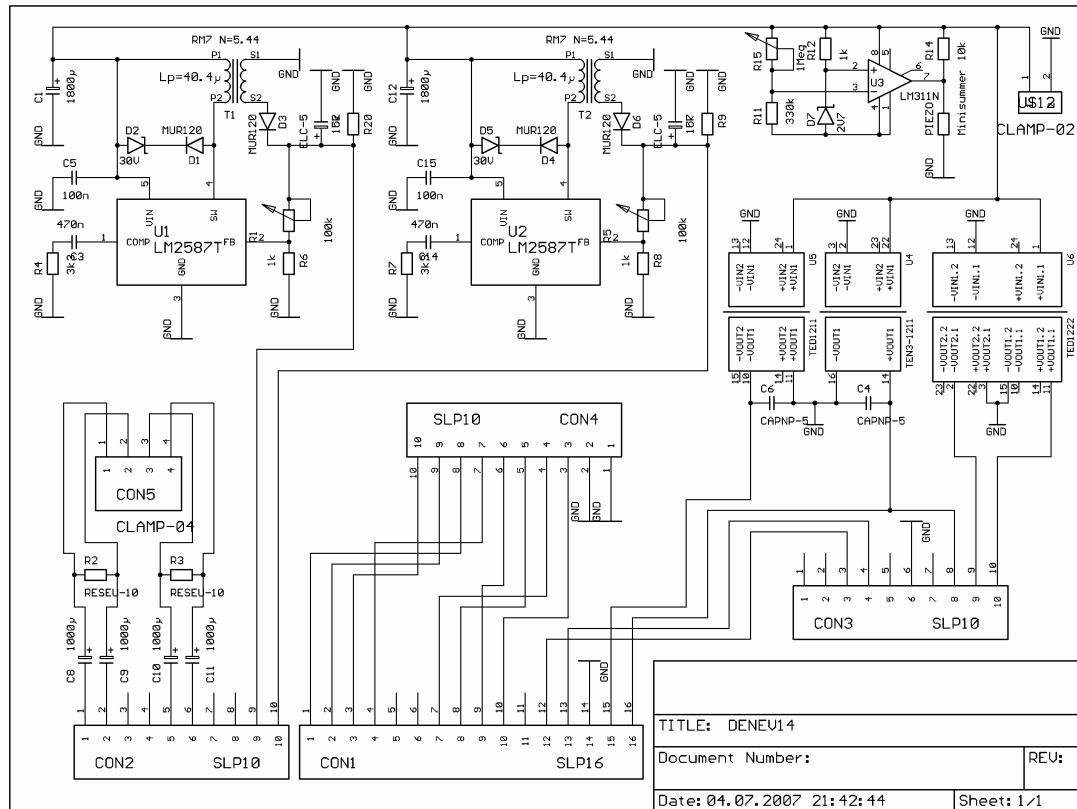


Figure 3.13: Circuit diagram of the power supply including the capacitors for decoupling the two output channels of the stimulator and the connections between control unit and output stage.

Control Unit:

All functions of the stimulation device are controlled by the micro processor based control unit. Easy and safe handling by the patient is one the key features of the stimulator. This was accomplished by reducing the operating elements of the user interface at the front panel of the stimulator. The patient can only choose one of the pre-programmed stimulation programmes, start or stop the programme, and adjust the stimulation intensity for each channel within given limits. An infrared interface enables connection to a notebook PC or palmtop for programming the stimulation device at the outpatient clinic. Wireless communication was selected to prevent any physical connection between the stimulator and external devices in order to maintain line isolation.

The control unit records all training activities by the patient and stores program, date, time of activation and amount of stimulation impulses applied in the memory of the main processor board (Figure 3.14). Every time when the patient has an examination at the outpatient clinic the data can be read out via the interface. Since the personal digital assistants (PDA) for programming and reading out the stimulators memory are more comfortable to carry around and are compared to notebook PCs much cheaper, a software application for PDA was developed. The application is written for Palm OS[®] v3.0 providing the same functions as the application for the notebook PC. In order to provide full operation with the different PDAs running Palm OS[®] continuous maintenance of the application was necessary, the most current version of the software is compatible with Palm OS[®] v5.4.9 (listing of the programme see appendix A).

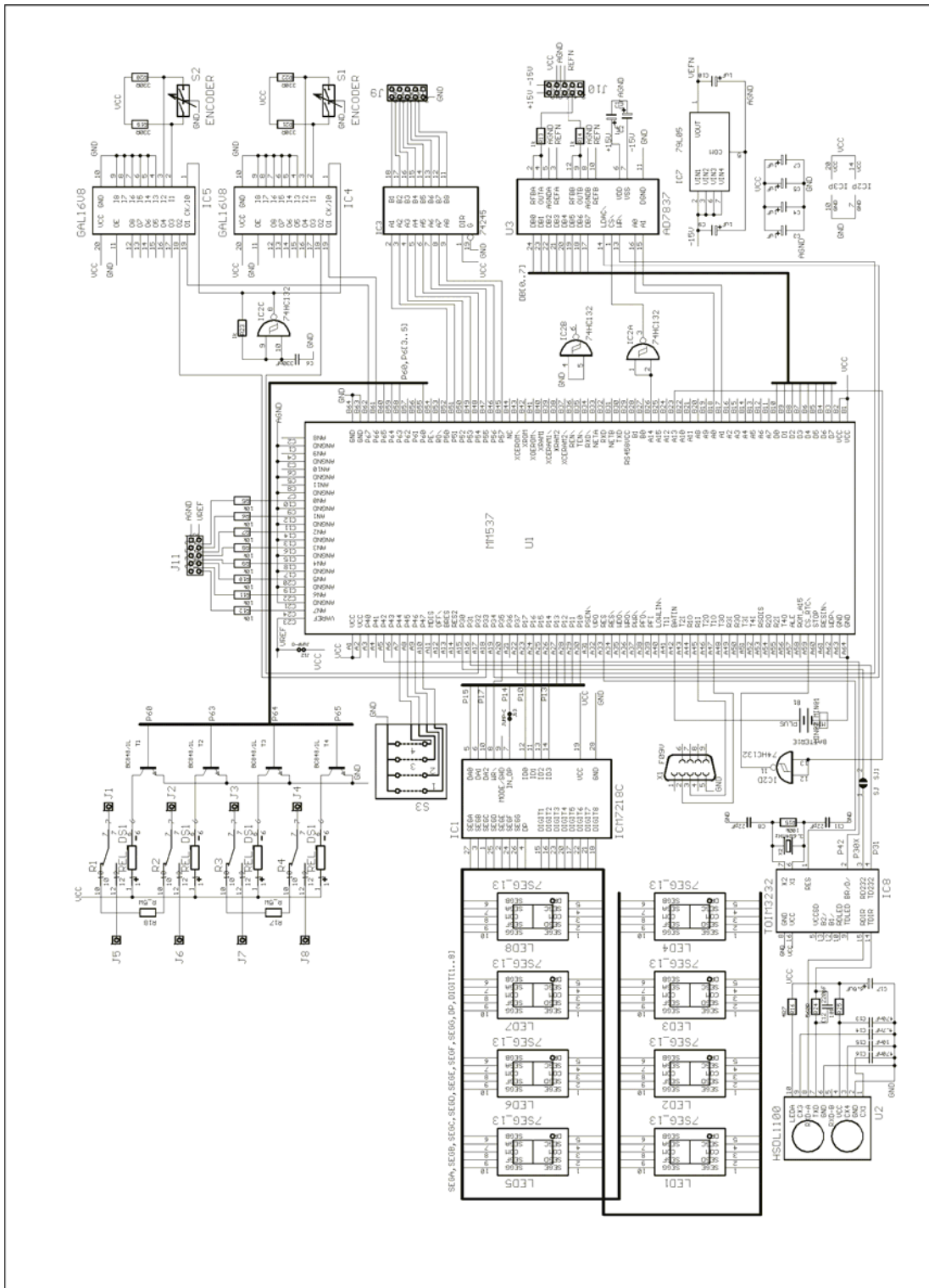


Figure 3.14: Circuit diagram of the control unit with the panel coders for adjusting the stimulation intensity, 7 segment LED displays and the four pushbuttons for selecting, starting and stopping the pre-programmed stimulation programs.

Output stage:

The two channel output stage is designed for constant voltage stimulation with adjustable limitation of maximum stimulation current. Stimulation intensity is controlled by high-voltage adjustable regulators which are also applied for limiting the maximal stimulation current. Since the channels are completely separated not only intensity but also all other stimulation parameters can be adjusted independently. In the current version of the stimulator this is not used so far but could be easily activated with an update of the stimulator's firmware. Implemented in the output stage as well, are circuits for measuring the actual applied stimulation voltage and current for monitoring of the impedance of the stimulation circuit.

Evaluation of the impedance is used for stopping the stimulation in case of electrode short circuit or electrode peeling (Figure 3.15).

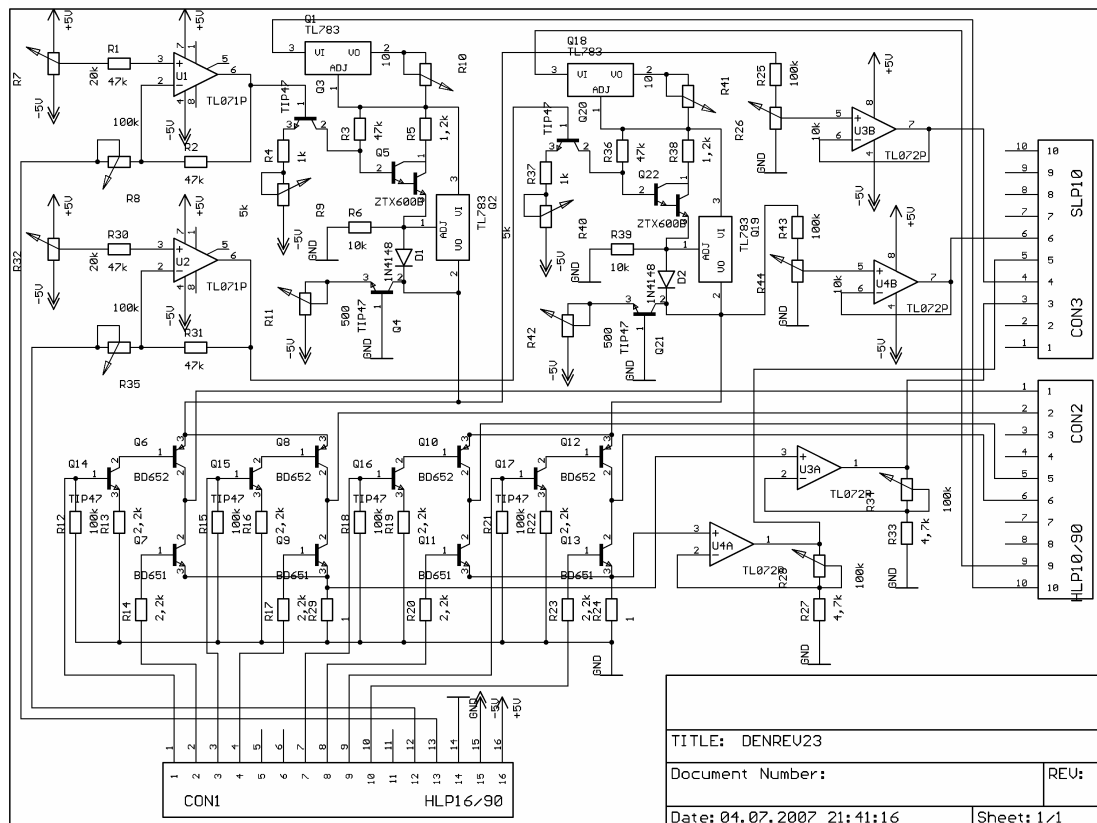


Figure 3.15: Circuit diagram of the stimulator's constant voltage output stage with two independent stimulation channels. High-voltage adjustable regulators (Q2, Q19) are used for controlling the stimulation intensity and for limiting the maximal output current (Q1, Q18).

3.7 Solution for experimental use (Experimental stimulator)

A small single channel stimulation device based on a new designed regulated switching power supply was built for experimental use. The device can be customized for different measurement protocols used in patients with denervated or innervated muscles. This is achieved by an interchangeable microcontroller which is pre-programmed for different tasks.

The main functional units of the device are the switching power supply, the microcontroller with the associated binary coded switches and the output stage. If necessary the stimulator can be fully controlled by an external computer in this case the microcontroller is bypassed.

This switching power supply is controlled by the potentiometer for adjusting the stimulation output intensity. It directly generates the desired output from the battery voltage. Normally needed additional regulators used for setting the output intensity, causing a drop in the efficiency of the stimulation device are not necessary.

For limiting the output current a voltage regulator controlling the voltage drop across an adjustable shunt is used. It allows limiting the stimulation current to a range which is safe for the application in patients.

The switching power supply is build up with a commercially available regulator (LM2587T by National Semiconductor) in a fly-back converter configuration and the standard design for the feedback circuit was altered allowing an adjustment of the output voltage from about 2 V up to 70 V. The desired output voltage is preset by a potentiometer and buffered by an electrometer amplifier and subtracted from the fed back output voltage (Figure 3.16). To keep the regulator stable over the whole output range the standard values for the compensation network were altered.

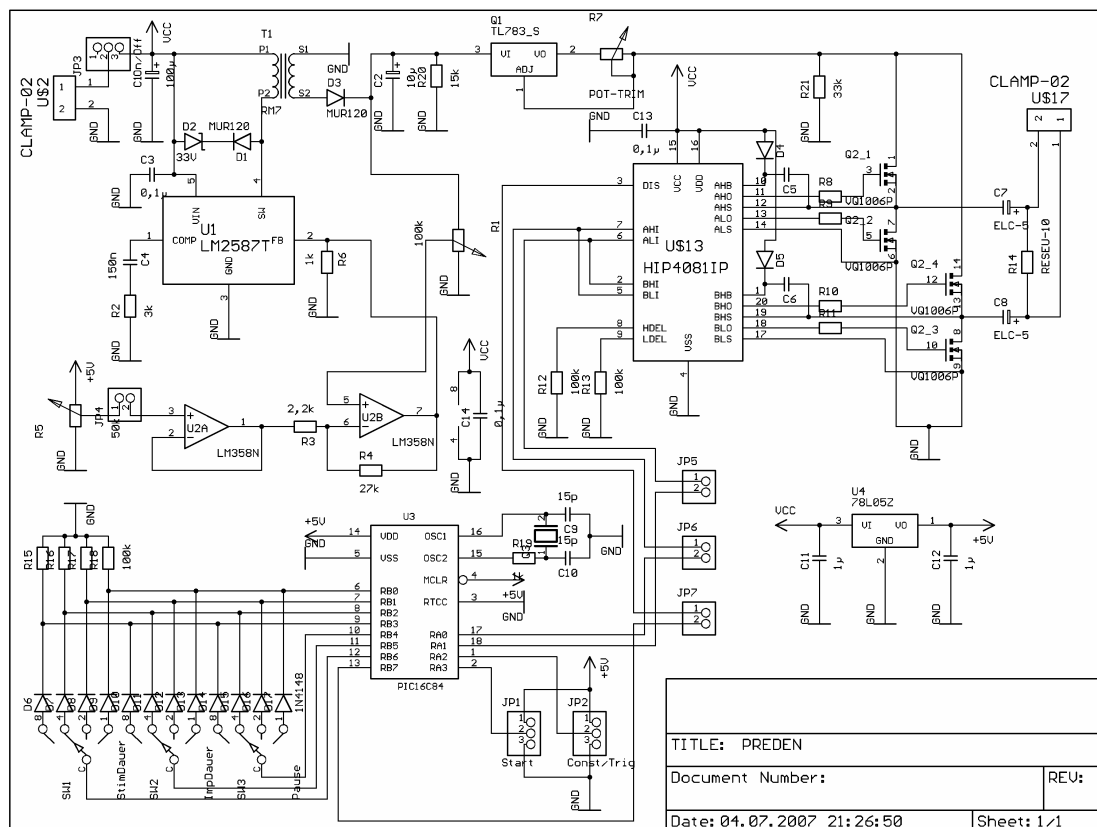


Figure 3.16: Circuit diagram of the stimulation device for experimental use. The main functional units are the switching power supply for generating the output voltage consisting of the LM2587T voltage regulator and the circuit for setting the desired output voltage level (Potentiometer R5 and the operational amplifier LM358N) together with regulator used for limitation of the stimulation current. A microcontroller (Microchip PIC16C84) and three binary coded switches controlling the stimulation parameters pulse with, frequency and number of stimuli applied. The output stage consisting of the bridge driver (Harris HIP4081IP) and the transistor switches. To prevent direct current stimulation even in case of device defect the stimulation pulses are decoupled by output capacitors. By opening the jumpers JP4, JP5, JP6 and JP7 the stimulator can be fully controlled by an external waveform generator or PC.

The stimulator is capable of generating single pulses, pulse trains with a given number of applied stimuli and continuous stimulation. A trigger output allows synchronization with recording devices or other stimulators.

The device is fast adaptable to different stimulation modes and parameters by changing the built in pre-programmed microcontroller. Easy and fast adjustment is provided by the simple user interface of the stimulator consisting of three binary coded switches, a push-button for triggering the stimulator, a switch for selecting continuous or triggered stimulation mode and the potentiometer for setting the output intensity (Figure 3.17).



Figure 3.17: Picture showing the front plate of the stimulator with the jacks for the electrode cables, output indicator LED, switch and push-button for triggering the stimulation and activating the continuous mode respectively, binary coded switches for setting the stimulation parameters, potentiometer for setting the output voltage and power on indicator LED (from left to right).

Depending on the programming of the microcontroller the pulse width can be modified from 0.1 ms up to 200 ms, the interval between consecutive pulses from 1 ms up to 2000 ms and the number of stimuli within a train from 1 up to 256 pulses.

4 Functional assessment of the denervated muscle

4.1 Stimulation Needle EMG / M-Wave

During an action potential small currents in the tissue are generated by the exchange of ions across the muscle fibre membrane. These currents are inducing changes of the potential in the tissue around the muscle fibre which can be measured. The recorded signal is called the electromyogram (EMG). The methods for measuring the EMG are distinguished in non-invasive techniques using surface electrodes and invasive methods using needle or fine-wire electrodes.

When recorded from the skin surface, the EMG signal has to pass various layers of connective tissue, subcutaneous fat and the skin before it is detected by the surface electrodes. This means that the signal is extremely attenuated and the higher frequency components are suppressed due to the low pass filter properties of the tissue. These effects are not essentially limiting the use of surface EMG for recording the activity of a muscle or muscle group where a large number of muscle fibres is active. However to record the action potentials of few or even a single muscle fibre one has to apply invasive techniques to pick up the signal in the immediate vicinity of the active fibre.

In subjects with denervation no voluntary activation of the affected muscle is possible since the nerve normally activating it is destroyed. Therefore electrical stimulation is used to elicit the muscle artificially. Stimulation of denervated muscle with surface electrodes works only if wide pulse widths and high intensities are applied, because the fibres within the denervated muscle have to be depolarised by the electrical current directly. The high stimulation intensity causes large artefacts driving the amplifiers for measurement of the EMG into overload whereas the long pulse duration causes a superposition of the stimulus artefact and the response of the activated fibres. In both cases it is impossible to measure and analyse the response of the muscle to the electrical stimulus. Therefore an invasive method for both activating and recording the response of the muscle fibres was chosen.

Activation of muscle fibres:

A monopolar needle electrode with insulated shaft and a small active area at the tip of 5 mm² (Medtronic, Skovlunde, Denmark, Ref. No. 9013R0232) was used for activation of a few muscle fibres in the direct vicinity of the needles tip (Figure 4.1 A). The needle was positioned about 10-15 cm proximal to the upper edge of the patella on the connection line between the spina iliaca anterior superior and the centre of the patella. A few centimetres away from the entry point of the needle a self adhesive electrode applied to the skin served as indifferent electrode. For activating the muscle fibres symmetric biphasic rectangular impulses with a duration of 100 μ s (50 μ s each phase) were applied with a constant voltage stimulator (see Chapter 3.7).

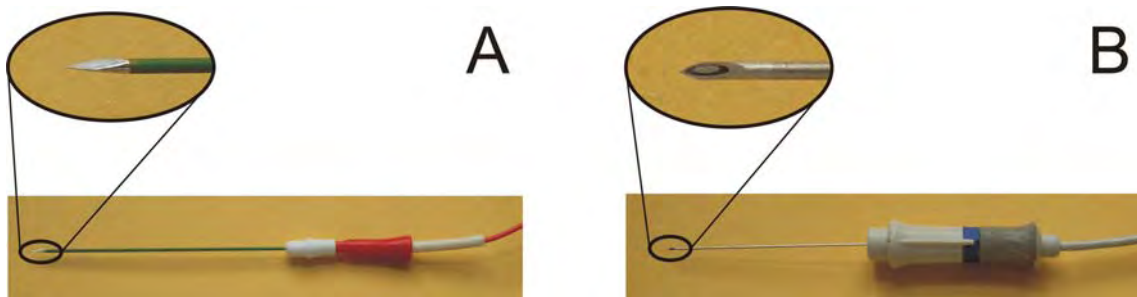


Figure 4.1: Different EMG needle types used for assessment of electrophysiological properties of denervated muscle. (A) Monopolar needle for activation of a few denervated muscle fibres in direct vicinity of the needles tip. Active area: 5 mm². (B) Concentric needle for recording action potentials from the activated muscle fibres. It is made up of a wire (core) inserted into a cannula. The core serves as recording electrode (active area: 0.07 mm²) and the cannula serves as reference electrode.

Recording:

The second needle inserted into the muscle, a concentric needle electrode (Medtronic DCN37, Ref. No. 9013S0031), records the extracellular potentials evoked by the volume conducted action potentials of the activated muscle fibres (Figure 4.1 B). This needle was placed about 3 cm distally to the monopolar needle used for stimulation. After insertion of the recording electrode, single stimuli with a frequency of 1 Hz were delivered to the muscle by the monopolar needle electrode and the recording needle was repositioned until reproducible polyphasic potentials were recorded.

All recordings were conducted with the subjects lying in supine position with the legs extended. In each subject stimulation and recording needle electrodes were repositioned three times in order to examine different parts of the muscle. Accurate needle placement was crucial and sometimes not easy to achieve because of severe muscle atrophy.

4.1.1 Muscle fibre conduction velocity

The muscle fibre conduction velocity (MFCV) is the propagation speed of the action potential along the membrane of the muscle fibre. This parameter influences the transmission of the depolarisation throughout the whole fibre which is important in the process from the depolarisation of the sarcolemma (fibre membrane) to the contraction of the muscle fibre. The action potential is conducted into the interior of the muscle fibre by the T-tubules small invaginations of the sarcolemma where the signal triggers the calcium (Ca^{2+}) release from the sarcoplasmic reticulum. The Ca^{2+} diffuses among the thick and thin filaments where it binds to troponin on the thin filaments. This turns on the interaction between actin and myosin and the sarcomere contracts (Silbernagl and Despopoulos 1991, Dulhunty 2006). Since, normal conduction velocity provided, the action potential arrives almost simultaneously at the ends of all the tubules of the T system, the sarcomeres of the muscle fibre contract at the same time.

For measuring the MFCV single pulses were applied to the vastus intermedius muscle with the monopolar needle electrode. The interval between the stimuli was about 1 s or longer in order to provide enough time for the activated fibres to return to their initial state. This is important since the conduction velocity of the muscle fibres changes if consecutive stimuli are delivered to the muscle within too short time (Mihelin et al. 1991). The responses picked up by the concentric needle electrode inserted into the muscle a few centimetres away, were pre-amplified and band-pass filtered with a low frequency setting of 13 Hz and a high frequency setting of 11 kHz. After the pre-processing the signal was digitised by an A/D converter at a sampling frequency of 50 kHz and stored for off-line analyses on a personal computer. In order to calculate the MFCV the latencies of all positive peaks greater than 50 μV were determined (Figure 4.2).

In each thigh of the patient three different locations were measured by repositioning stimulation and recording needle in order to assess different parts of the muscle. For each needle position the maximum, minimum and mean MFCV were determined.

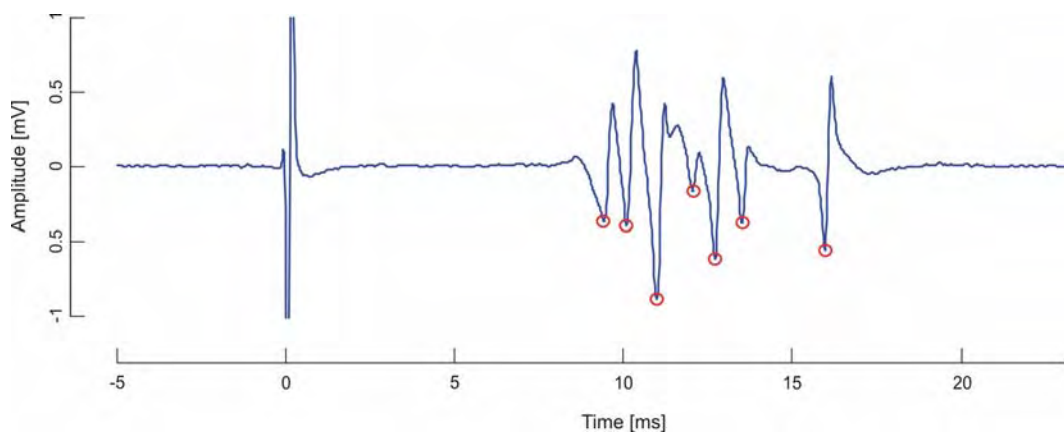


Figure 4.2: Stimulated EMG recording from the vastus intermedius muscle of a subject denervated for 50 months (35 months before starting FES therapy and 15 months of FES training). The first spike at 0 ms is the stimulus artefact. For calculating the MFCV the latencies of all positive spikes greater than 50 μV are determined (marked by red circles). The distance between the monopolar needle for stimulation and the concentric needle electrode for recording the responses was 29 mm. In this example the fastest fibre (first spike) showed a CV of 3.1 m/s, the slowest fibre of 1.8 m/s and the mean MFCV was 2.4 m/s.

4.1.2 Muscle fibre refractory period

The refractory period is defined as the time following an action potential when the sarcolemma of the muscle fibre or any other excitable membrane can not produce another action potential after a further stimulus. This period can be further divided into the absolute and the relative refractory period. During the absolute refractory no stimulus regardless of its intensity triggers an action potential whereas during the relative period abnormally large stimuli will evoke another action potential.

In this study the muscle fibre refractory period (MFRP) was investigated with the same setup used for measuring the MFCV. Because the muscle fibres had to be activated artificially, the moment of triggering an action potential could be controlled by electrical stimulation. The shortest inter-stimulus interval (ISI) showing still a response to the second stimulus was determined by measuring the responses of the fibres to double pulse stimulation where two stimuli with the same intensity and varying intervals are applied. This provides information about the electrophysiological recovery of the muscle fibre membrane after discharge by an action potential (Figure 4.3).

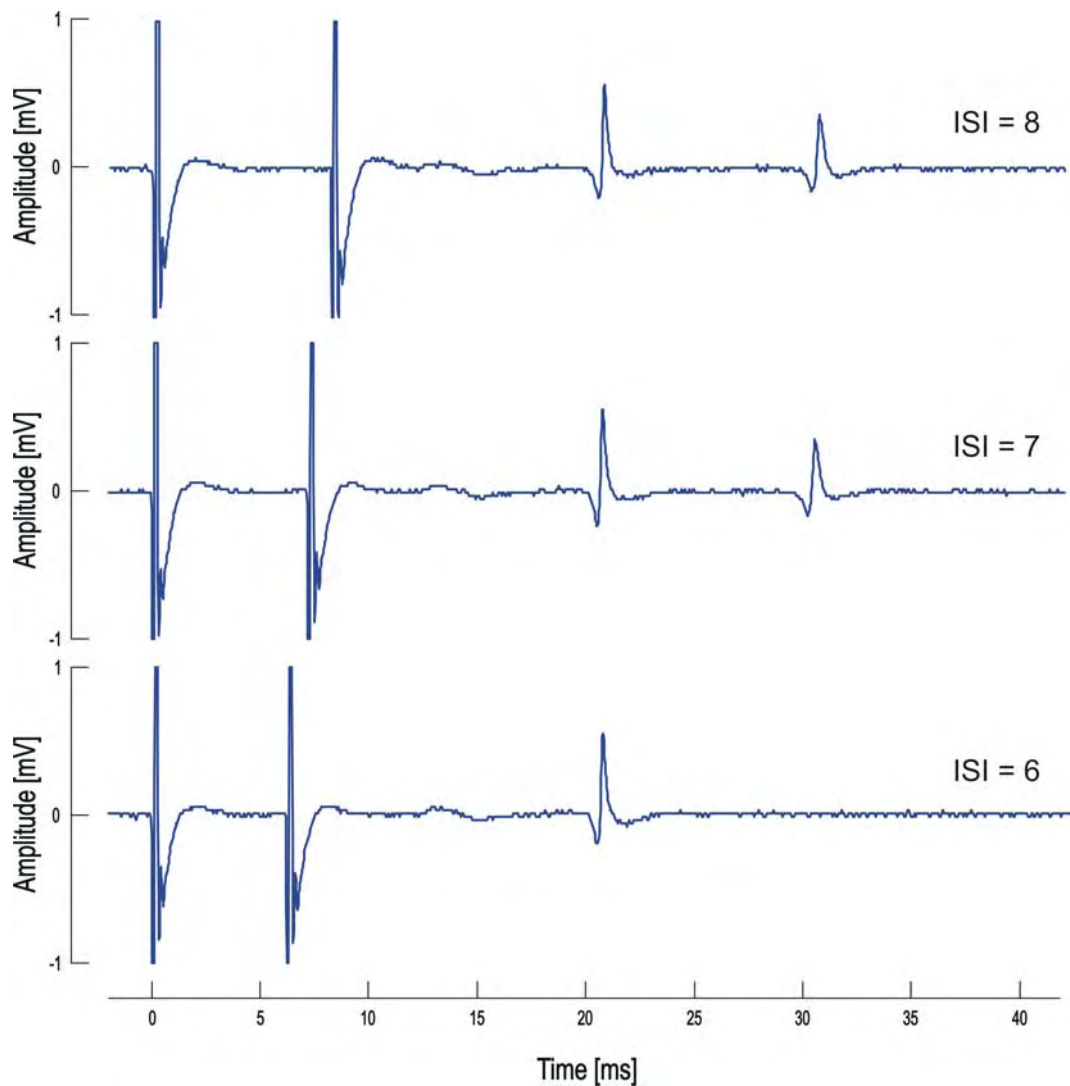


Figure 4.3: Double pulse recordings from a subject denervated for 20 months. The two first spikes in each trace at 0 ms and 6, 7, 8 ms respectively are artefacts caused by the stimulation pulses followed by the responses of a single muscle fibre. In contrast to most of the recordings in this study responses from only one muscle fibre are picked up in the example shown. At about 20 ms the response to the first stimulus and at 30 ms the response to the second stimulus is shown. In this case the fibre shows no refractory behaviour for pulses with an inter-stimulus interval of 7 and 8 ms. At an ISI of 6 ms the muscle fibre is refractory to the second pulse.

In contrast to nerve conduction studies and invasive electromyography (EMG), measurement of MFCV and MFRP is not routinely used as diagnostic tool in neuromuscular disorders. One reason might be that commonly used techniques are time consuming and difficult to handle. Nevertheless the influence of several neuromuscular diseases on MFCV and MFRP has been studied (Gruener et al. 1979, Hoeven van der et al. 1989, Mihelin et al. 1991, Cruz-Martinez and Arpa 1999).

4.2 In vivo assessment of conduction velocity and refractory period of denervated muscle fibres

This work was published in *Artificial Organs* 2005; 29(6):436-9.

4.2.1 Abstract

Stimulation needle electromyography was used to study the muscle fibre conduction velocity and refractory period in 4 patients with long-term denervation of the lower limb muscles due to lesion of the conus cauda or cauda equina (2 untrained and 2 trained by functional electrical stimulation). In untrained patients the results demonstrated that propagation velocity is reduced and refractory period of the muscle fibre is increased with time of denervation. The patients performing electrical stimulation training showed higher conduction velocities and reduced refractory periods despite of longer lasting denervation. This suggests that electrical stimulation training is effective to improve the electrical properties of the muscle fibre. Since the obtained data show a good correlation to other clinical tests and biopsy investigations, this method could serve as an additional measurement technique to specify the status of the denervated muscle. Further animal experiments and clinical studies are necessary to proof the results in comparison to more invasive established techniques.

4.2.2 Introduction

Stimulation needle electromyography (SNEMG) is a method which is usually not applied during routine electrodiagnostic patient examination. However several research groups have performed studies with different methods and patient groups, because this technique seems to provide valuable additional information about the status of the muscles examined.

The methods applied for measuring muscle fibre conduction velocity (MFCV) comprise surface EMG (Sollie et al. 1985, Hoeven van der et al. 1993) as well as different invasive techniques with concentric needles (Buchthal et al. 1955, Hoeven van der et al. 1993), monopolar needles (Chino et al. 1984) or single fibre needle electrodes (Trontelj and Stålberg 1983, Troni et al. 1983, Cruz Martinez 1989, Mihelin et al. 1991). A second valuable parameter, the shortest inter-stimulus interval (ISI) of a double pulse stimulation showing still a second response can be obtained with the same measurement setup. This parameter is providing information about the muscle fibre refractory period (MFRP). In this work both muscle fibre conduction velocity as well as muscle fibre refractory period was

investigated in patients with permanent (chronic) denervation of the quadriceps muscle due to a lesion of the conus cauda or cauda equina.

The recordings were performed in conjunction with the European project "RISE" that deals with functional electrical stimulation (FES) of denervated muscles (Mayr et al. 2004).

4.2.3 Materials and methods

The method applied in this study is similar to the one reported by v. d. Hoeven et al. (1993) in the biceps brachii muscle.

Stimulation:

For direct activation of the denervated muscle fibres or muscle fibre bundles a monopolar needle (Medtronic, Skovlunde, Denmark, Ref. No. 9013R0232) with an active area of the uninsulated tip of 5 mm² was inserted into the vastus intermedius muscle. The needle position was about 10-15 cm proximal to the upper edge of the patella on the connection line between the spina iliaca anterior superior and the centre of the patella with the patient lying in supine position, the leg fully extended. A silicone rubber electrode applied with gel to the skin surface was placed about 2 cm proximal to the needle acting as the indifferent stimulation electrode (Figures 4.4 and 4.5).

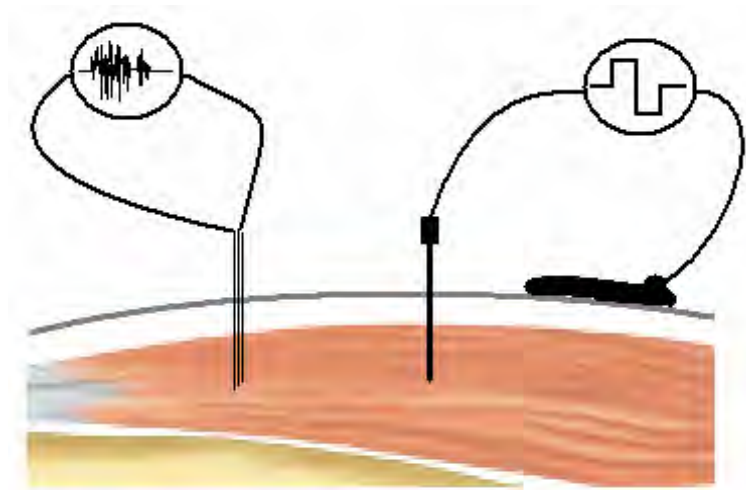


Figure 4.4: Schematic drawing of the SNEMG measurement setup. The monopolar needle with an uninsulated tip is stimulating against a surface electrode. The response of the activated muscle fibres is recorded by a concentric needle electrode placed in the muscle about 3 cm distally.

The muscle fibres were activated with a constant voltage stimulator delivering symmetric biphasic rectangular impulses with a duration of 0.1 ms (50 μ s each phase). Single impulses or double pulses (doublets) with inter-stimulus intervals between 1 ms and 15 ms were applied.

With this stimulation setup only a small number of muscle fibres in immediate vicinity of the tip of the needle is activated since the current density is decreasing very quick with increasing distance from the needle tip.

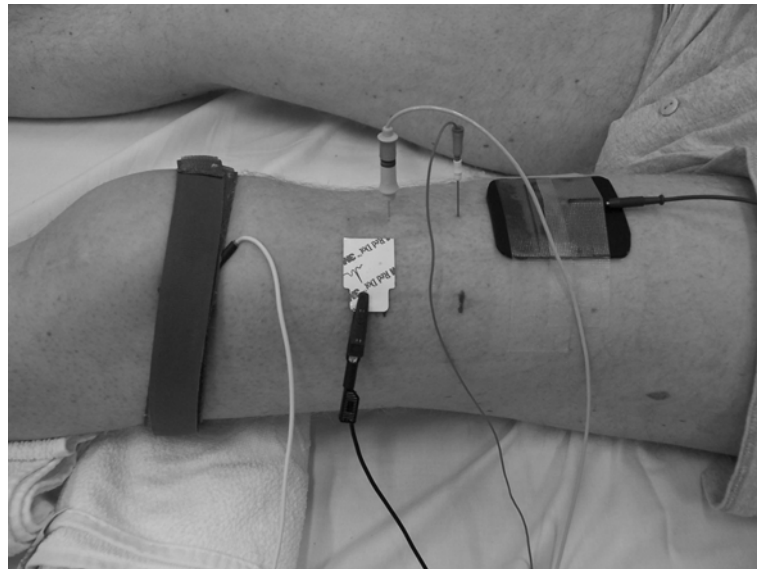


Figure 4.5: Picture of the clinical SNEMG measurement setup. The stimulation needle is placed approximately 15 cm proximal to the upper edge of the patella. A silicone rubber surface electrode placed proximal to the needle is the indifferent stimulation electrode. The concentric needle electrode inserted into the muscle distally records the muscle fibre response to the stimulus. In this setup two different types of ground electrodes were used.

Recording:

The concentric recording needle electrode (Medtronic DCN37 Ref. No. 9013S0031) was placed in the muscle about 3 cm distally from the stimulating needle electrode (Figures 4.4 and 4.5). Care was taken to position both needles perpendicular to the skin surface and in parallel to each other. The recording electrode was repositioned until reproducible polyphasic potentials were recorded (Figure 4.6). The signal was pre-amplified ($v = 100$) and bandpass filtered (13 Hz –11 kHz).

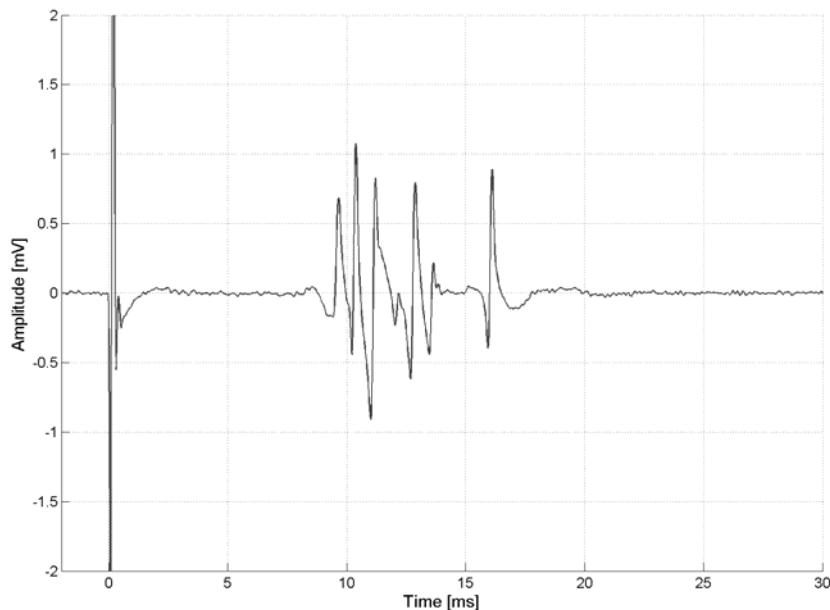


Figure 4.6: Example of a polyphasic response of the denervated vastus intermedius muscle to a single pulse stimulation recorded with SNEMG. The first spike (at 0 ms) in the trace is the stimulus artefact.

With a custom built amplifier designed to meet the special requirements for this measurement method: extremely high input impedance, very low input bias and offset currents, driven ground electrode and driven cable shield for minimizing the effect of the cable capacity.

After pre-amplification and filtering the EMG was digitized via a 12bit A/D-converter at a sampling rate f_s of 50 kHz and stored for off-line analysis of the data.

Patients:

For our measurements we selected two untrained spinal cord injured (SCI) patients (denervated for 10 and 30 months) and two SCI patients (denervated for 33 and 65 months) which had already performed an electrical stimulation training for 6 and 15 months in accordance to the protocol of the "RISE" patient study (Mayr et al. 2004). The patients have all a permanent denervation of the thigh muscles due to lower motor neuron lesion.

4.2.4 Results

MFCV: Till present we have assessed the maximum MFCV by measuring the latency between stimulus and response onset (Figure 4.7). In the patients without electrical stimulation training the maximum conduction velocity (unilateral samples) was 2.4 m/s (10 months denervated) and 1.2 m/s (30 months denervated). The FES trained patients showed a higher maximum MFCV. In the patient with 6 months of training the values for the maximum MFCV were 2.6 m/s in the left and 2.5 m/s in the right leg. The patient with 15 months of FES training showed a maximum MFCV of 3.6 m/s (left side) and 3.2 m/s (right side).

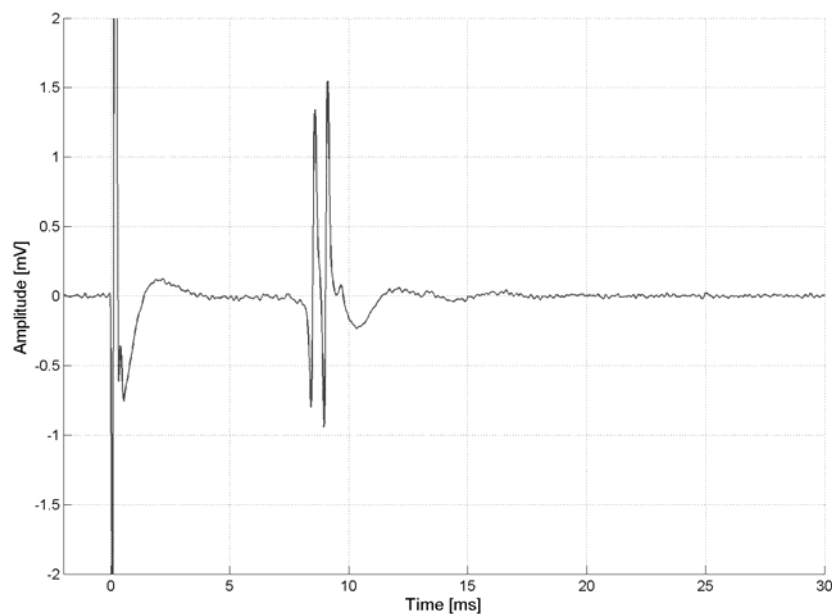


Figure 4.7: A SNEMG recording from the patient with 15 months of FES training (denervated for 65 months). Response of the vastus intermedius muscle to a single pulse stimulation. The first spike (at 0 ms) in the trace is the stimulus artefact. Stimulation amplitude was 25 V and impulse duration 0.1 ms.

MFRP: The MFRP is determined by the shortest ISI with response to the second stimulus (Figure 4.8). For a measured shortest ISI with the second pulse eliciting response the actual value of the MFRP is in the range between the measured ISI and 1 ms below. This uncertainty is caused by the applied measurement method using steps of 1 ms for gradually reducing the ISI.

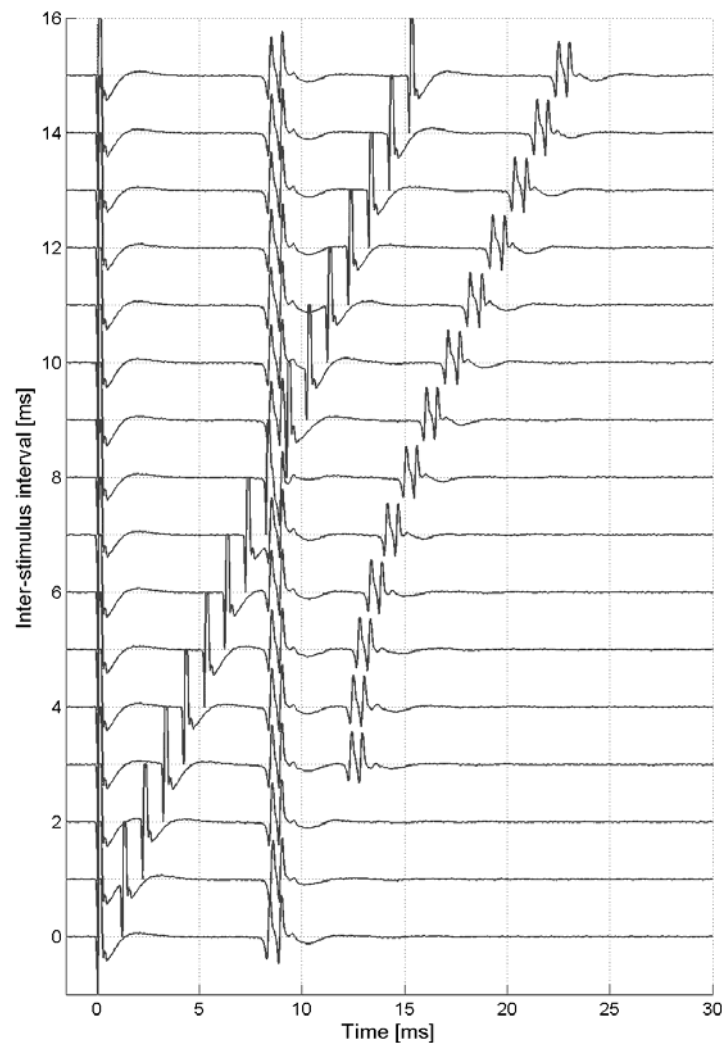


Figure 4.8: SNEMG recording sequence with double pulse stimulation. The ISI is step by step reduced from 15 ms to 1 ms while all other stimulation parameters are held constant (from top to bottom). In the last trace on the bottom the response to single pulse is displayed. In this example the examined muscle fibres are showing a shortest ISI with response of 3 ms (4th trace counted from bottom). The propagation velocity of the second response decreases in the transient area between 3 and 7 ms ISI. Recording from the patient with 15 months of FES training (denervated for 65 months).

The patients without FES training showed a shortest ISI with response of 8 ms (30 months denervated) and 4 ms (10 months denervated). In the patient with 6 months of FES training (33 months denervated) the shortest

ISI was 5 ms in both legs and in the 15 months FES trained patient (65 months denervated) the shortest ISI was 2-3 ms in the left and 3 ms in the right leg (Table 4.1).

Patient	Denervation time months	FES training months	MFCV [m/s]		MFRP [ms]	
			left	right	left	right
A.C.	10	-	2.4	-	4	-
H.T.	30	-	-	1.2	-	8
G.H.	33	6	2.6	2.5	5	5
M.S.	65	15	3.6	3.2	3	2-3

Table 4.1: Summary of the results from the measurements performed in the two untrained and two FES trained patients. Only unilateral measurement was performed in the untrained patients. For comparison, Cruz-Martinez reported a maximum MFCV of 4.48 m/s in the vastus medialis muscle of healthy adult volunteers (Cruz-Martinez 1989).

4.2.5 Discussion

The difference of MFCV in the untrained patients can be explained due to the different period of denervation (10 and 30 months) and consequently a different degree of atrophy of the denervated thigh muscles. The muscle fibre diameter is known to be a main variable determining fibre conduction velocity (Håkansson 1956). Another factor reducing the propagation velocity is the decrease of the muscle fibre membrane resting potential as a consequence by long-term denervation. It is known that between 12 and 24 months of denervation muscle degeneration starts in addition to the ongoing atrophy process. This is accompanied by changes in the depolarization rate and capacitance of the muscle fibre membrane which will additionally decrease the MFCV (Gruener et al. 1979). It is likely that these changes in the muscle membrane properties are also responsible for the markedly difference in the MFRP in the untrained patients. The measurements in the FES trained patients are showing higher conduction velocities up to 3.6 m/s. Moreover the shortest ISI with response was in the range of or below the values of the untrained patients although they were denervated for a longer period. This suggests that electrical stimulation

training is able to improve the electro physiological properties of the long-term denervated muscle fibre.

4.2.6 Conclusions

The obtained data seem to show a good correlation to other clinical tests and biopsy investigations. The method could serve as a powerful new clinical measurement method for quantification of the actual excitability status of a denervated muscle. This could be especially helpful in the supervision of home based FES training for restoration of long-term denervated degenerated muscles, as the method is simple enough to apply in routine check-ups.

Of course it is necessary to confirm the results in both animal and clinical experiments to proof the reproducibility and ensure validity of results in comparison to more invasive but established techniques like biopsy analyses.

4.3 Computed tomography

Computed tomography (CT), also known as computed axial tomography (CAT or CT scan), was developed by Sir Godfrey N. Hounsfield in the early 1970s at the Thorn EMI Central Research Laboratories, England. The first clinical application of the CT a brain-scan was made in 1972.

A CT scanner is an X-ray machine which produces cross-sectional, two dimensional images of the body. It generates a fan-shaped beam of X-rays rotating around the body. The X-rays pass through the body and are detected by a ring of electronic sensors sensitive to radiation located around the patient's body (Figure 4.9). Depending on the radio-density of the tissue between the X-ray source and the detector the beam is attenuated.

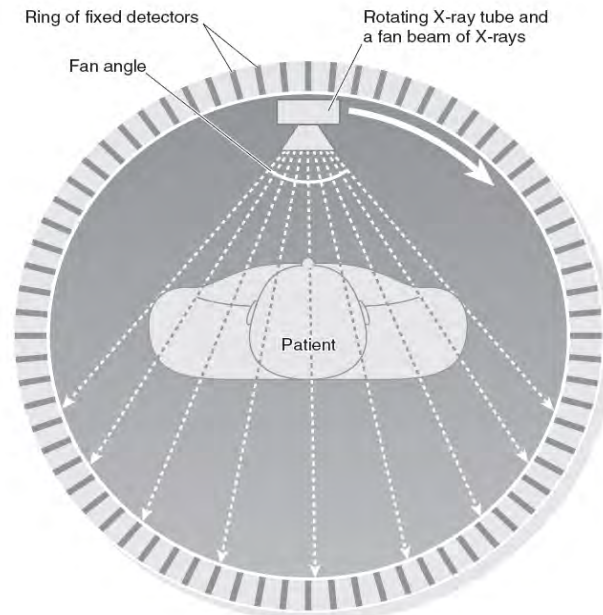


Figure 4.9: Schematic drawing showing the principle of acquiring a CT scan. An X-ray source is rotating around the patient and the radiation emitted is detected on the opposite side either by a rotating segment or a fixed ring of detectors. (from 'Introduction to CT physics', www.intl.elsevierhealth.com/e-books/pdf/940.pdf).

The acquired CT slices are divided into a matrix of 512x512 volume elements (voxels). These intensity readings are passed to a computer, which then calculates the attenuation value of each voxel within the cross-section (slice) of the body. The image is then calculated from this array of voxels converting it into a matrix of 512x512 picture elements (pixels) with each pixel assigned the attenuation value of the corresponding voxel.

The attenuation values are mapped on a scale ranging from -1024 up to $+1023$ ($+3071$) arbitrary units named Hounsfield units (HU). On this scale water is assigned an attenuation value of 0 and air -1024 (Figure 4.10).

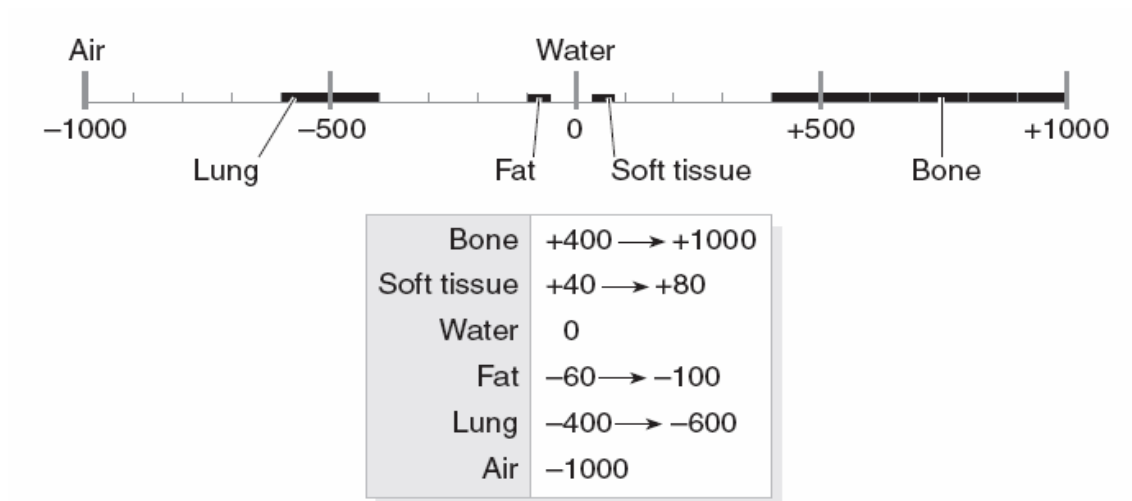


Figure 4.10: The Hounsfield scale of CT numbers. The scale assigns water an HU value of 0 and air -1000 . Modern CT scanners have an extended scale ranging from -1024 up to 3071 (from 'Introduction to CT physics', www.intl.elsevierhealth.com/e-books/pdf/940.pdf).

In the image generated from this data pixels with a HU value of -1024 are displayed black and pixels with $+1023$ ($+3071$) are displayed in white colour. All CT numbers in between are represented by different shades of grey. Since the human eye is not able to distinguish between 2000 different shades of grey, only a limited range (window) of the scale is displayed, this is called 'windowing'.

The term 'window centre' or 'window level' designates the central CT number or HU of all the numbers within the window. The window width is set that it covers the HU of all the tissues of interest and these are displayed as 256 shades of grey. Tissues with CT numbers outside this range are displayed as either black or white. In all of the CT-scans shown in this work the window centre was set to 50 and the window width to 350. This setting is used for examination of muscle tissue since healthy muscle has an average HU value of 45.

4.3.1 Muscle cross-sectional area measured by computed tomography

Muscle complete cross-sectional area and density (measured in HU) of quadriceps m. and hamstrings were determined as described in Mödlin et al. (2005). Patients were positioned in a way that the top of the trochanter major of both femur bones was aligned in the same plane of the CT-scan. This provided a baseline for all further measurements which were done at distances of 10, 20, 30 and sometimes 40 cm below this reference plane (Figure 4.11). The measurement protocol is routinely carried out at the Department of Radiology at the Wilhelminenspital Wien for many years. The protocol has been retained unchanged in order to keep the acquired data comparable to previous made measurements from other studies. Since the CT-scan 20 cm below the baseline scan normally shows the largest cross-sectional area and therefore the biggest changes this scan was chosen for most of the analyses.

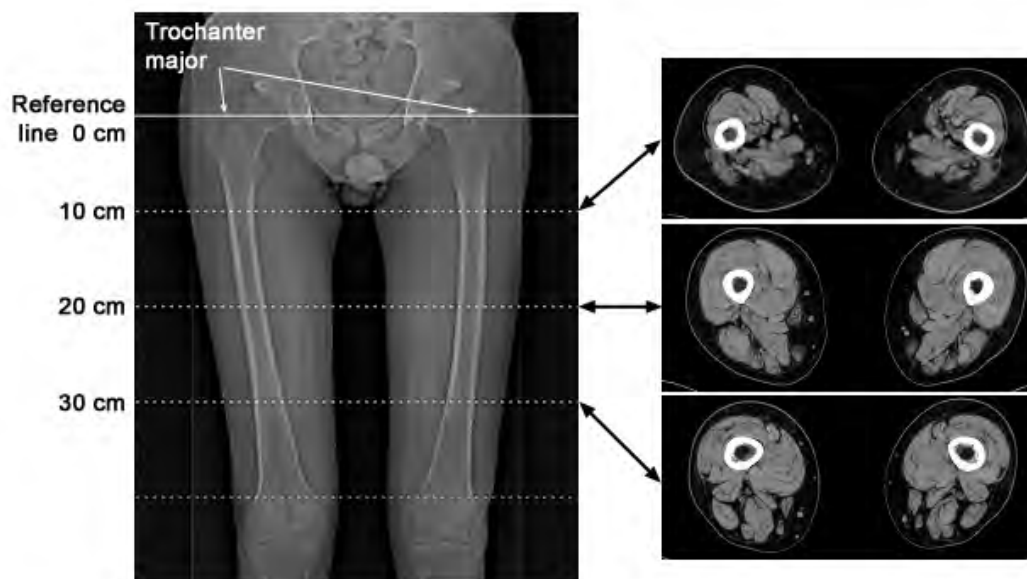


Figure 4.11: Left: CT scan showing a frontal view of a patient's thigh. The thin white line connecting the trochanter major of both thigh bones serves as baseline for the further scans made at different levels below this baseline (dotted lines). Right: CT scans showing the corresponding cross-sections of the thighs 10 cm, 20 cm and 30 cm below the reference line.

The cross-sectional area was determined by manually marking the muscles belonging to the quadriceps muscle group and the hamstrings respectively (Figure 4.12). In patients with severe atrophy of the thigh muscles it was sometimes very difficult to identify the muscles forming the quadriceps or hamstrings group. The data acquired by computer tomography with a Siemens Somatom Plus 4 was converted into DICOM format and stored. This allows exchange and analysis of the acquired images with software independent from manufacturer of the device used for data acquisition.



Figure 4.12: CT scan showing the cross-section of the right thigh 20 cm below the trochanter major from a patient denervated for 5.4 years. The highlighted area marks the quadriceps muscle.

To analyse the scans of the patient's thighs a software for image analysis with a graphical user interface was written in Matlab[®]. It provides functions for cutting out measurement artefacts, zooming for easier marking small regions of interest and automated calculation of the cross-sectional area and the corresponding mean tissue density (CT number or Hounsfield units) of the selected area (Matlab[®] script see appendix B). A screenshot of the developed software is shown in Figure 4.13. The processed images are saved for reviewing the analysed data or comparison to other scans later on.

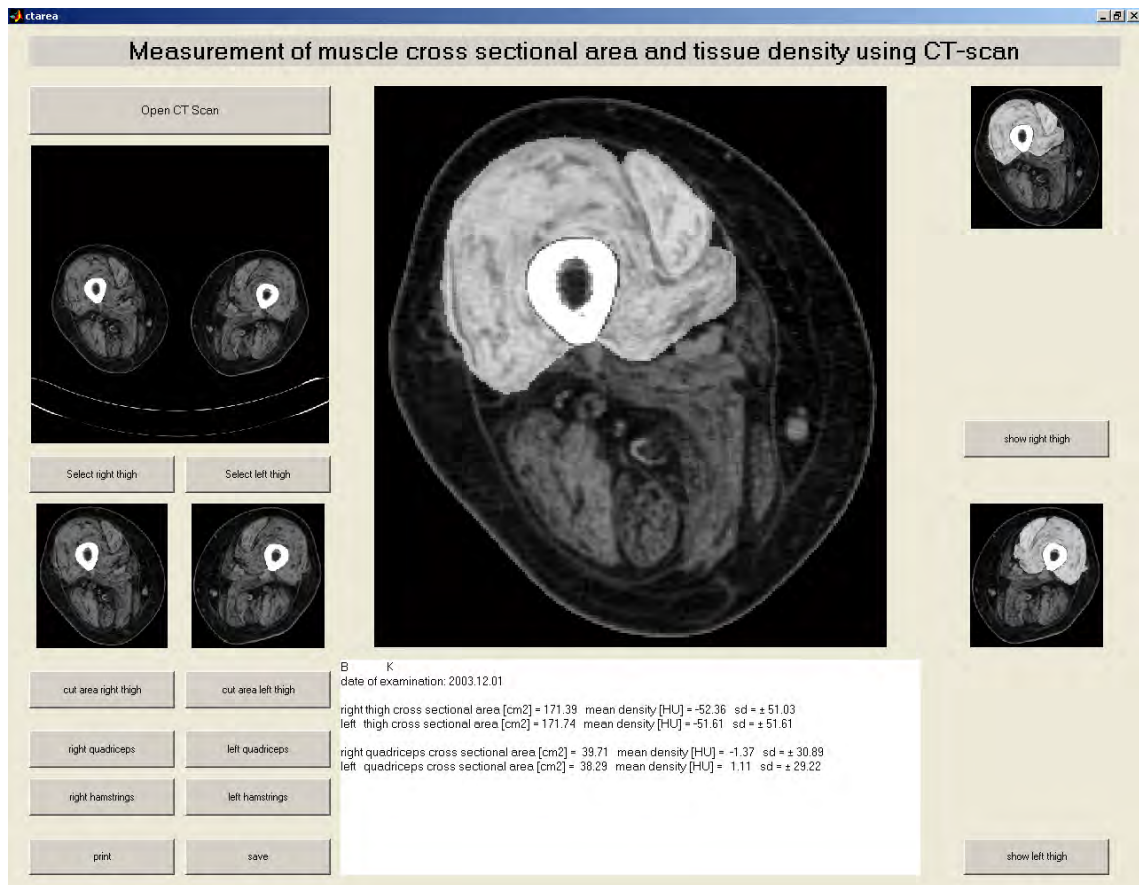


Figure 4.13: Screenshot showing the graphical user interface of the software developed. The centre window is used for zooming into image and marking the region of interest to be analysed. The left upper window displays the whole image acquired by the CT scanner below the cut out regions showing the right and left thigh. On the right side right and left thighs are pictured with the already analysed regions highlighted. By invoking the image of the right or left thigh the image is displayed in the centre window for checking and if necessary editing the marked regions. Example from a patient denervated for 5.4 years.

To illustrate the morphological changes induced by complete denervation of the thigh muscles in the figure below CT-scans of four patients denervated for different periods of time are shown (Figure 4.14).

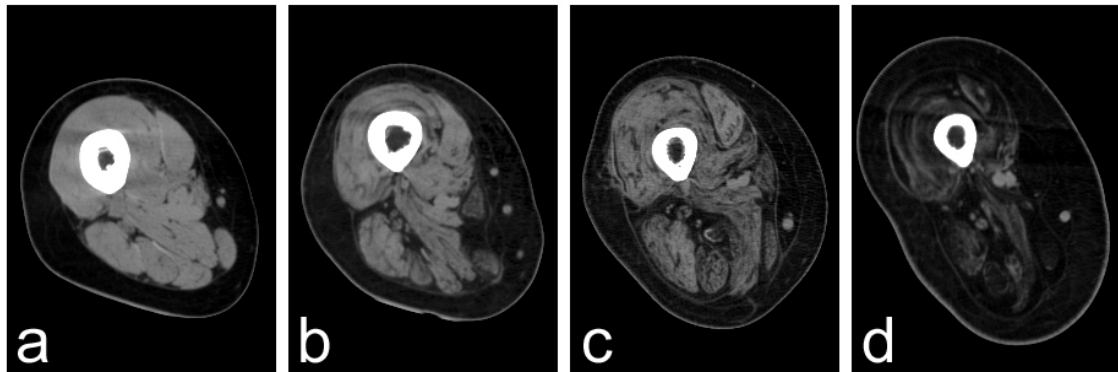


Figure 4.14: CT-scans showing a cross-section of the right thigh 20 cm below the trochanter major. Four patients denervated for different periods of time: a) 0.8, b) 1.7, c) 5.4 and d) 7.7 years. All patients suffered from denervation due to lesion of the conus cauda or cauda equina.

During the early stages of denervation the severe muscle atrophy is the most prominent alteration in the affected limb. In panel a) the right thigh of a male patient denervated for 0.8 years is shown. The measured cross-sectional area of the quadriceps muscle was 31.6 cm². Compared to the results of studies in healthy subjects (Bulcke et al. 1979, Termote et al. 1980 and Maughan et al. 1983) which showed an average cross-sectional area of about 80 cm² for male subjects, this means a reduction in muscle area of 60.5% within the first year. All other muscles, shown in the thigh cross-section above are affected very similar. Within the muscle no alterations compared to normal innervated muscles are visible in the CT-scan.

At later stages of denervation, with progression of atrophy, an enlarged space between the individual muscles of the thigh is observed in the CT-scans. These intermuscular areas are filled predominantly with fat and loose connective tissue (see Figure 4.14 panel b, c and d). Within the muscles an increase of adipose, collagenous and connective tissue is observed by analyses of muscle biopsy. Due to the lower radio density and therefore low attenuation values of these tissues the denervated muscles are displayed in darker shades of grey compared to normal muscle in the CT-scans (Figure 4.14 panel c, d).

The reduction of muscle cross-sectional area is not necessarily in conjunction with a reduced cross-sectional area or reduced circumference of

the thigh, due to the fact that in many patients muscle atrophy is accompanied with an increase of subcutaneous fatty tissue.

4.3.2 Quantification of tissue components, thigh and muscle composition (Distribution of density of tissue)

Measurement of cross-sectional area is one method to describe the state of the muscle, but looking only at the area could be misleading, since as already mentioned above the composition of the tissue within the cross-section is crucial too. A muscle highly infiltrated with non contractile tissue might have a large cross-sectional area however is not able to produce sufficient force. Therefore, to quantify the composition of the muscle or whole thigh the distribution of the tissue density within the muscle or thigh was analysed.

The density distribution was calculated with the help of an image analysing software especially designed for examination of the thighs. It allows zooming out the left and right thigh from the standard CT-scans made at the different levels below the greater trochanter of the thigh bone. Within each thigh it is possible to mark two different regions of interest (ROIs) to be analysed (Figure 4.15). In this work the knee extensor and flexor muscles respectively were chosen for analysis.

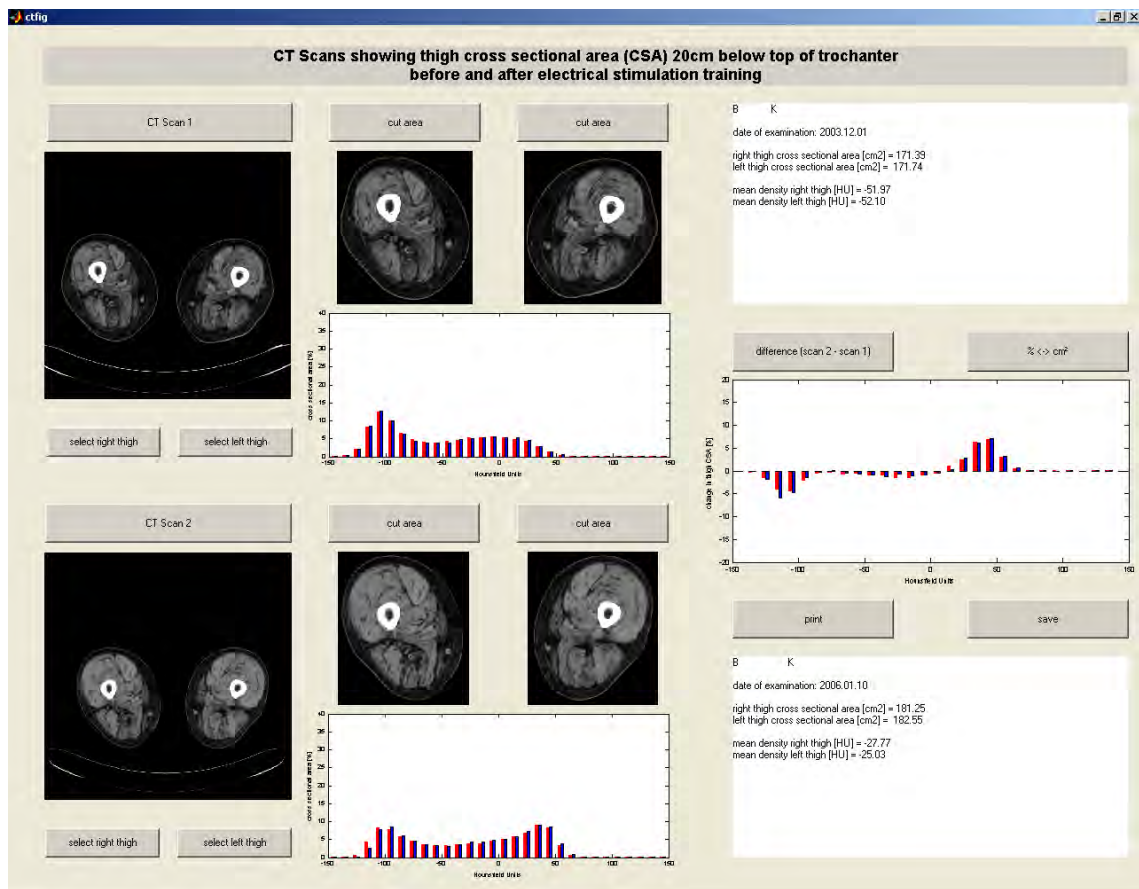


Figure 4.15: Screenshot of the software developed for analysing the tissue composition of the thigh cross-section. In the upper left and centre the CT scan of both, left and right thigh as well as the histogram showing the density distribution before commencing electrical stimulation training is displayed. Below the CT scan and histogram after 2 years electrical stimulation training is displayed. On the right side the difference of the two histograms is presented, indicating an increase of tissue with a density in the range of about +50 HU and decrease of less dense tissue. Data displayed is normalised to the thigh cross-sectional area. Example from a patient denervated for 5.4 years.

For each selected region the cross-sectional area, the mean tissue density and the standard deviation was calculated. The histogram of the density distribution was determined by sorting all pixels within the ROI according to their assigned density value into bins. Bin size was 10 HUs and the range was from -200 up to +1000 HU. For displaying the analysed data this range was limited to -150 up to 150 HU, since all tissues of interest have densities within this range, e.g. muscle tissue approximately 40 – 60 HU and fat about -100 HU (Figure 4.16). Bone tissue is suppressed with this setting. In contrast to other studies (Goodpaster et al. 2000) the range of analysed muscle attenuation was not limited to 0 – 100 HU because also changes in

the content of intermuscular adipose tissue within a selected ROI was considered. All histograms were normalized with the corresponding area of the analysed ROI to allow comparison of different muscles or muscle groups within a patient or between different patients.

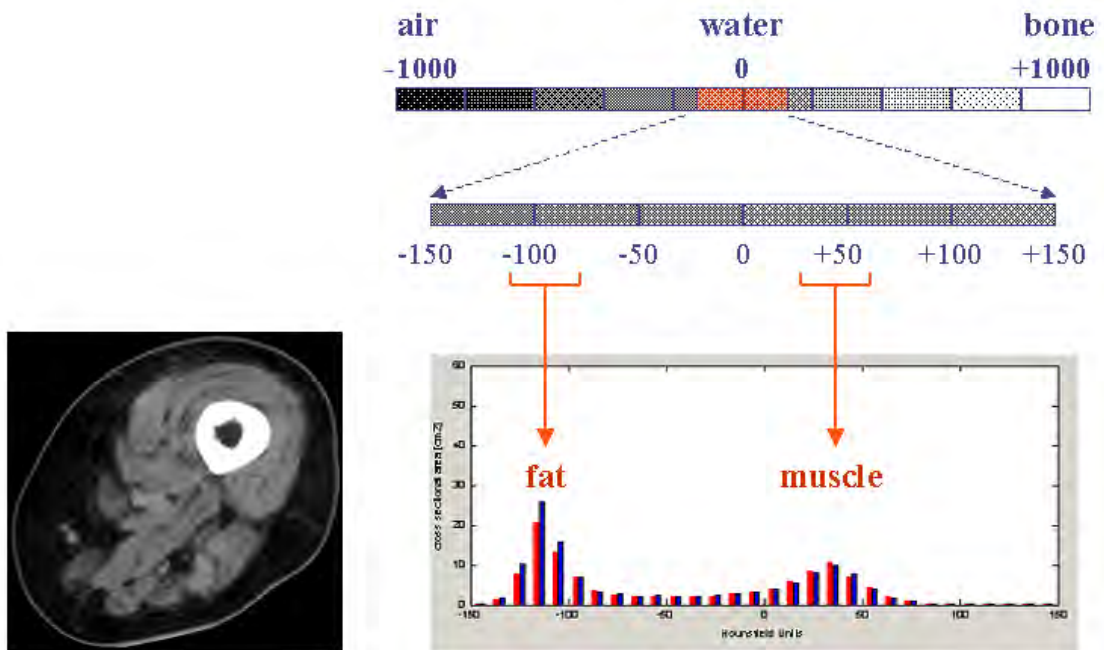


Figure 4.16: Illustration showing the Hounsfield scale and the histogram of the density distribution of the cross-section from the left thigh of a patient.

Two different methods were used to analyse the density distribution within selected areas. An automatic method for analysing the whole thigh and a method where ROIs within the thigh are selected manually. The automatic selection of the ROI is very fast and able to deliver information of the composition of the whole thigh. Changes in content of tissue with different density before and after stimulation training are easily detected by this method. Disadvantage is that the results are influenced by weight gain or loss of the patient and it is not possible to analyse certain tissues (muscles, fat) within the thigh. This is due to the fact that the ROI is determined by detecting changes in density of the analysed pixels, this works fine for interfaces between materials or tissues with a large difference in CT attenuation e.g. air and skin surface of the thigh. For analysing particular muscles or muscle groups within the thigh the ROI has to be selected manually especially in denervated, degenerated muscle highly infiltrated with fat and connective tissue.

To demonstrate how the density of the quadriceps muscle is influenced by longstanding denervation the density distribution in four patients with different periods of denervation is shown in figure 4.17.

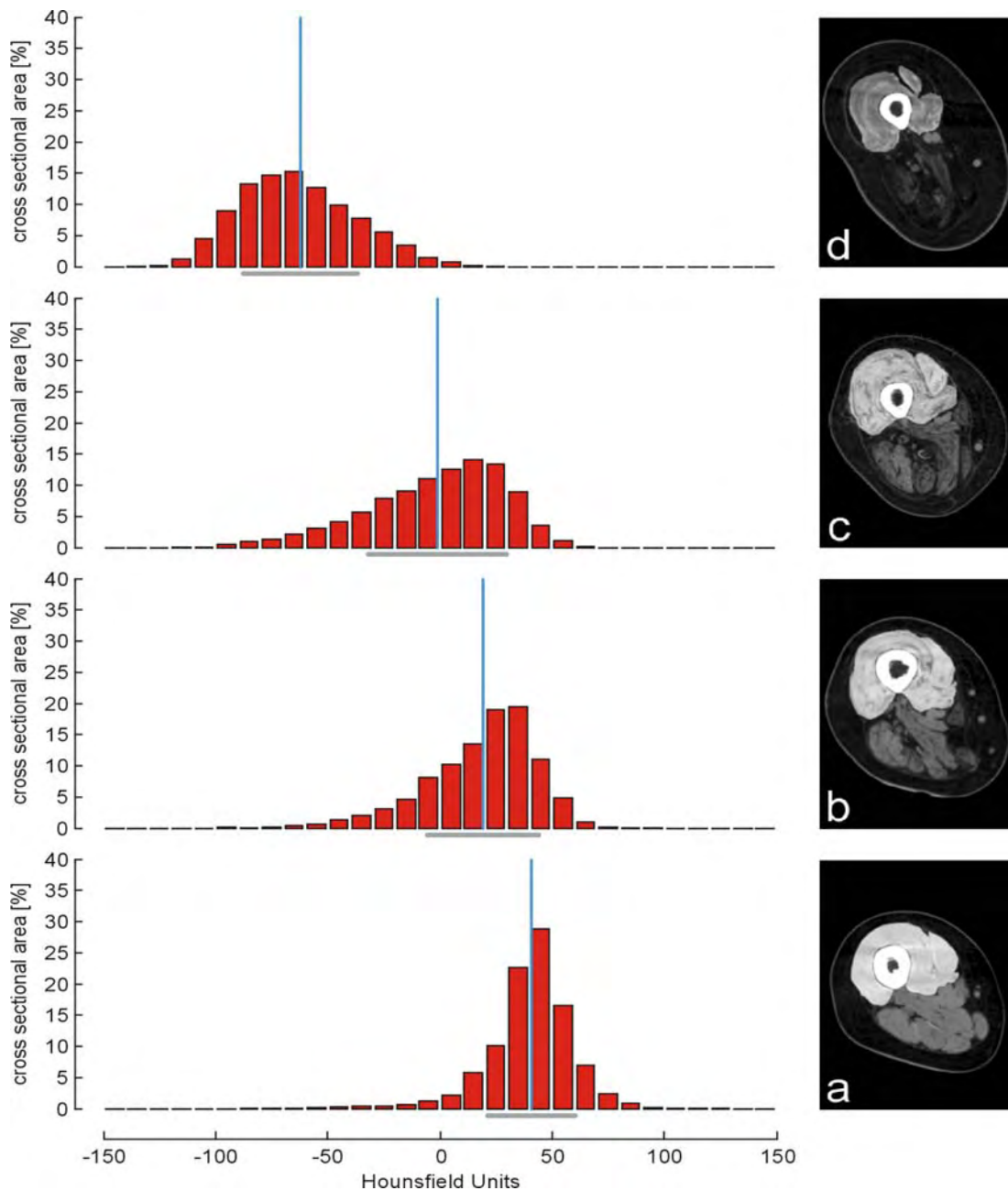


Figure 4.17: Illustration showing the tissue density distribution of the quadriceps muscle and the corresponding CT scan with the quadriceps muscle highlighted in patients with different time of denervation. Examples from the same four patients as in figure 4.14 denervated for a) 0.8, b) 1.7, c) 5.4 and d) 7.7 years. Blue lines are indicating the mean tissue density, the grey bars below the histograms the standard deviation (± 1 SD) from the mean.

4.4 Isometric strength testing, knee extension torque

To assess the contractile properties of the denervated knee extensor muscles a custom-made knee dynamometer was used. The subjects sat on the chair with approximate 100° hip angle secured by a strap fastening the hip. Measurements were made at 90° knee angle with the lower leg fixed to the lever of the dynamometer just above the ankle. The axis of rotation of the knee joint was aligned with the axis of rotation of the lever. Strain gauges attached to the lever near the axis measured the knee extension torque exerted by the stimulated thigh muscles. Before start of each measurement the torque was set to zero in order to preclude any bias by gravity, temperature drift or altered position of the leg. Each lower limb was assessed separately to rule out any influences by the non activated limb (Figure 4.18).

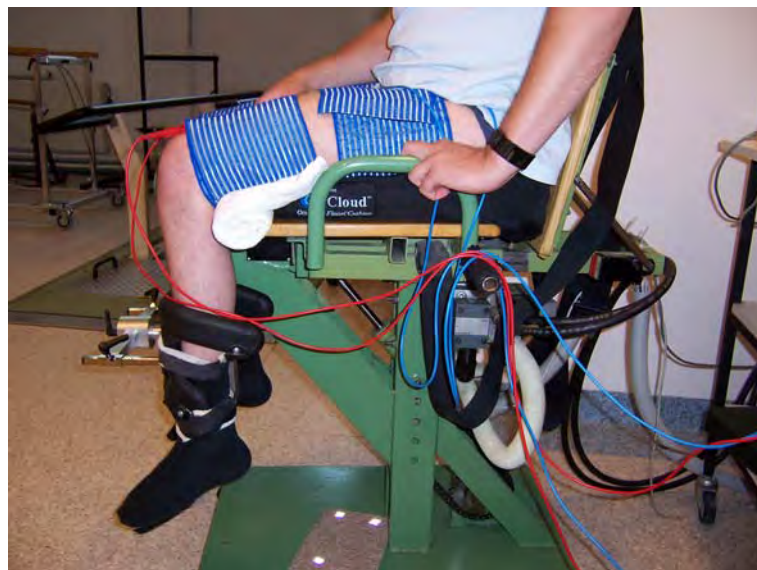


Figure 4.18: Subject sitting on the knee dynamometer. Silicon rubber electrodes for activation of the quadriceps muscle attached with bandages to the thigh.

To obtain information about the necessary stimulation pulse width for activation of the denervated quadriceps muscle, single pulse twitch torque measurements were carried out on the knee dynamometer. For this purpose the muscle was activated by single stimuli with varying pulse width (from

1.3 to 145.4 ms) and maximum stimulation current of ± 250 mA. The knee extension torque produced by the muscle twitch was recorded.

Force generation capacity of the quadriceps muscle was tested by measuring the knee extension torque produced by tetanic contraction. Pulse trains with a frequency of 20 Hz, pulse width of 36.3 ms and duration of 2 s were applied to the muscle and the stimulation intensity was stepwise increased up to a maximal stimulation current of ± 250 mA. The development of force with increasing stimulation intensity and the maximal contraction force were analysed.

The measurements were performed three times throughout the study: at inclusion before FES training, after one year and at the end of the study after two years of electrical stimulation training.

5 Human application (patient study)

The patient study was carried out in the context of the research project "Use of electrical stimulation to restore standing in paraplegics with long-term denervated degenerated muscles (DDM)" (acronym: "RISE") funded by the European Community within the 5th Framework Program. The consortium included thirteen European partner institutions from Austria, United Kingdom, Italy, Slovenia, Germany and Iceland and additional six subcontractors from Austria and Germany. Nine out of the nineteen were spinal cord injury centres. The project started with November 1, 2001 and ended with May 31, 2006.

Based on preliminary work (Kern 1995, Kern et al. 1999 and 2002, Mayr et al. 2001 and 2002, Zrunek et al. 1991) the aim of the project was to develop a novel clinical rehabilitation method and the associated technical equipment for patients suffering from long-term flaccid paraplegia (denervated degenerated muscles - DDM) with no chance of recovery of the nervous system.

5.1 Patients

Patients suffering from flaccid paraplegia (denervation of lower extremity muscles, conus cauda syndrome) were selected for the study because they are especially good candidates for this approach. After receiving the positive vote from our local ethical committee recruitment of the patients was started. A first screening of the patients was carried out at the participating rehabilitation centres. Patients who met the inclusion criteria and were willing to participate in the study were invited to Vienna.

In Vienna the patients were checked again if they were fulfilling the inclusion criteria and after obtaining their informed consent, a comprehensive assessment procedure was carried out in order to get detailed information about their neurophysiologic and muscular status at inclusion into the study. Demographic data of the patients included into the study is shown in table 5.1.

Subject	Sex	Birthday	Entry date	Paraplegic since	Skeletal level of lesion	Sensory level of lesion
B.A.	m	16.05.1983	12.08.2003	03.11.2002	L1	T11
B.B.T.	m	15.02.1979	15.08.2003	27.07.1999	T12,L1	T10
B.K.	m	01.10.1956	01.12.2003	07.07.1998	T11/12	T9
B.D.	m	06.05.1966	17.02.2003	03.10.2001	T12	T11
C.A.	m	18.01.1965	17.08.2004	28.10.2003	T11/12	T8
C.M.	m	12.02.1976	24.04.2003	12.07.2001		
D.D.	m	30.06.1979	08.03.2004	29.05.2003	T11/12	T12
E.J.	m	19.01.1949	18.08.2003	19.01.1996	T12,L1	T9
E.R.	m	02.05.1951	01.09.2003	04.03.2000	T12,L1	T6
F.R.	m	20.04.1955	16.09.2003	23.05.2000	T9/10	T9
H.B.	f	19.09.1957	17.03.2003	23.06.1994	T11/12	T12
H.G.	m	12.11.1966	20.01.2004	18.05.2002	T11/12	T10
J.W.	m	03.02.1973	26.04.2004	24.03.2003	T12,L4/5	T10
J.P.I.	m	20.04.1962	05.07.2004	25.04.2003	T12,L1	L2
L.M.	m	27.08.1966	17.11.2003	04.10.1997	T12	L1
L.U.	m	12.04.1960	19.04.2004	21.02.1998	T12,L1	T12
L.K.	f	11.02.1974	22.09.2003	18.01.1996	T5	T4
N.T.	m	13.03.1984	20.04.2004	26.06.2003	T11	T10
P.B.	m	08.05.1977	09.12.2003	09.03.2002	L1	L1
S.M.	f	18.07.1965	05.05.2003	27.08.2002	T12	T11
S.M.	m	03.08.1959	19.05.2003	09.06.2000	T12	T10
S.A.	m	27.05.1965	15.12.2003	30.10.1997	T8/9,T11	above T6
S.AS.	m	20.07.1973	24.11.2003	27.02.2003	T11,T12	T9
ST.A.	m	01.03.1950	04.08.2003	26.06.1966	T12	T12
T.M.	m	29.04.1969	30.12.2003	01.09.1985	T12	T10
T.H.	f	24.06.1955	06.07.2004	19.04.2001	T12,L1	T11
T.B.	m	04.09.1974	19.01.2004	15.03.2003	T11/12	T10
W.E.	f	25.07.1948	07.04.2003	05.08.1994	L1	T11

Table 5.1: Data showing the skeletal and neurological level of lesion of the 28 subjects included into the RISE study. Only 5 subjects were female, the mean age was 37.9 years (range from 20.1-54.7 yrs) and the mean denervation time was 5.12 years (range from 0.69 up to 37.13). Marked grey are the subjects which left the study prematurely.

Drop out: Six patients left the study premature during the first year and two in the second year of the study. The reasons for drop out were different. In five cases the motivation and compliance to perform the electrical stimulation training were bad, one patient reported on constipation due to electrical stimulation, one had osteomyelitis in the spine and another had to cancel the stimulation due to a broken femur and implantation of a femoral nail.

Twenty patients finished the study. For the final examinations the patients had to come to Vienna again and underwent the same assessment procedure as at the beginning to rule out any signs of reinnervation. This provides evidence that the improvements in the patients quadriceps muscles are due to the electrical stimulation training and not because of

changes in peripheral nerve system. Only one patient showed discrete signs of reinnervation (needle EMG discrete MUAP discharge in one limb).

5.1.1 Inclusion criteria

- complete or incomplete conus and cauda equina paraplegia (T12-L1) with denervation of muscles
- innervation lacking for up to 9 years
- complete or nearly complete absence of sensation, particularly in the thigh
- neurologically demonstrated flaccid paralysis with no spasticity
- intact skin (no decubital ulcers)
- EMG: fibrillations, spontaneous activity, absence of voluntary activity
- m. quadriceps femoris not excitable with current pulses of 100mA and duration 5 ms
- no hazardous infections or diseases

5.1.2 Neurophysiologic assessment

To assess the neurophysiologic status of the patient at the time of inclusion into the study a comprehensive protocol was setup. This has been carried out for two reasons: (i) to ensure that the patient meets the inclusion criteria for the study and (ii) to describe the patients neurophysiologic condition accurately. The same procedure was repeated at the end of the study after two years of electrical stimulation training. By comparing the results from the beginning and end of the study any changes in the neurophysiologic status of the patients were detected. This made it possible to rule out that changes in the properties of the denervated muscle were due to reinnervation or other regeneration processes.

The protocol consisted of two parts a clinical protocol performed by a experienced physician manually testing and scoring the patient and a laboratory protocol where the patients were examined with different electrophysiological methods providing a very detailed insight on the patients condition.

The clinical protocol consisted of the neurological examination of motor and sensory function below and above the level of the lesion. The motor function protocol comprised a description of muscle group size, the range of passive and active movement of all limb joints, stretch reflexes, and scores from manual testing of muscles including evaluation of preserved and impaired functional movements. Sensory functions were evaluated qualitatively for all four modalities: touch, vibration, pinprick and temperature. After recording the threshold for perception of all four modalities within all corresponding lumbar and sacral dermatomes also the presence and distribution of altered sensation such as allodynia and dysesthesia and sensation was examined. Temporal and spatial summation of short lasting afferent inputs after repetitive stimulation within the same or different locations were evaluated as well.

Laboratory methods were used to evaluate motor unit activity elicited by stretch reflex, H-reflex, cutaneous muscle reflexes, and reinforcement manoeuvres. Sixteen channel poly-electromyography recording, with surface electrodes attached to muscle groups of lower limbs and trunk was used to record muscle activity during several different active and passive manoeuvres. Standard needle EMG and measurements of conduction time were performed, together with transcranial and lumbosacral magnetic stimulation. The sympathetic skin response, the change in skin potential following arousal stimulation, was recorded.

5.2 Stimulation training protocols, execution of training and time expenditure

The patients were carefully instructed how to perform their electrical stimulation training properly. Handling of the stimulator and donning and doffing the electrodes were practiced at the Wilhelminenspital during their four day visit for assessment at the time of inclusion into the study. An operating manual for the patients describing the handling of the stimulation device and the associated equipment, as well as a programming manual for the physician was written in order to provide additional information (see appendix C). Based on the experience from our pilot work (Kern et al. 1999 and 2002) an electrical stimulation protocol especially adapted to the needs of denervated muscles was setup.

In general all patients used the following electrical stimulation parameters:

1. frequency 2Hz, impulse duration 120ms, impulse pause 500ms, On 5s/ Off2s;
2. frequency 20Hz impulse duration 40ms, impulse pause 10ms, On 2s/ Off2s.
3. Once a day 30 minutes for each muscle group.

The electrical stimulation training was carried out at home by the patients with the pre-programmed stimulation device (Hofer et al. 2002). Although the quadriceps muscle was the target muscle in the study most of the patients stimulated also their gluteus and calf muscles to maintain these muscles too. Regular check up visits at their responsible rehabilitation centre provided support in case of problems related to the stimulation training or other medical problems.

In the first year of stimulation the patients used rubber electrodes, placed in a wet sponge pouch. This type of electrodes allows a safe application of the stimulation therapy but due to the relative high impedance of this electrode attachment the training intensity is reduced. No side effects- in particular burnings were seen during this stage of training.

After one year of stimulation the rubber electrodes were applied with gel directly on the skin to increase stimulation intensity (Figure 5.1). In this case some of the patients had rare skin burnings at the edges of the electrodes.

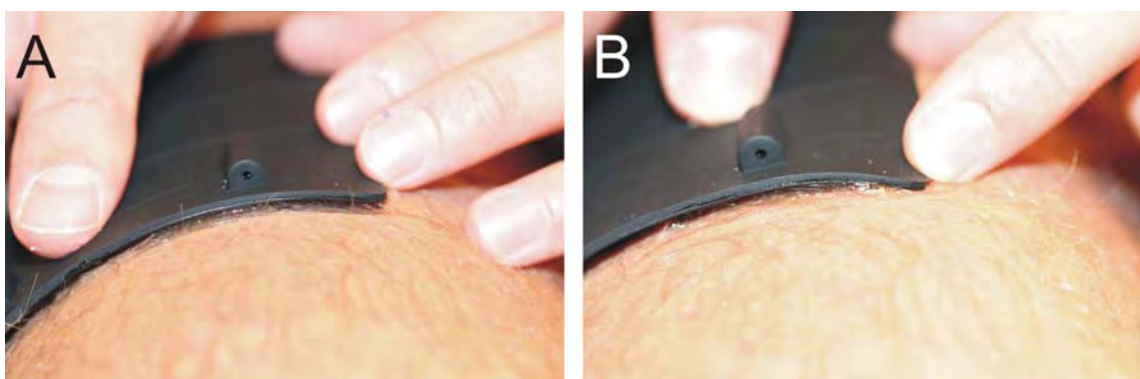


Figure 5.1: Commercially available standard rubber electrodes attached to the skin surface with conductive gel. (A) Illustration of an electrode attached with constant pressure over the whole area. (B) Demonstration of inhomogeneous contact pressure with higher pressure at the electrodes edges. The conductive gel is spilled out from the gap between the electrode and the skin surface. Burnings due to the direct contact between the electrode and the skin could be caused.

Therefore a new safety electrode was developed (Mayr 2007) with a special geometry preventing increased contact pressure at the edges and direct contact of the rubber electrode to the skin. In addition the prominent isolated border on the skin faced electrode side prevents the conductive gel from being spilled out ensuring a homogeneous distribution of the stimulation current across the whole electrode area (Figure 5.2).

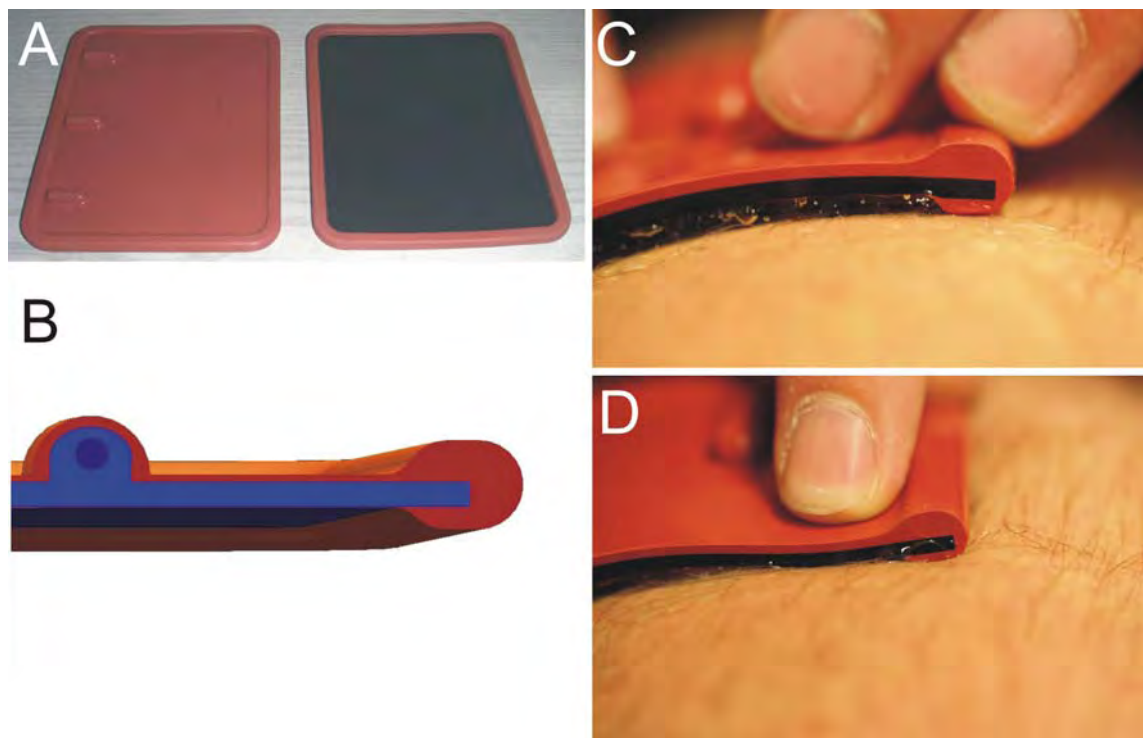


Figure 5.2: Safety electrode. (A) Picture showing the isolated backside of the electrode and the active side applied to the skin with a small isolated border. (B) Cross-section of the electrode: blue conductive rubber material, red isolating silicon rubber. (C, D) Pictures demonstrating the application of the electrode to the skin surface. (C) Normal evenly distributed contact pressure. (D) Inhomogeneous contact pressure with higher pressure at the electrode edges.

5.3 Results

5.3.1 Required pulse duration for activation of denervated muscles

The average twitch force of all twenty subjects measured after one and two years increased with stimulation training for all measured pulse widths.

Maximal activation of the quadriceps muscle was achieved with 72.7 ms long stimulation pulses. This was the same for both measurements. By analysing the single twitch torque normalised with the maximum twitch torque it is easy to recognise that the characteristics did not change. That means that there was no shift to shorter pulse widths between the first and second year of electrical stimulation training (Figure 5.3). For stimulation training a pulse width in the range of about 40 ms was chosen because at this duration the muscle already produces approximately 90% of its maximal twitch force and the stimulation pulses are short enough to allow stimulation with a frequency of 20 Hz. This is crucial for generating tetanic muscle contractions.

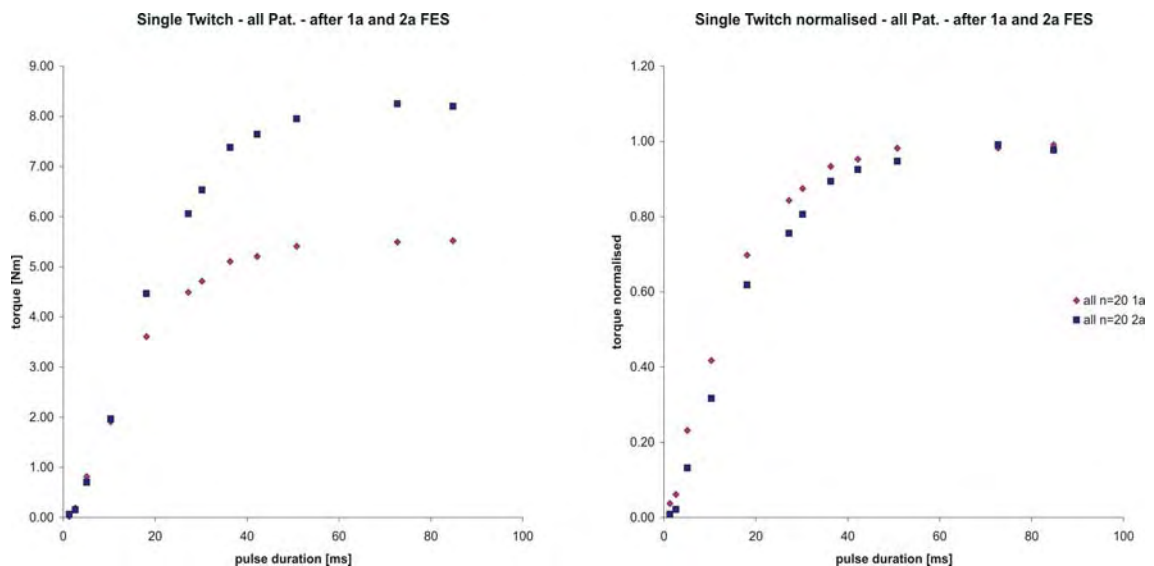


Figure 5.3: Twitch torque elicited by single pulse stimulation with varying pulse width. Left diagram is showing mean developed single twitch torque of all subjects ($n=20$) after one and two years of stimulation therapy. The diagram on the right side shows the twitch torque referenced to the maximum twitch torque. Measurements were performed with maximum amplitude of ± 250 mA and symmetric rectangular biphasic impulses.

When viewing the data divided into the three subject groups according to their maximum tetanic muscle force at the end of the study (see chapter 5.3.2) it is interesting that all groups show the same behaviour regarding the pulse width needed for maximal twitch force. Of course the level of developed force is different. Also the increase of single twitch torque between the first and second year of electrical stimulation therapy is varying with the largest increase in the "strong" group and no change in the "weak" group (Figure 5.4).

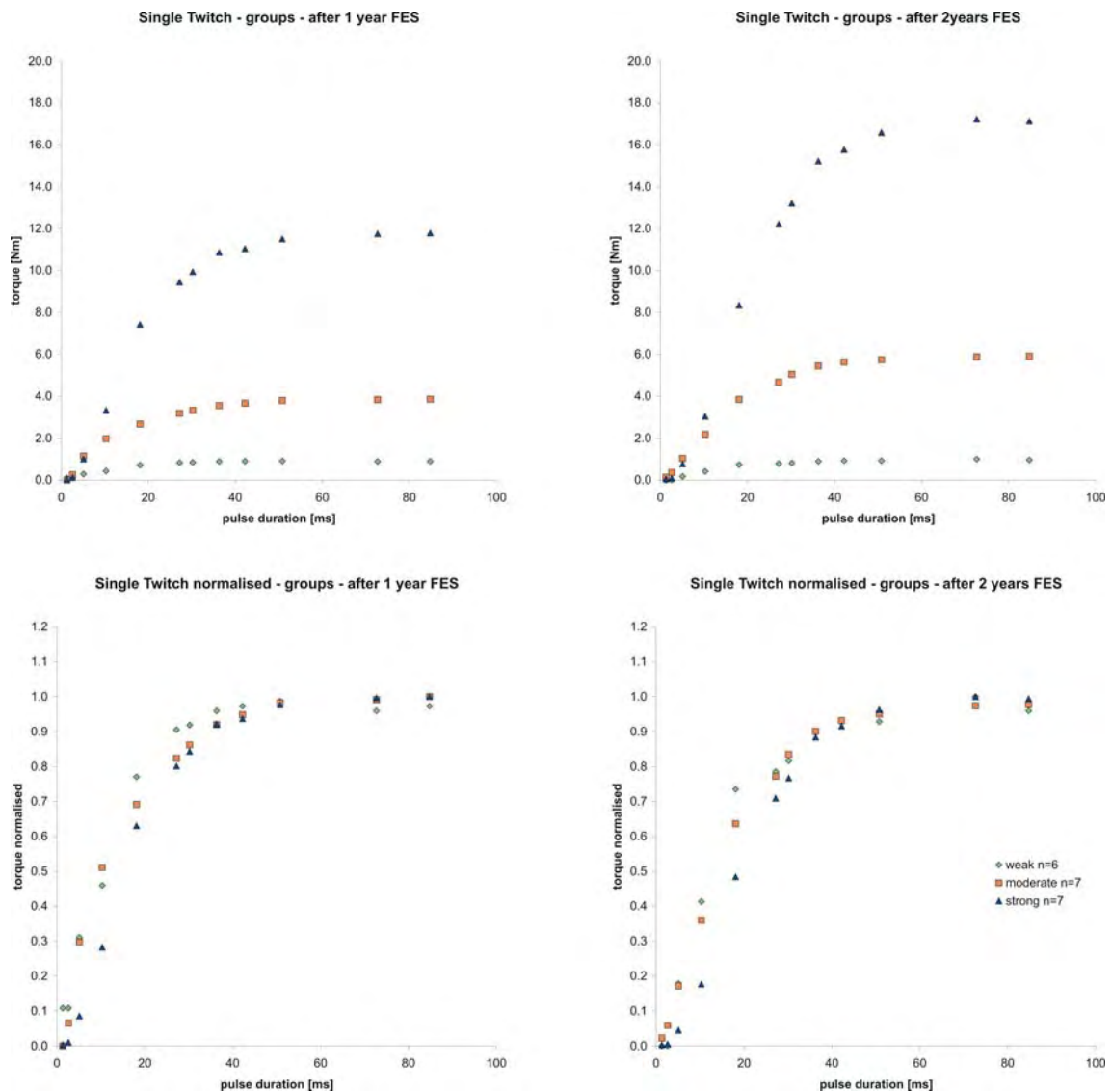


Figure 5.4: Single twitch torque measurement after one (left side) and two years (right side) of electrical stimulation training. The subjects were divided into three groups according to their maximum knee extension torque after two years of electrical stimulation training (see chapter 5.3.2). Diagrams in the top row showing the absolute value of the mean twitch torque for the three groups (weak, moderate and strong). Below the data is depicted normalised with the maximum elicited twitch torque for each group. Measurements were performed with maximum amplitude of ± 250 mA and symmetric rectangular biphasic impulses.

Four subjects had additional twitch torque measurements after six month of electrical stimulation therapy. It is apparent by looking at the normalised twitch torque, that at this earlier stage of training wider pulse widths are necessary to achieve maximal contraction force from the denervated

muscle. The stimulation pulse width for generating 90% of the maximal torque was doubled compared to the measurements after one and two years of training respectively (Figure 5.5).

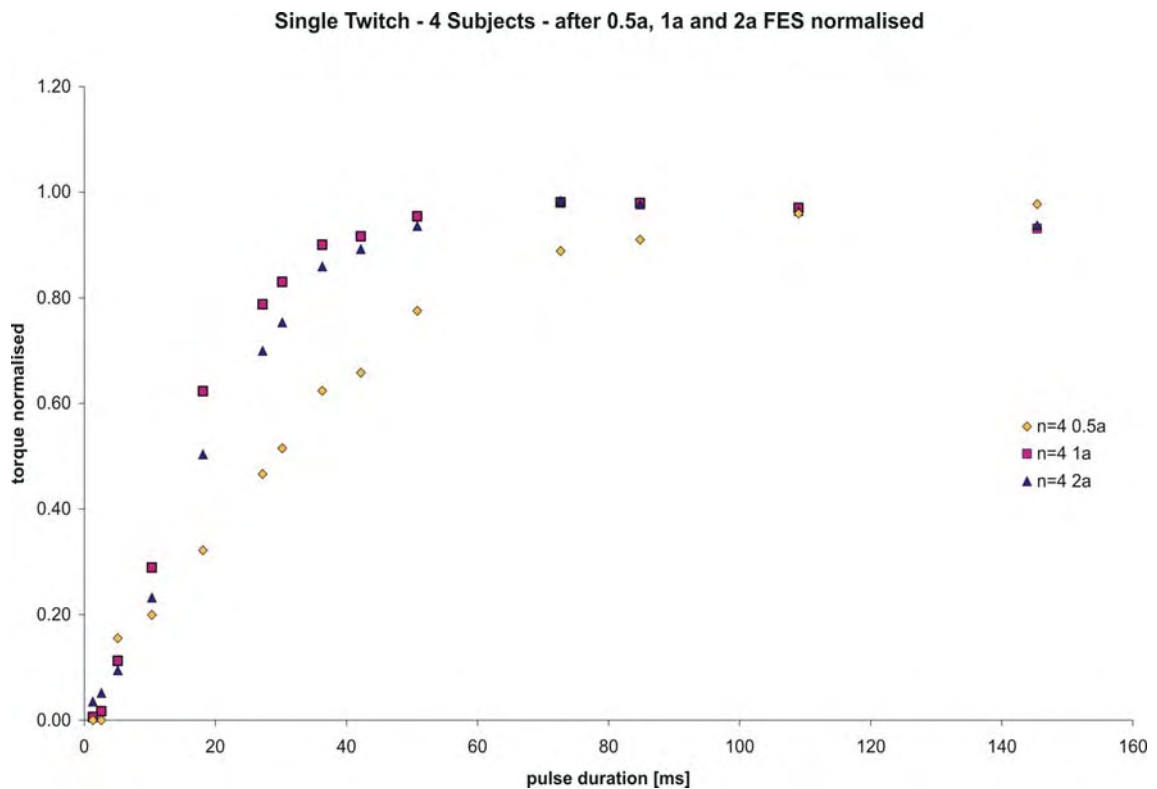


Figure 5.5: Single twitch torque measured at different pulse widths normalised by maximal elicited twitch torque, measured with a stimulation pulse amplitude of ± 250 mA and symmetric rectangular biphasic impulses.

5.3.2 Increase of knee extension torque

Isometric measurement of the knee extension torque was carried out three times within the clinical study: at the inclusion into the study prior to any electrical stimulation, after one year of therapy and at the end of the study. During the first assessment the subjects showed zero or very low knee extension torque (below 1 Nm) only in three subjects a somewhat higher torque between 1 and 5 Nm was measured. This means that their quadriceps muscle could not be activated by electrical stimulation at the initial stage of training or if the muscle was activated it failed to generate mechanical output. Only some slight contraction was observed in some of the subjects when looking at the surface of the thigh. After the first year of electrical stimulation training the knee extension torque increased in three

subjects to values above 15 Nm, in seven subjects the torque was between 5 – 15 Nm and in the remaining ten almost no improvement was seen (below 5 Nm). At the end of the study in seven subjects a knee extension torque above 15 Nm (max. 30.6 Nm) was elicited by electrical activation of the quadriceps muscle. Seven subjects had an extension torque of 5 – 10 Nm and six were still under 5 Nm. The mean isometric torque for all patients is displayed in Figure 5.6. The differences in torque are highly significant ($p < 0.001$) between the measurements at the beginning and after the first year of therapy and significant ($p < 0.01$) for mean torque after the first and the second year of electrical stimulation training.

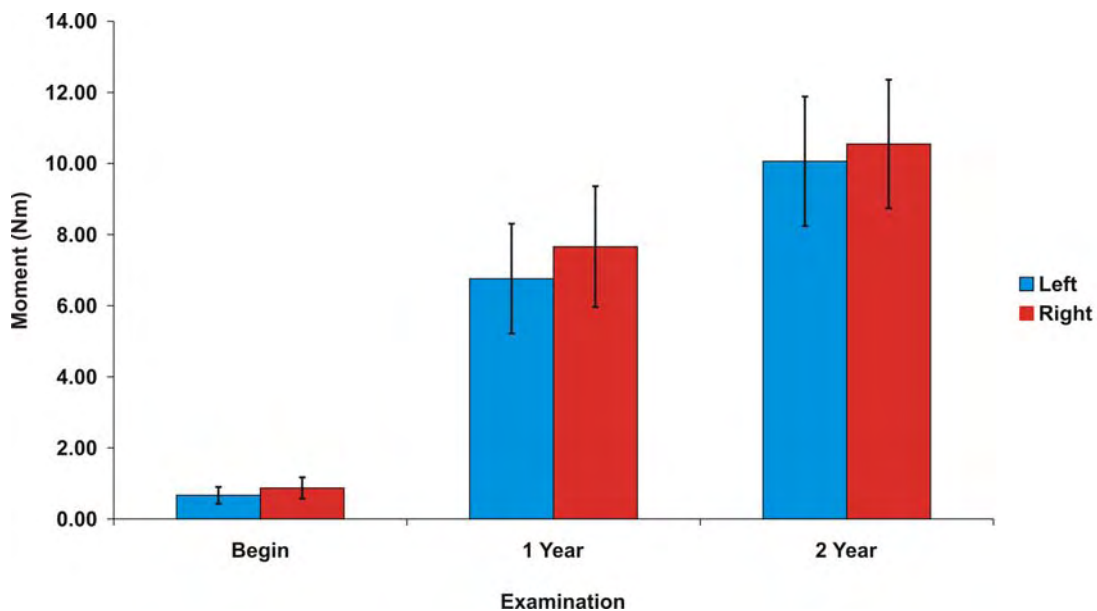


Figure 5.6: Isometric knee extension torque measured while activating the quadriceps muscle by electrical stimulation. Knee angle during measurement was 90°. Error bars indicating the standard error of the mean (SEM).

Depending on time elapsed between the injury and the start of the electrical stimulation therapy the patients showed varying degrees of improvement. Patients with a denervation time under 3 years benefited from the electrical stimulation therapy much more than longer denervated ones. But even those with long standing denervation showed slight improvements in knee extension torque (Figure 5.7).

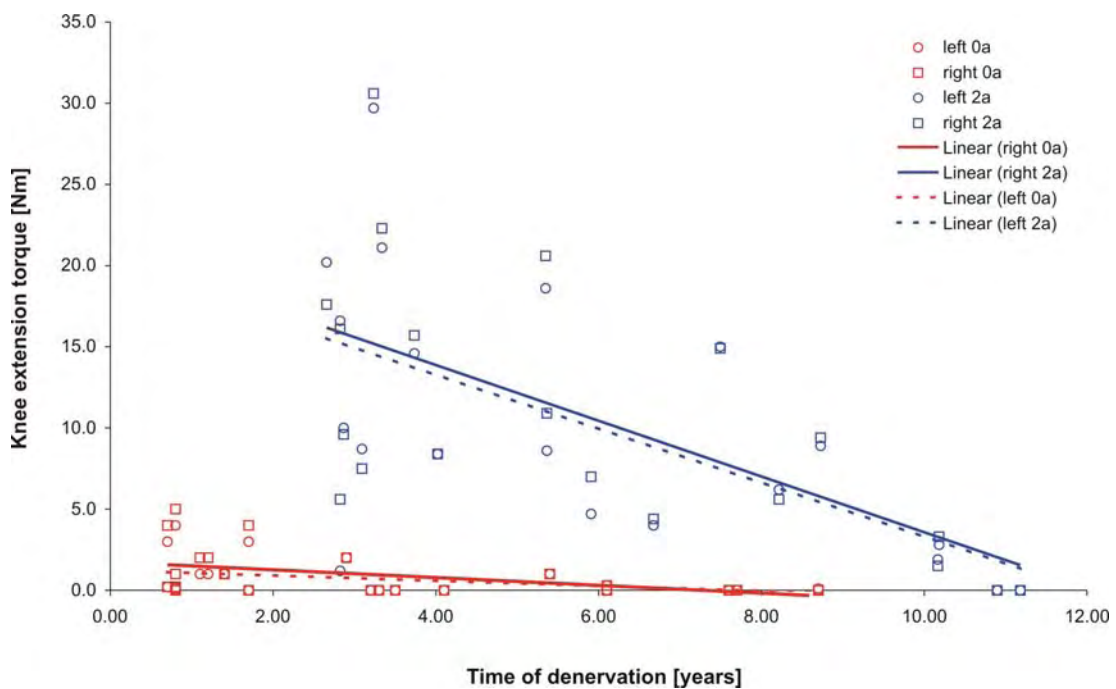


Figure 5.7: Diagram showing the maximal knee extension torque elicited by electrical activation of the quadriceps muscle. Red circles and squares at the inclusion into the study without any prior training, blue after two years of electrical stimulation therapy. Despite of the longer time since onset of the paralysis almost all subjects showed an increase in knee extension torque. It is obvious that in subjects denervated for a longer period the increase in knee extension torque was smaller than short time denervated subjects.

According to the outcome of the force measurement at the end of the study the subjects were divided into three groups. The first group of subjects with a big improvement of knee extension torque were called the “strong” responders. Patients in this group showed a knee extension torque above 15 Nm at the end of the study. The ones with a torque between 5 and 15 Nm were called “moderate” responders. All remaining subjects with a torque below 5 Nm were called the “weak” responders. In this group of patients the electrical stimulation training did not improve the force generation capacity of the quadriceps muscle. The three groups “weak”, “moderate” and “strong” were used also for the following analyses of data from CT-scans, electrophysiological measurements.

5.3.3 Change in size of muscle (muscle cross-sectional area)

Muscle cross-sectional area was determined by CT scan three times throughout the study. For most of the analyses the data of the CT scan 20

cm below the trochanter major was chosen since this scan is near the maximal muscle bulk in all studied subjects. Comparison of the mean cross-sectional quadriceps muscle area of all 20 subjects at the beginning and the end of the study showed a significant ($p < 0.001$) increase from 26.1 cm² up to 37.7 cm² (Figure 5.8).

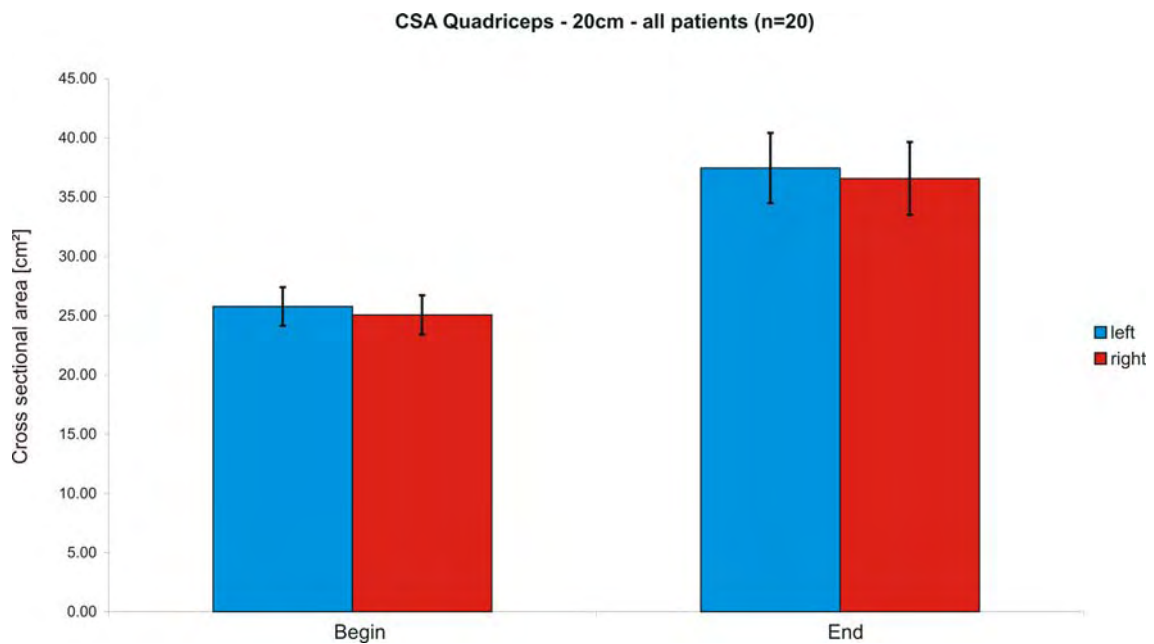


Figure 5.8: Cross-sectional area of the quadriceps muscle of all patients measured 20 cm distal to the greater trochanter of femoral bone. Measurements were taken after inclusion into the study but before commencing electrical stimulation training and after two years of training showing a mean increase in muscle cross-sectional area of 45.6%. Error bars are indicating \pm SEM.

When splitting the patients into the three groups according to the outcome of the torque measurements (weak, moderate and strong group), the results of the regarding the muscle cross-sectional area show similar characteristics. The group with no or almost no improvement in developed muscle force also exhibits only a slight, not significant ($p > 0.05$) increase of muscle cross-sectional area from 22.3 cm² up to 26.1 cm². Whereas in the other two groups the size of the muscle bulk increases significantly, with the largest change in the "strong" group from 30.6 cm² up to 51.3 cm² (Figure 5.9).

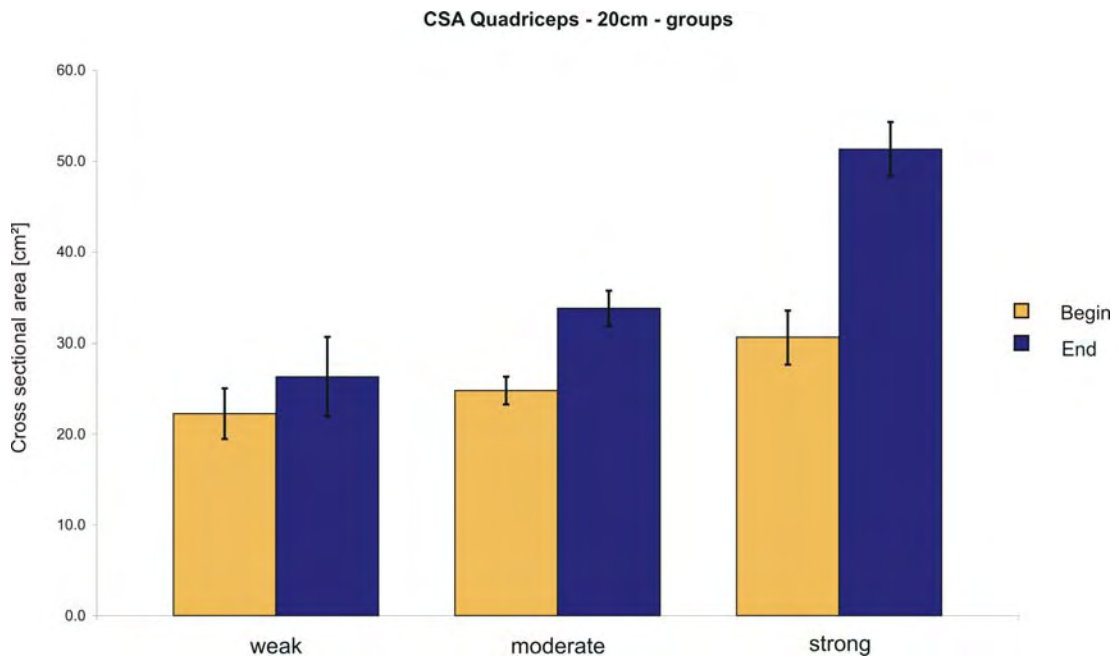


Figure 5.9: Increase of quadriceps muscle cross-sectional area after two years of electrical stimulation training. Grouping of the patients (“weak”, “moderate” and “strong”) according to the knee extension moment measured at the end of the study. Changes are significant for the groups “moderate” ($p < 0.01$) and “strong” ($p < 0.001$). Values are means \pm SEM.

Although the electrical stimulation therapy was focused on the quadriceps muscle with the electrodes attached to the front side of the thigh the hamstrings muscles were activated by the applied electrical stimuli also. This effect is proved not only by the palpable contraction in these muscles but also in the increase of muscle cross-sectional area measured by CT scans. Comparing the hamstrings muscles area before commencing the stimulation training and at the end of the study a significant ($p < 0.001$) increase from 24.1 cm² to 29.1 cm² was detected (Figure 5.10).

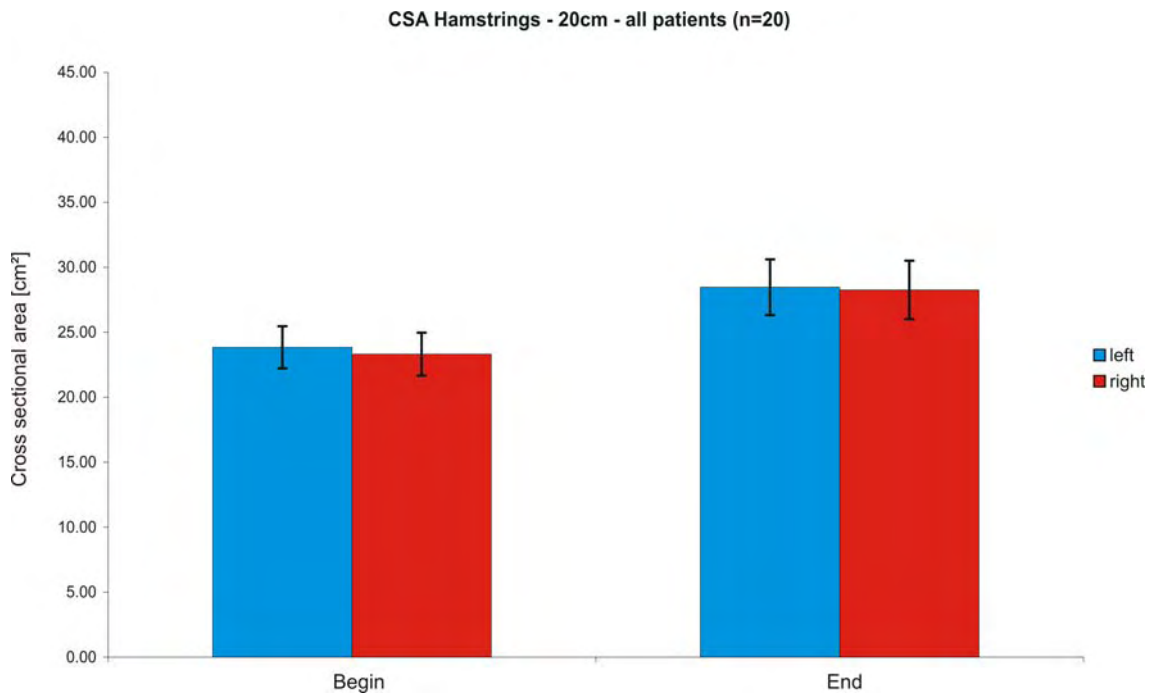


Figure 5.10: Cross-sectional area of the hamstrings muscles of all patients measured 20 cm distal to the greater trochanter of femoral bone. Measurements were taken after inclusion into the study but before commencing electrical stimulation training and after two years of training showing an increase in mean muscle cross-sectional area of 20.3%. Error bars are indicating \pm SEM.

The muscle cross-sectional area of the quadriceps in the CT scans at the level 10 cm below the greater trochanter changed significantly from 18.0 cm² to 21.8 cm² whereas the hamstrings muscles area remained unchanged 31.2 cm² before and 31.0 after stimulation training

At the level 30 cm below the greater trochanter significant increases in cross-sectional area were found for both quadriceps and hamstrings muscles. The area of the quadriceps was 23.2 cm² before and 32.3 cm² after training and the hamstrings muscle area increased from 17.7 cm² to 22.4 cm².

All data regarding the muscle cross-sectional area at the different CT scan levels before and after the stimulation training is summarized in table 5.2.

Patient group		all (n=20)	weak (n=6)	medium (n=7)	strong (n=7)
Quad Area [cm ²]					
Scan level	FES				
10cm	before	18.03 ± 1.36	15.11 ± 2.24	16.39 ± 1.76	22.17 ± 2.34
	after	21.81 ± 1.91 †	15.26 ± 2.11	18.44 ± 0.88	30.80 ± 2.77 ‡
20cm	before	26.07 ± 1.57	22.26 ± 2.79	24.80 ± 1.53	30.61 ± 2.95
	after	37.69 ± 2.94 ‡	26.13 ± 4.34	33.79 ± 1.94 †	51.34 ± 3.01 ‡
30cm	before	23.23 ± 1.70	19.99 ± 3.13	21.75 ± 2.80	27.49 ± 2.53
	after	32.34 ± 2.48 ‡	25.52 ± 2.75 *	29.22 ± 2.45 *	41.32 ± 4.76 †
Ham Area [cm ²]					
Scan level	FES				
10cm	before	31.18 ± 2.25	23.66 ± 2.28	29.94 ± 2.73	38.86 ± 4.06
	after	30.97 ± 1.94	25.28 ± 1.71	27.58 ± 2.41	39.22 ± 2.89
20cm	before	24.14 ± 1.60	19.77 ± 1.47	22.80 ± 1.65	29.24 ± 3.42
	after	29.10 ± 2.15 ‡	22.37 ± 2.11	25.62 ± 2.14	38.36 ± 3.38 ‡
30cm	before	17.70 ± 1.37	14.52 ± 1.79	17.38 ± 1.46	20.74 ± 3.08
	after	22.41 ± 2.01 †	16.45 ± 2.20	18.93 ± 2.00	30.99 ± 3.09 *

Table 5.2: Muscle cross sectional area at different CT scan levels before and after training for all patients and divided into the groups according to maximum developed knee extension torque after 2 years of FES. Significant differences between pre and post training area are denoted *, † and ‡ for $p < 0.05$, $p < 0.01$ and $p < 0.001$, respectively.

5.3.4 Change in tissue composition

Additional information about the condition of the denervated muscle apart from the muscle cross-sectional area was obtained by analysing the attenuation of the X-ray radiation in the CT scans. The quadriceps and hamstrings muscles in the thigh cross-section were marked manually. Afterwards the CT number or Hounsfield Unit (HU) of each pixel within the selected region of interest (ROI) was determined and the mean density within the ROI as well as a histogram showing the density distribution was calculated. In order to prepare a histogram with the mean density distribution of all patients, the data for each patient was normalized with the area of the corresponding ROI.

Analysing the quadriceps muscle of all patients the mean density was significantly ($p < 0.01$) increased by the stimulation training. Splitting into the different groups according to their force output reveals a slight not significant ($p > 0.05$) decrease of density in the patients with no measurable force output after 2 years of FES in contrast to a significant ($p < 0.05$) and highly significant increase ($p < 0.001$) for the moderate and strong group, respectively (Figure 5.11).

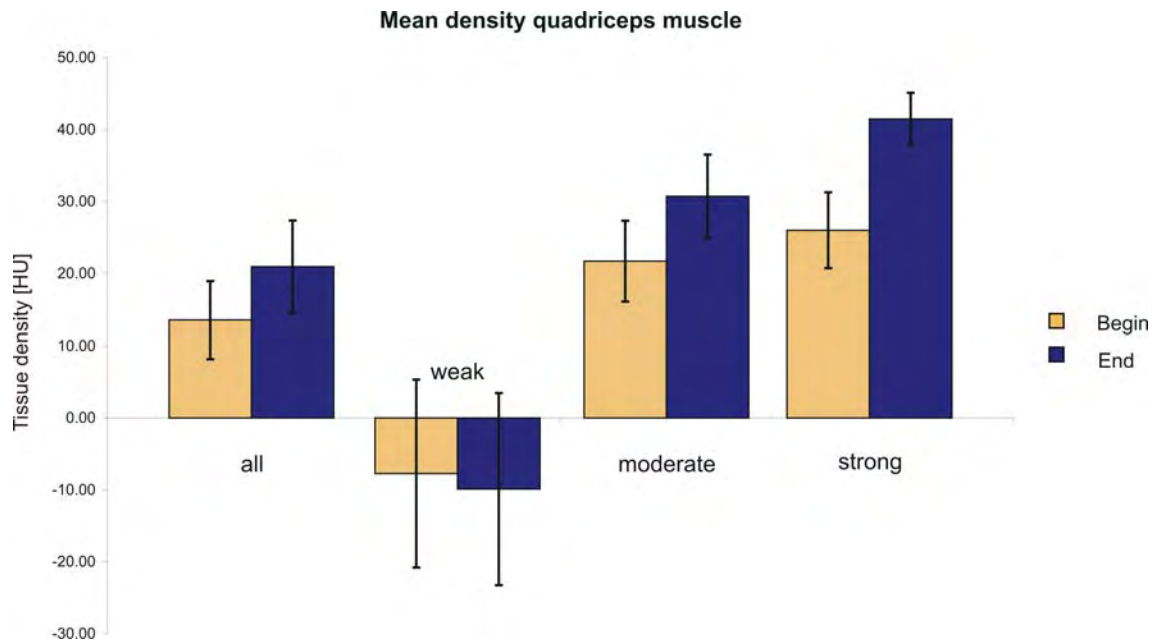


Figure 5.11: Mean density of the quadriceps muscle before and after 2 years of FES training of all patients ($n = 20$) and grouped according to the outcome of the force measurements (weak $n = 6$, moderate $n = 7$, strong $n = 7$). Bars are indicating \pm SEM.

Figure 5.12 (A & B) shows the histogram of the quadriceps muscle density 20 cm below the greater trochanter before (Figure 5.12 A) and after two years (Figure 5.12 B) of electrical stimulation training. Comparing the two histograms it is evident that the distribution is shifted to the right side denoting an increase of more dense tissue above 40 HU and decrease of tissue with lower densities below 40 HU (Figure 5.12 C). This indicates a reduction of tissues (e.g. fat, collagen) with lower CT density in the examined muscles.

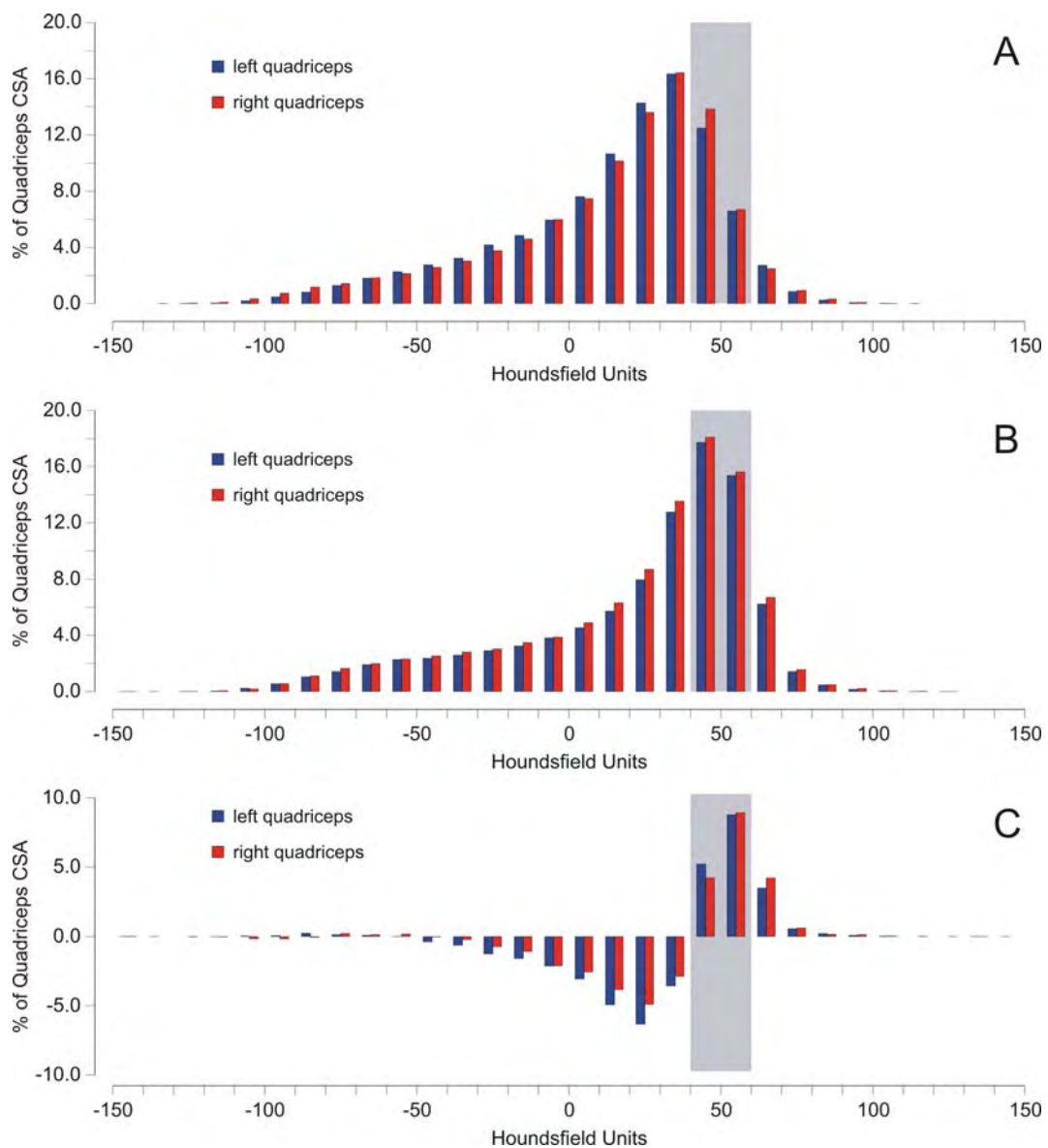


Figure 5.12: Histogram showing the CT density distribution of the quadriceps muscle 20 cm below the greater trochanter (mean of all patients $n = 20$). (A) Before starting the electrical stimulation training. (B) After two years of electrical stimulation training. (C) Histogram showing the difference in the density distribution before and after training. Grey shaded areas marking the HU range of healthy muscle.

The muscle density distribution in the three patient groups weak, moderate and strong showed differences in the shape. At the beginning of the study the group (weak) of subjects developing almost no knee extension torque exhibited a flat distribution without a distinct peak. Whereas in the other two groups (medium, strong) a distribution with a peak in the range of 30 – 40 HU was found (Figure 5.13).

After two years of FES training the density distribution in the weak group was similar to the beginning. In the strong and moderate group the distribution was shifted to the right side equivalent with an increase of tissue with high and decrease of tissue with low density. This indicates a rise in content of muscle fibres within the analysed muscle area and a reduction of fat and collagen. Since the strong and moderate group exhibited very similar behaviour only the distribution of the strong group is displayed in Figure 5.13.

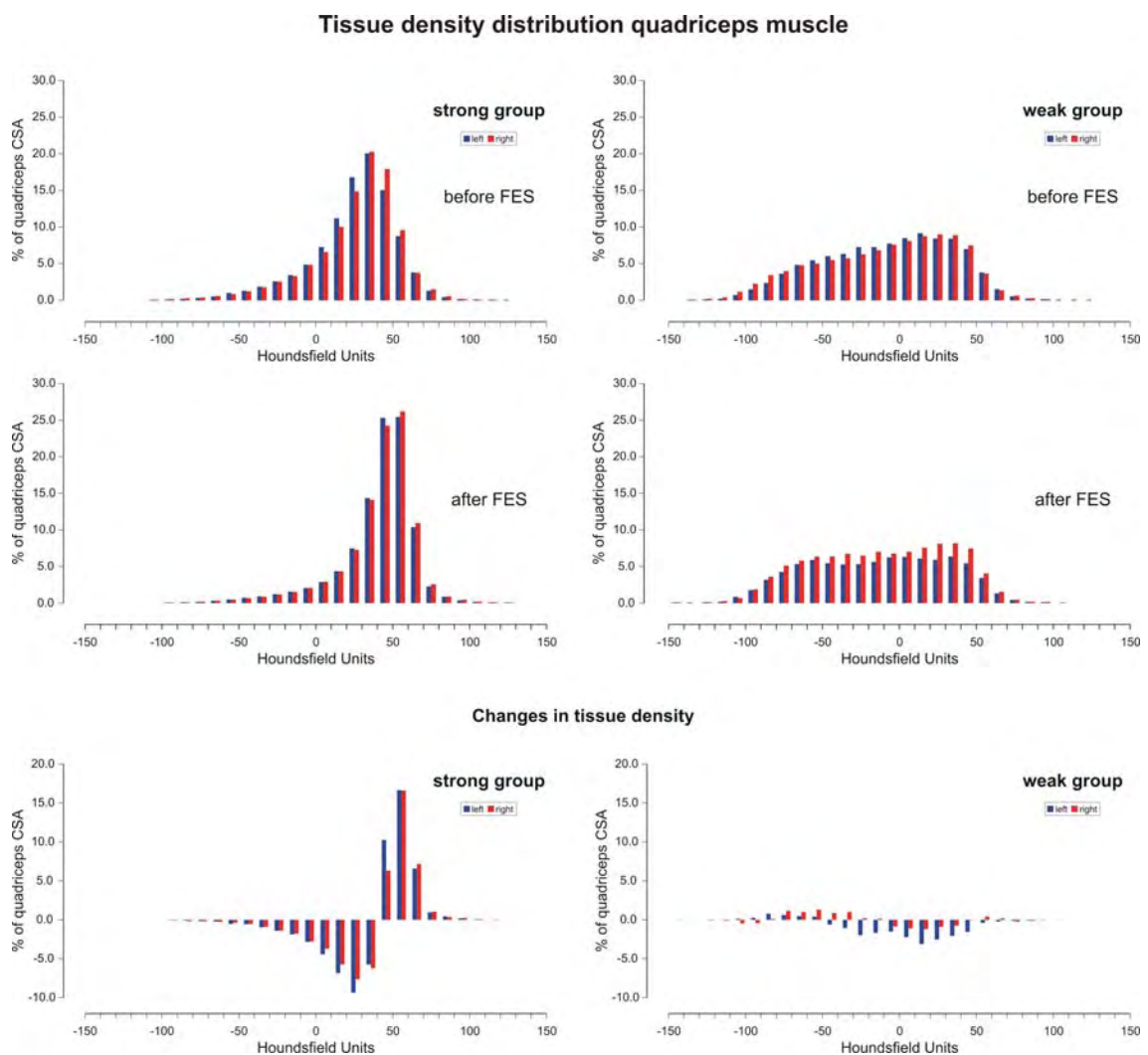


Figure 5.13: Histograms showing the CT density distribution of the quadriceps muscle 20 cm below the greater trochanter in patients with big improvement (left column: strong group $n = 7$) in muscle function and with in patients with no response (right column: weak group $n = 6$). Top and central histograms are showing the distribution before starting and after two years of electrical stimulation training, respectively. The bottom histograms are showing the difference in the density distribution before and after training.

5.3.5 Electrophysiological changes (MFCV, ISI)

In three patients MFCV and ISI was measured at the time of inclusion into the RISE study without prior FES training and again after two years of FES training according to the therapy protocol. Two of them with a relatively short period of denervation of approximately one year had mean MFCV of about 2 m/s. The patient which was denervated for 3.2 years had a considerably slower mean MFCV of 1.0 m/s. The shortest ISI with response was 4 ms for the one year denervated and 8 ms for the 3.2 years denervated patient. After two years of FES therapy the differences in the electrophysiological parameters MFCV and ISI between the three patients disappeared (Table 5.3).

Subject			S1	S2	S3
Denervation Time	yrs		0.8	1.2	3.2
before FES	MFCV				
	mean	m/s	2.14	1.97	1.00
	max.	m/s	2.34	3.65	1.18
	min.	m/s	1.53	1.12	0.77
	ISI	ms	4.0	4.2	8.0
after FES	MFCV				
	mean	m/s	2.44	2.26	2.22
	max.	m/s	3.19	3.20	3.05
	min.	m/s	1.77	1.02	1.59
	ISI	ms	3.3	3.2	3.0

Table 5.3: MFCV and shortest ISI of the three subjects assessed at inclusion into the RISE study and after two years of FES training. Denervation time is defined as the period between onset of denervation and start of FES training.

Analysing the MFCV of the thirteen patients which were examined after one year and again after two years of electrical stimulation training, they showed a significant ($p < 0.05$) increase in conduction velocity for mean and maximum MFCV and a slight but not significant increase for the minimum MFCV (Figure 5.14).

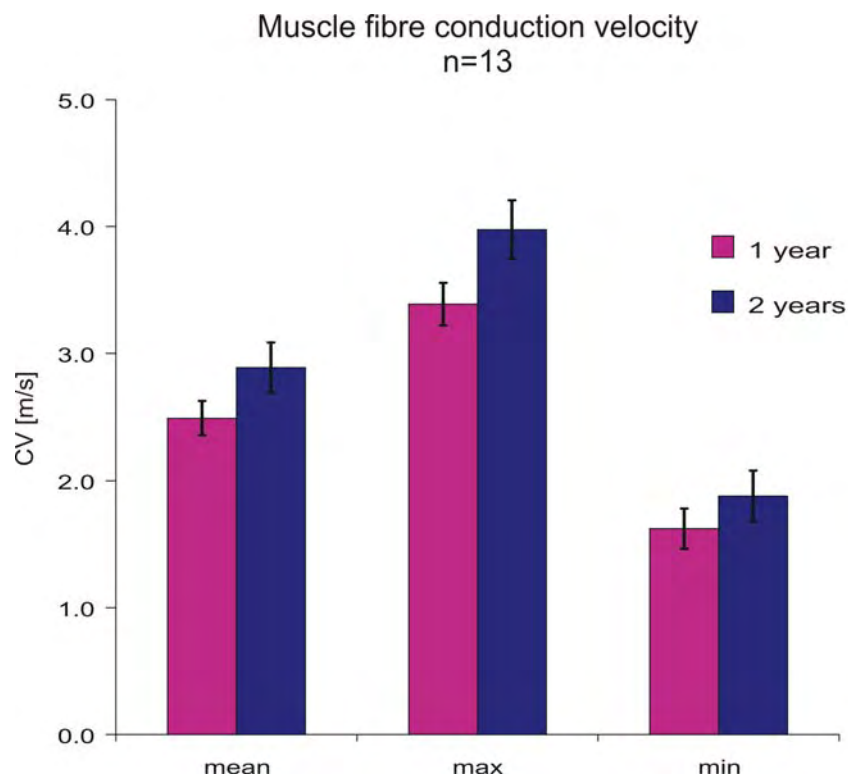


Figure 5.14: MFCV measured in the quadriceps muscle of thirteen patients after one and again after two years of electrical stimulation training. The differences are significant for mean and maximum MFCV ($p < 0.05$). Error bars are indicating \pm SEM.

Pooling all measured muscle fibres after one and two years of electrical therapy and calculating the distribution of the CV confirms this finding (Figure 5.15). Even after two years of training there are still some very slow conducting muscle fibres ($CV < 1.0$ m/s) detected which explain that the minimum MFCV is not altered severely. Otherwise there is an apparent increase of fast conducting fibres responsible for the significant increase in the mean (from 2.5 to 2.9 m/s) and maximum MFCV (from 3.4 to 4.0 m/s).

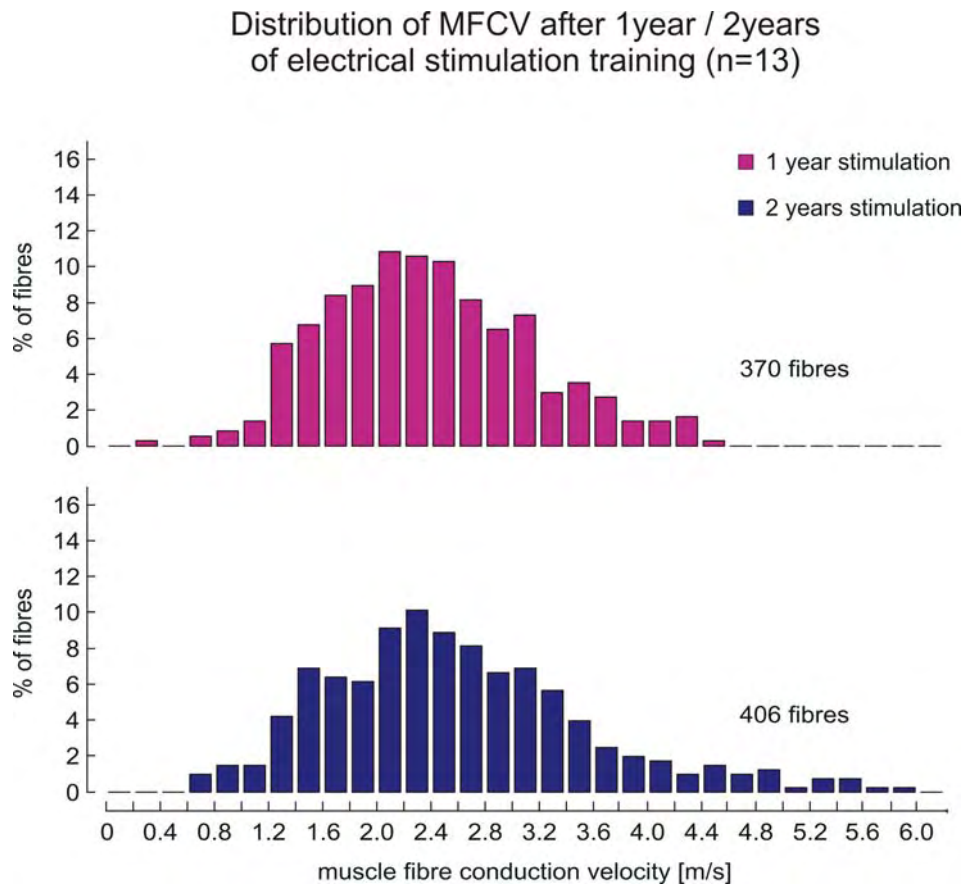


Figure 5.15: Distribution of MFCV of all measured muscle fibres in the patients which were measured after one and two years of stimulation training. Data is normalised with the number of measured fibres.

When examining the data acquired at the end of study divided into the three groups according to the maximal tetanic force developed, the most obvious difference between the three groups is, that the distribution of MFCV lost the Gaussian shape in the “weak” and “moderate” group (Figure 5.16). Compared to healthy muscle the distribution of the “strong” group is of similar shape but shifted to the left which means that these muscles consist of slower conducting fibres.

The mean conduction velocity is 2.2 m/s for the weak group and 2.5 m/s for the other two groups with a smaller standard deviation of ± 0.8 m/s compared to ± 1.3 m/s for the “strong” group. It is evident that by analysing only the mean MFCV the differences between the three groups are not characterized well.

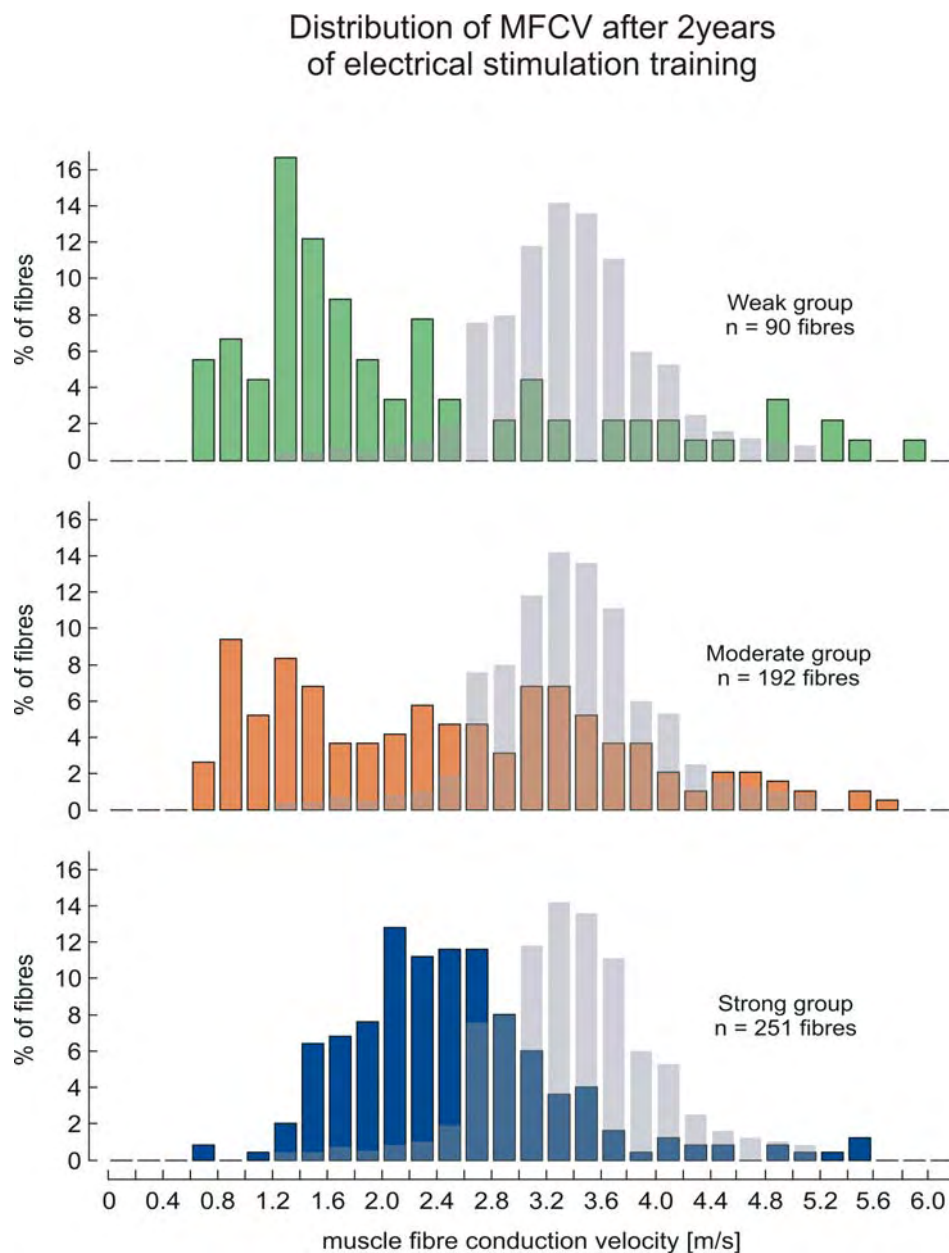


Figure 5.16: Distribution of the MFCV of all measured muscle fibres at the end of the study. Shaded grey distribution in the background shows the data of healthy subjects measured by Cruz-Martinez 1989. The shape of the distribution of the strong group is almost Gaussian again whereas the other two groups are showing a widespread distribution of MFCV without any distinct shape.

Regarding the muscle fibre refractory period the quadriceps muscle of the patients exhibits a slight decrease of shortest ISI (Figure 5.17). This reduction in shortest ISI from 4.7 ms after the first year of electrical

stimulation training down to 3.9 ms after the second year was not significant.

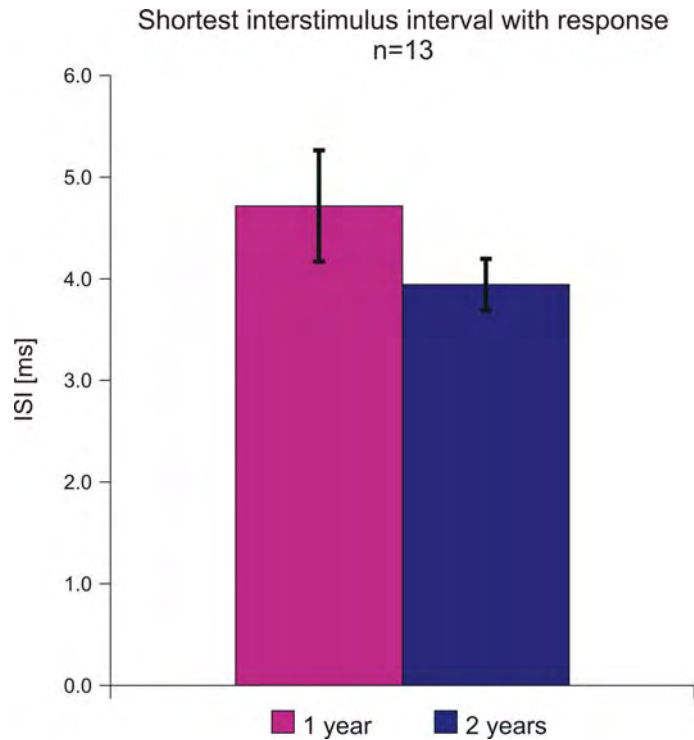


Figure 5.17: Changes in the muscle fibre refractory period between the first and second year of electrical stimulation training. Error bars are indicating \pm SEM.

5.3.6 Functional outcome

At the end of the study 9 patients were able to perform full knee extension while sitting on a bed or chair with the quadriceps muscle activated by electrical stimulation. This test was conducted without additional weight on the ankle, lifting the lower leg against gravity to horizontal position. None of the patients was able to perform full knee extension at the time of inclusion without any prior stimulation training.

Five patients were able to perform standing-up and sitting down exercises with their electrically activated thigh muscles supported by their arms using specially developed training aids. Moreover three of them were already able to step on place simulating the swing phase of gait by alternately switching on and off stimulation of the right and left leg respectively. During this the

patients stood in a standing frame using their arms for keeping balance and partially supporting their body weight. After some exercises in the standing frame two subjects were also able to walk with special mobile parallel bars. The distance covered was ranging from 6 to 37 meters. Stimulation of the quadriceps muscle is controlled by a switch mounted on the supporting device operated by the patient with the fingers of the left or right hand. For bringing the leg forward during the swing phase the stimulation of the quadriceps muscle on the corresponding side is turned off and the leg is moved forward by elevating and rotating the pelvis with the intact trunk muscles. Since the patients are paralysed completely there is no sensory feedback from the lower limbs for this reason the foot is positioned under visual control and the balance is kept by the subject's arms (Figure 5.17 A - D).



Figure 5.17: (A) First stand-up trial with electrical stimulation training of m. quadriceps. (B) Standing in parallel-bar with supported electrical stimulation of m. quadriceps. (C) Stand-up training performed in a standing-frame, switching of loading between right and left leg. (D) Patient walking with electrically activated quadriceps muscles supported by special mobile parallel bars.

6 Discussion

Stimulation equipment. With the currently applied training protocol it is necessary for the patient to perform stimulation therapy 5 times a week (e.g. 2 days stimulation, 1 day pause, 3 stimulation, 1 day pause). Therefore a device suited for home-based therapy was built.

The concept of a microprocessor controlled stimulation device with preset programmes individually adapted to the patient's condition proved to work well. None of the patients had troubles with operating the device and all were satisfied with the reliability. The only point for critics was the battery life time since after about one year of use, the capacity dropped and it was not possible to perform the whole daily training programme with a fully charged device. This rather fast drop in capacity was ascribed to the high impulse currents drawn by the stimulator. Hence, the battery pack had to be replaced by a more stable pack made of high performance cells after the first year of the study during the follow up examination at the Wilhelminenspital.

Overall the developed stimulators are adequate for therapy of denervated, degenerated muscles. The range of stimulation impulse width is wide enough to ensure sufficient stimulation for all stages of denervation induced atrophy and degeneration. Nevertheless the applied therapy protocol is very time consuming and calls for considerable commitment from the patient. Even with the two channel device the daily time expenditure for FES therapy of three different muscle groups per limb (gluteus, quadriceps and calf muscles) exceeds two hours (3 times 30 minutes and time for donning and doffing).

In three patients with long-standing denervation, thus a high amount of intramuscular fat and connective tissue as well as a thick subcutaneous fat layer (Figure 6.1), it appears that the stimulation intensity was not sufficient to increase their muscles cross-sectional area and improve the ability to produce force, although they were compliant and regularly carried out the training program.

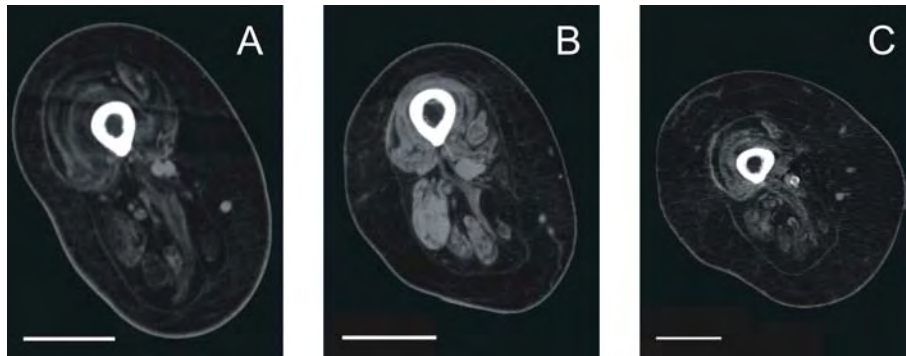


Figure 6.1: CT scans of three patients not responding the FES therapy. Displayed is the cross-section of the right thigh 20 cm below the greater trochanter at the time of inclusion into the clinical study. Patients were denervated for (A) 7.7, (B) 8.7 and (C) 8.7 years respectively. Bars 5 cm.

A further increase of stimulation intensity above the present limit of ± 250 mA is problematic, since it is very difficult to safely apply such high currents. Even small changes in the contact resistance between electrode and skin could lead to high local current densities causing skin burns.

Main requirements for the next generation of stimulation equipment for patients with denervated lower limb muscles are therefore, stimulators with more than two (four or six) independent output channels and e.g. segmented safety electrodes with built in circuitries for controlling the current density. Benefits of such a multi-channel system would be a reduction in time expenditure for training since all relevant muscle groups could be treated simultaneously and better coordinated more natural movement during functional applications such as standing up and walking. Electrode garments with integrated electrodes and cables would simplify donning and doffing, resulting in further reduction of training time and simultaneous improvement of safety by preventing inappropriate connections and electrode placement, as well as providing more evenly distributed contact pressure.

The suggested safety electrodes in combination with circuits for control of the applied current density should provide safe application of the even higher maximum current intensities than our present limit, which could provide new prospective for patients not benefiting from the currently applied protocol.

Stimulation protocol, excitability. Defining an optimal therapy protocol and stimulation parameters is limited by several constraints.

The current daily training time per muscle or muscle group of 30 minutes has to be seen as upper limit. This seems to be not very long, but for treating two or more muscle groups per limb the total therapy time per day is 2 hours or more, as already mentioned above. Longer stimulation times would therefore interfere too much with the patients' life, since many of them have a profession.

The stimulation intensity is limited by the skin's capacity to conduct the stimulation currents without getting damaged. With the currently applied equipment a maximum impulse current of ± 250 mA is the limit for safe application of FES training. In fact this limit is sometimes critical, if the electrodes are not properly applied or peel off during the stimulation training. The new safety electrode developed by Mayr (2007) with a special geometry preventing high current densities at the edges partially solves the problem of applying high stimulation currents safely (Figure 5.2)

Excitation of the denervated muscles needs long duration impulses, this limits the maximal stimulation frequency. However, since the denervated muscles exhibit slower contraction characteristics, as described in animal studies on rats (Carraro et al. 1982, Al-Amood and Lewis 1989) and rabbits (Ashley et al. 2007), even with the reduced stimulation frequency a fused tetanus is achieved after a conditioning training phase.

Experiences made in preliminary studies showed, that even in well trained patients, treated with FES for many years, biphasic rectangular pulses with a minimum pulse width of 40 ms are necessary to activate the denervated muscle (Kern 1995). The results of the single twitch measurements carried out during the RISE clinical study demonstrate that after two years of FES therapy a pulse width of 40 ms is necessary to elicit twitches developing 90% of the maximum twitch torque in the examined muscle. The maximum twitch torque of the quadriceps muscle was determined by applying impulses with maximum intensity of ± 250 mA and increasing pulse width from 1.3 ms up to 145 ms. When looking at the data normalised to the maximum twitch torque no difference regarding the necessary pulse width for activation of the muscle can be found between the three patient groups "strong", "moderate" and "weak", although there is a huge difference in the level of developed twitch force (Figure 5.4). With the applied training protocols and stimulation equipment a further reduction in the required pulse width for 90% twitch torque is not expected, as the muscles already

showed the same behaviour after the first year of training (Figures 5.3). This leads to the assumption that an increase in excitability of the denervated muscle takes place during the first year of FES therapy. Measurements made in four patients after the first 6 months of training confirm this assumption, because at this earlier stage training pulses with a duration of about 80 ms were necessary to elicit 90% of the muscle maximum twitch torque (Figure 5.5). Despite of the reduction of the required pulse duration for activation in any case the denervated muscles remained still much less excitable than innervated muscles.

With the above described limitation regarding the required pulse width, the inter-pulse interval was reduced to 10 ms in order to attain a minimum stimulation frequency of 20 Hz. This is necessary for eliciting fused tetanic contractions to induce a strong muscle fibre tension, constituting a hypertrophy stimulus in the denervated muscle fibres.

Taking into account all constraints the resulting stimulation parameters for ES training were: pulse current up to ± 250 mA; biphasic rectangular pulses with 40 ms pulse duration and 10 ms inter-pulse interval; stimulation burst duration of 2 s and 2 s pause between the bursts; total training time per muscle or muscle group 30 minutes.

Assessing the denervated muscle:

Systematic stimulation of the denervated muscle artificially generating contractile activity enhanced the capacity to generate force, increased the cross-sectional area as well as the density in CT-scans and improved the electrophysiological properties (excitability, MFCV, MFRP) of the muscle.

Force generation. At the beginning all of the studied patients were not able to produce a maximum isometric knee extension torque above 5 Nm at 90° knee angle. Stimulation brought about a significant increase of torque to 10.3 Nm (average over all studied patients) with a measured maximum torque of 30.6 Nm in one male and 19.6 Nm in one female patient. This is still only approximately 10 % of the maximum voluntary knee extension torques developed by healthy, young individuals (Maughan et al. 1983, Narici et al. 1996). One reason for low the value can be found in the torque measurement procedure for assessing the quadriceps muscle. The applied stimulation parameters induce an electrical field which is not only confined to the knee extensor muscles but also activates part of the hamstrings muscles simultaneously. Therefore, the resulting knee extension torque measured with the knee dynamometer is reduced by antagonistic co-

contraction (Figure 6.2). To quantify the influence of co-activating the hamstrings muscles a new measurement technique based on a pendulum test was designed (Gallasch et al. 2005). The future results gained by this method will help to evaluate the impact of the hamstrings muscles on the torque measurement.

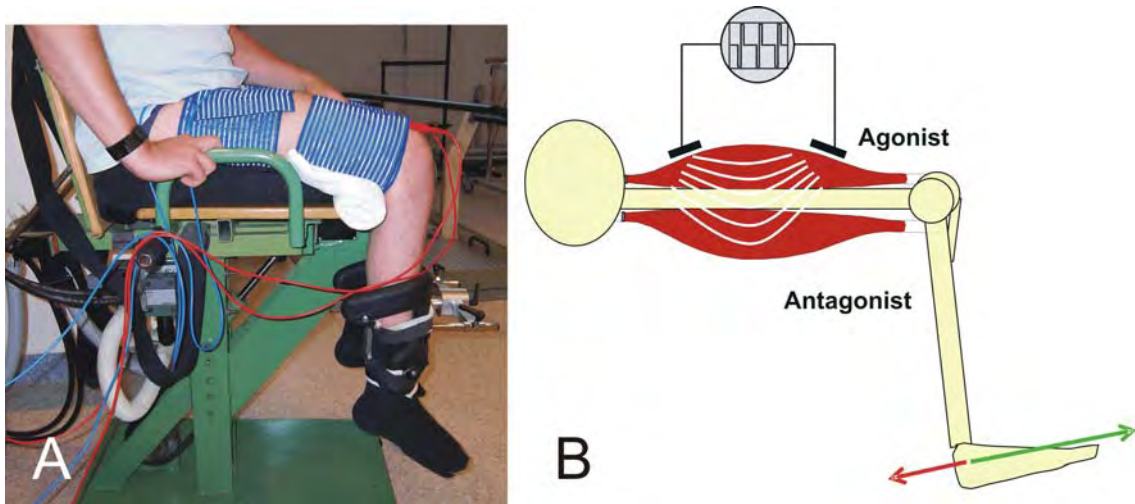


Figure 6.2: Measurement of knee extension torque. (A) Picture showing the subject placed on the knee dynamometer. Electrodes attached to the front of the thigh. (B) Drawing illustrating electrical field distribution in the thigh. Since the electrical field is spread also to the hamstring muscles (antagonists) the measured torque is reduced. The green arrow indicates the extension torque generated by the quadriceps muscle and the red arrow the torque produced by the hamstrings. With the dynamometer only the resulting knee torque is detected.

However, the co-activation of the antagonists can not be hold responsible alone for the very low measured torque. Results of an animal study conducted in the scope of the RISE project demonstrated that the maximum tetanic force of denervated-stimulated muscle was only half that of innervated control muscles. The reduced capacity to generate force was ascribed to incomplete restoration of muscle cross-sectional area and the proportion of that area occupied by muscle fibres, since the specific tension in maximal tetanic contractions measured in those muscles was not different from their innervated control (Ashley et al. 2008).

Cross-sectional area. Analysing the data acquired from CT scans showed a significant improvement in the cross-sectional area of the denervated-stimulated quadriceps muscle with the largest increase (+ 68 %) in the "strong" group (Figures 5.8 & 5.9). The area measured at the end of the study corresponds to 45 % and 64 % of healthy subjects for mean of all

studied patients and mean of patients belonging to the “strong” group, respectively (healthy reference: Bulcke et al. 1979, Termote et al. 1980, Maughan et al.1983). It seems that the FES therapy was more effective in restoring the muscle size than the capacity to generate force, which is in line with the outcome of the rabbit study (Ashley et al. 2007).

Nevertheless a correlation between the cross-sectional area of the quadriceps muscle and the developed knee extension torque is observed (Figure 6.3).

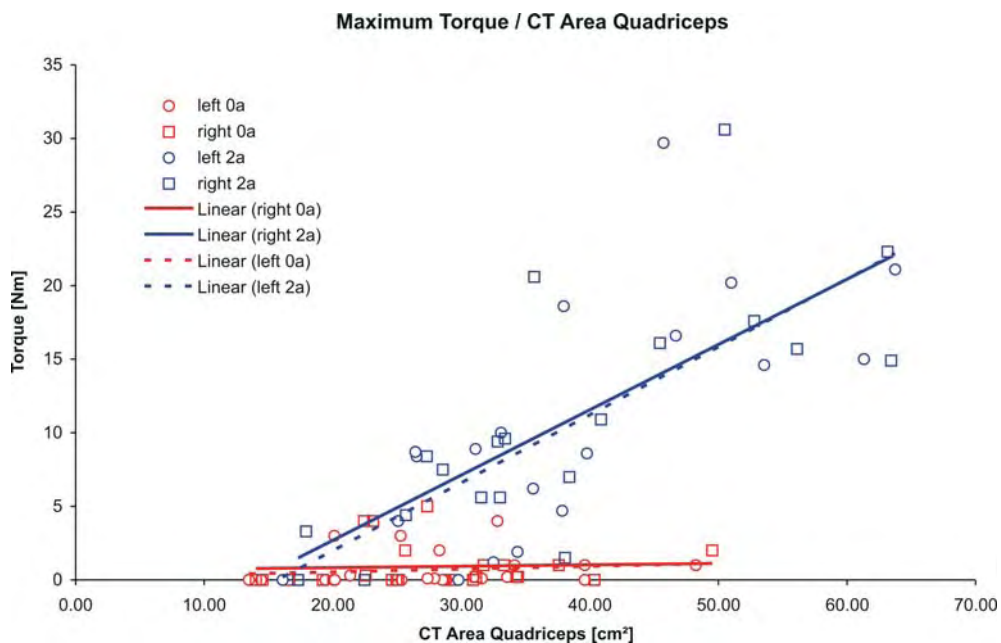


Figure 6.3: Diagram showing the relation between developed knee extension torque against the muscle cross-sectional area for left and right limb at the beginning and after 2 years of FES therapy (n = 20). Linear regression for the 2 year measurement: left $r = 0.71$, $p < 0.001$; right $r = 0.75$, $p < 0.001$.

CT density, density distribution. However, the mean density of 21.1 HU in the quadriceps muscles of all patients after two years of FES training was considerably lower compared to healthy innervated muscle with a density of 50 - 60 HU, leading to the assumption that within the analysed area the content of muscle fibres is reduced. This result derived from the analysis of the CT scan data is confirmed by the biopsies harvested from the quadriceps muscle at the beginning and the end of the study. The tissue composition of the samples, indicates an increase of non-contractile intra muscular tissue such as loose connective tissue, fat and collagen compared to normal (Figure 6.3). Electrical stimulation slightly improves the muscle

fibre content but it is still far below normal muscle with approximately 90% muscle fibre content.

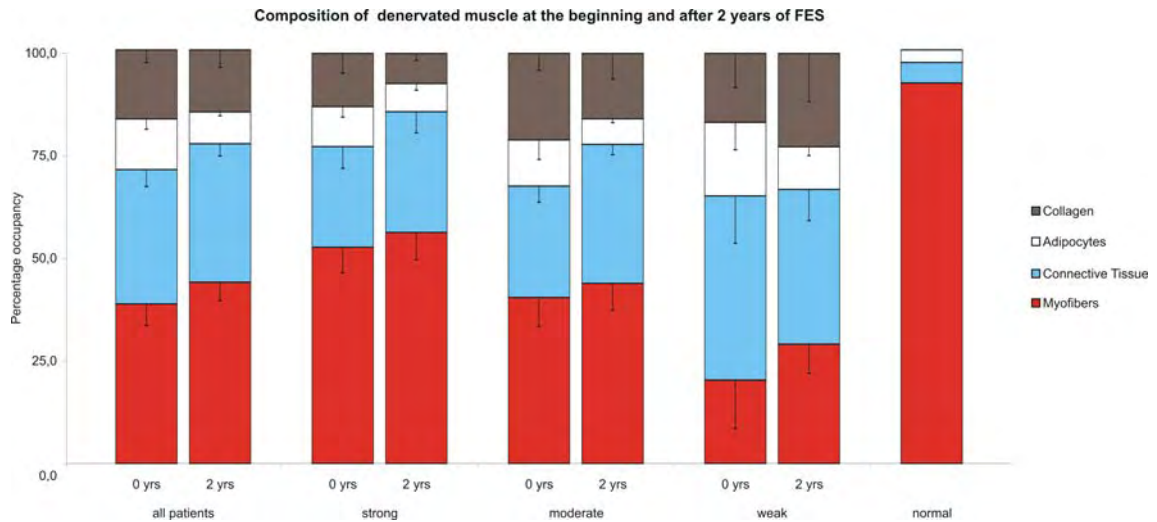


Figure 6.3: Column chart displaying the tissue composition in the muscle biopsies of the RISE patients before and after FES therapy. The rightmost column shows the tissue composition in a muscle biopsy from a normal healthy subject.

The reduced muscle fibre content together with the co-activation of the hamstrings muscles may explain the inconsistency between the restoration of the muscle cross-sectional area and the maximal knee extension torque measured.

Considering the results of the CT density measurement, made at the beginning of the study prior to any FES, it is evident that the muscle density is much lower and the density distribution appears different in the weak group compared to the other two groups (Figure 5.11 and 5.13). The patients of the moderate and strong groups are not distinguishable by the density measurement before FES therapy. Two years of treatment did not cause any significant changes regarding the density in the patients of the weak group, whereas in the moderate and strong groups a significant increase of muscle density was measured.

The finding suggests that determining the distribution of CT density within the muscle before treatment could be a useful tool to predict if a patient would benefit from FES therapy with the currently available technology and application protocol.

MFCV, MFRP. Initial aim was to setup a non-invasive method for assessing the electrophysiological parameters MFCV and MFRP but due to the limitations described in chapter 4.1 a minimal invasive method by inserting two needles into the investigated muscle, the SNEMG was the final outcome. The recorded parameters allow monitoring of changes in the electrophysiological properties of individual muscle fibres within the denervated muscle. In contrast to other studies (Cruz-Martinez 1989, Hoeven van der et al. 1993) placement of the recording needle was often not guided by a visible or palpable muscle twitches because in many cases the few activated fibres were lying under a thick layer of subcutaneous fat and the contractions elicited by needle stimulation were too weak to provide reliable contraction feedback. Movement of the stimulation needle was often useful to indicate the fibre orientation and helped to position the needle. The quadriceps muscle is a pennate muscle meaning that the exact orientation of the fibres is difficult to guess making the positioning of the needles even more difficult. This seems to be one the reasons why many studies investigating the MFCV were carried out in non-pennate muscles e.g. the biceps muscle where the fibres are oriented along the long axis of the muscle (Troni et al. 1983, Chino et al. 1984, Hoeven van der et al. 1993). Nevertheless with the developed technique the examination time for both thighs was reduced to about 45 minutes a time span which was well tolerated by the patients.

MFCV in the recorded in thirteen patients after the first and second year of FES therapy showed a significant increase for the fastest and mean CV of all measured fibres. No significant change was found in the minimum MFCV. By analysing the recorded data not for each patient individually, but pooling all fibres measured after one and two years of FES, the results are confirmed, because even after two years of training very slow conducting fibres (< 1.2 m/s) were detected (Figure 5.15).

Apart from electrophysiological parameters like the resting membrane potential (Gruener et al. 1979), the main factor influencing the CV is the fibre diameter (Håkansson 1956), suggesting that the results of the MFCV measurement and the muscle fibre diameter analysed by the biopsies should be related. Comparing the distribution of the fibre diameter for the patients grouped according to their functional outcome and the distribution of the MFCV after two years of training, strengthens this assumption (Figure 5.16 and 6.4).

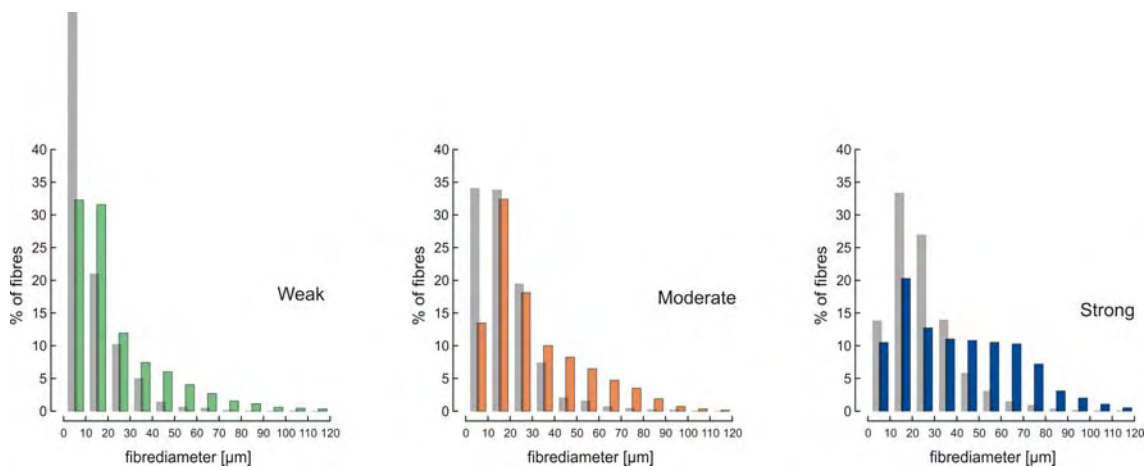


Figure 6.4: Histograms displaying the distribution of fibre diameter in the quadriceps muscle after 2 years of electrical stimulation training. Grouping according to the knee extension torque developed at the end of the study. Left shifted grey columns in the background are the initial values at inclusion into the study (Biopsies harvested in the course of the RISE study, prepared by U. Carraro).

The distribution of the fibre diameter in the weak and strong group indicates that most of the fibres are still very small in diameter and the shape of the distribution is not Gaussian like. In the moderate group slightly more medium sized fibres are found and both groups show some very big fibres which is also reflected in the MFCV distribution, where some very fast conducting fibres in these groups were detected. A reduced amount of small fibres with an increased number of medium sized fibres in the strong group indicates a distribution that is more similar to normal innervated muscle, but still the shape is not Gaussian. Contrary to the findings derived from the biopsy the MFCV in this group shows only very few slow conducting fibres and an almost Gaussian distribution. An explanation could be found in the fact that the fibres with a larger diameter exhibit a lower threshold for activation by ES. In the case of a muscle with a mixed sized fibre population this means that fibres with a larger diameter are activated more likely and therefore the results of the MFCV measurement will be biased to fibres with a larger diameter and consequently higher conduction velocity. Nevertheless even in this group of patients with the largest improvements and rather good muscle function MFCV was not fully restored (Figure 5.16).

MFRP measured by the shortest ISI with response showed no significant changes between first and second year of FES training, this corresponds to

the single twitch measurements where also no changes were detected after the first year of training (see above or chapter 5.3.1). In three patients, denervated for 0.8, 1.2 and 3.2 years, measurements at the time of inclusion into the study and after two years of FES showed a reduction in the shortest ISI in all patients with the most pronounced change in longest denervated one (Table 5.2). The results suggest that most of the improvements regarding the muscle fibre membrane properties take place during the first year of FES therapy, which is in good correlation to the single twitch measurements giving information on the excitability of the muscle fibres (see above).

Conclusions. The developed stimulation device and associated equipment is appropriate for treating denervated, degenerated muscles. All stimulation parameters required by the currently used training protocols can be realised with the equipment. A further increase of the output intensity is problematic, because it is very difficult to apply the stimulation current safely without damaging the skin. Next generation of stimulation equipment should provide more than two stimulation channels to reduce overall daily therapy time by simultaneous training of different muscle groups e.g. quadriceps, gluteus and calf muscles. This would also allow a functional training with a better more physiologic stand up and gait pattern.

The data acquired by the new assessment methods MFCV, MFRP and morphometric distribution of tissue density within the muscle cross-section show good correlation to functional tests like force or torque measurement and biopsy investigations. This indicates that the methods could serve as powerful new clinical tools to quantify the actual status of a denervated muscle and in some respects replace more invasive examination procedures like muscle biopsies. That would be of great advantage for supervising FES training for restoration of long-term denervated degenerated muscles, as the methods are simple enough to be applied in routine check-ups. Measurement of the tissue density distribution within the muscle even allows predicting to a certain extent if the patient would benefit from FES therapy or not.

The work shows that artificially induced contraction activity is not capable of fully restoring the denervated muscle. There are, however, marked improvements regarding the muscle cross-sectional area and density, the

electrophysiological properties MFCV and MFRP, as well as a recovery in the ability of the muscle to generate force. Secondary benefits induced by the above described changes are better blood perfusion of muscle and skin, better muscle cushioning with improved pressure distribution along the skin surface and therefore a decreased propensity to develop pressure sores. From psychological point of view the improved cosmetic appearance of the lower limbs results in enhanced self-esteem of the patients. These results justify the design of the specialised equipment for training and assessment and the commitment by the patients.

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Appendix


```

294 * FUNCTION: Linescroll
295 * DESCRIPTION: Scroll text field n lines
296 *
297 * PARAMETERS: Number of lines to scroll, ID of text field, ID of scroll bar,
298 *             Boolean for redrawing scroll bar
299 *
300 * RETURNER: nothing
301 *
302 * REVISION HISTORY V 1.0 15/05/2000
303 *
304 static void Linescroll(int16 numLines, Uint16 fieldID, Uint16 scrollbarID, Boolean redraw)
305 {
306     FieldPtr field;
307     FormPtr fmp = FrmActiveForm();
308     static void Linescroll(int16 numLines, Uint16 fieldID, Uint16 scrollbarID, Boolean redraw)
309     {
310         FieldPtr field;
311         fmp = FrmActiveForm();
312         field = FrmGetObjectPtr(fmp, FrmGetObjectIndex(fmp, fieldID));
313         if (numLines > 0)
314             LinescrollField(fieldID, numLines, winObj);
315         else
316             LinescrollField(fieldID, numLines, winObj);
317         if ((FrmGetNumberOfBlankLines(fieldID) && numLines < 0) || redraw)
318             UpdateScrollbar(fieldID, scrollbarID);
319     }
320 }
321
322 * FUNCTION: PageScroll
323 * DESCRIPTION: Scroll text field one page up or down
324 *
325 * PARAMETERS: Direction to scroll, ID of text field, ID of scroll bar
326 *
327 * RETURNER: nothing
328 *
329 * REVISION HISTORY V 1.0 15/05/2000
330 *
331 static void PageScroll(Uint16 direction, Uint16 fieldID, Uint16 scrollbarID)
332 {
333     FormPtr fmp = FrmActiveForm();
334     FieldPtr field;
335     field = FrmGetObjectPtr(fmp, FrmGetObjectIndex(fmp, fieldID));
336     if (direction == DIR_UP)
337         LinescrollField(fieldID, -1);
338     else if (direction == DIR_DOWN)
339         LinescrollField(fieldID, 1);
340 }
341
342 * FUNCTION: SetHighlightType
343 * DESCRIPTION: Set the contents of the highlight list
344 *             according to used the stimulation device
345 *
346 * RETURNER: nothing
347 *
348 * REVISION HISTORY V 1.2 16/09/2003 16:15
349 *
350 static void SetHighlightType(void)
351 {
352     FormPtr fmp = FrmActiveForm();
353     Uint16 textPtr;
354     Char imp[10];
355     selectItem = LetterSelection(GetObjectPtr(MainImpList));
356     selectItemMF = LetterSelection(GetObjectPtr(MainImpList));
357     // When the MainForm is initialised selectItem can be invalid
358     if (selectItem < 0 || selectItem > 30)
359         if (selectItemMF < 0 || selectItemMF > 30)
360             selectItemMF = 0;
361     if (stringArrayFch)
362     {
363         MemHandleImpListContentArrayFch;
364         MemHandleFees(stringArrayFch);
365         MemHandleImpListContentArrayFch;
366         stringPtr = MemHandleImpListContentArrayFch;
367     }
368 }

```

```

194 return NULL;
195
196 StrCopy(MemHandleLock(textHandle), string);
197 MemHandleUnlock(textHandle);
198 return SetFieldFromHandle(fieldID, textHandle);
199 }
200
201 * FUNCTION: CopyStringFromFieldText
202 * DESCRIPTION: Copies the field's text to the string specified by the pointer
203 *             to it
204 *
205 * PARAMETERS: ID of text field, pointer to the string
206 *
207 * RETURNER: Nothing
208 *
209 * REVISION HISTORY V 1.0 11/05/2000
210 *
211 static void CopyStringFromFieldText(Uint16 fieldID, Char* string)
212 {
213     Char* text;
214     FieldPtr field;
215     FormPtr fmp = FrmActiveForm();
216     MemHandle textHandle;
217     field = FrmGetObjectPtr(fmp, FrmGetObjectIndex(fmp, fieldID));
218     text = MemHandleLock(textHandle);
219     if (textHandle)
220         field->text = text;
221     StrCopy(string, text);
222     MemHandleUnlock(textHandle);
223 }
224
225 * FUNCTION: ClearFieldText
226 * DESCRIPTION: Clears the text from field specified by the ID
227 *
228 * PARAMETERS: ID of field
229 *
230 * RETURNER: nothing
231 *
232 * REVISION HISTORY V 1.0 04/05/2000
233 *
234 static void ClearFieldText(Uint16 fieldID)
235 {
236     FormPtr fmp = FrmActiveForm();
237     FieldPtr field;
238     field = FrmGetObjectPtr(fmp, FrmGetObjectIndex(fmp, fieldID));
239     field->text = NULL;
240 }
241
242 * FUNCTION: UpdateScrollbar
243 * DESCRIPTION: Update scrollbar of text field
244 *
245 * PARAMETERS: ID of text field, ID of scroll bar
246 *
247 * RETURNER: nothing
248 *
249 * REVISION HISTORY V 1.0 15/05/2000
250 *
251 static void UpdateScrollbar(Uint16 fieldID, Uint16 scrollbarID)
252 {
253     FormPtr fmp = FrmActiveForm();
254     FieldPtr field;
255     field = FrmGetObjectPtr(fmp, FrmGetObjectIndex(fmp, fieldID));
256     if (field->text)
257         UpdateScrollbarField(fieldID, scrollbarID);
258 }
259
260 * FUNCTION: UpdateScrollbar
261 * DESCRIPTION: Update scrollbar of text field
262 *
263 * PARAMETERS: ID of text field, ID of scroll bar
264 *
265 * RETURNER: nothing
266 *
267 * REVISION HISTORY V 1.0 15/05/2000
268 *
269 static void UpdateScrollbar(Uint16 fieldID, Uint16 scrollbarID)
270 {
271     FormPtr fmp = FrmActiveForm();
272     FieldPtr field;
273     field = FrmGetObjectPtr(fmp, FrmGetObjectIndex(fmp, fieldID));
274     if (field->text)
275         UpdateScrollbarField(fieldID, scrollbarID);
276 }
277
278 * FUNCTION: UpdateScrollbar
279 * DESCRIPTION: Update scrollbar of text field
280 *
281 * PARAMETERS: ID of text field, ID of scroll bar
282 *
283 * RETURNER: nothing
284 *
285 * REVISION HISTORY V 1.0 15/05/2000
286 *
287 static void UpdateScrollbar(Uint16 fieldID, Uint16 scrollbarID)
288 {
289     FormPtr fmp = FrmActiveForm();
290     FieldPtr field;
291     field = FrmGetObjectPtr(fmp, FrmGetObjectIndex(fmp, fieldID));
292     if (field->text)
293         UpdateScrollbarField(fieldID, scrollbarID);
294 }

```



```

792 FieldP = FmncObjectIn(fmc, FmncObjectIn(fmc, TestField));
793 FmncObjectIn(fmc, TestField);
794 FmncObjectIn(fmc, TestField);
795 FmncObjectIn(fmc, TestField);
796 FmncObjectIn(fmc, TestField);
797 while (fmc)
798 {
799     FmncObjectIn(fmc, TestField);
800     return
801 }
802
803 .....
804
805 * FUNCTION: PulseShapeDraw
806 * DESCRIPTION: Draws the different pulse shapes depending on
807 *             the data of gadget
808
809 * PARAMETERS:
810 *
811 * RETURN: Nothing
812
813 * REVISION HISTORY V 1.0 05/06/2000 23:43
814
815 * static void PulseShapeDraw(Fmnc * fmc)
816 {
817     .....
818     .....
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1281 strcpy(sendString, "");
1282 count = SendSerialData(sendString);
1283
1284 // Anzeige für Anzahl der Programmabfrageversuche aktualisieren
1285 printf("Anzahl der Programmabfrageversuche: %d\n", i);
1286 ClearField(MainProgField);
1287 strcpy(sendString, "N");
1288 StrCat(sendString, StrFmt(halfSecr, halfover) + 6);
1289 count = SendSerialData(sendString);
1290 // laden vom programmierbaren Program Nr. 1 - 9
1291 if (g142Version == g142Version)
1292 {
1293     Impedanzmessung auf 9 abstellen
1294     strcpy(sendString, "yyyyf n");
1295     count = SendSerialData(sendString);
1296 // Impedanzmessung auf 7 abstellen
1297     strcpy(sendString, "20000 n");
1298     count = SendSerialData(sendString);
1299 }
1300 //
1301 //
1302 // Programm in Programmierer Nr. 1 - 9 übernehmen
1303 if (ClGetValue(GetObjectPtr(MainProgPushButton)) < 1)
1304 {
1305     strcpy(sendString, "N");
1306     strcpy(sendString, "02 n");
1307     strcpy(sendString, "03 n");
1308     strcpy(sendString, "04 n");
1309     strcpy(sendString, "05 n");
1310     strcpy(sendString, "06 n");
1311     strcpy(sendString, "07 n");
1312     strcpy(sendString, "08 n");
1313     strcpy(sendString, "09 n");
1314     strcpy(sendString, "0A n");
1315     strcpy(sendString, "0B n");
1316     strcpy(sendString, "0C n");
1317     strcpy(sendString, "0D n");
1318     strcpy(sendString, "0E n");
1319     strcpy(sendString, "0F n");
1320     count = SendSerialData(sendString);
1321 //
1322 //
1323 //
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1181 StrCat(sendString, " ");
1182 count = SendSerialData(sendString);
1183
1184 // Encoder Max fix auf 09 einstellen
1185 strcpy(sendString, "9");
1186 StrCat(sendString, StrFmt(halfSecr, halfover) + 6);
1187 count = SendSerialData(sendString);
1188 //
1189 //
1190 //
1191 //
1192 //
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```


B Matlab scripts for CT analysis and MFCV & MFRP

C:\Dokumente und Einstellungen\Admin\Eigene Dateien\ctarea.m
Printed at 21:03 on 23 Apr 2008

Page 1 of 11

```

1 function varargout = ctarea(varargin)
2 %
3 % CTAREA M-file for ctarea.fig by Christian Hofer
4 % Analysis of the CT scans showing the cross section of thigh calculating
5 % the area and the density (mean and histogram of distribution) of the
6 % selected ROIs
7 %
8 % CTAREA, by itself, creates a new CTAREA or raises the existing
9 % singleton*.
10 %
11 % H = CTAREA returns the handle to a new CTAREA or the handle to
12 % the existing singleton*.
13 %
14 % CTAREA('CALLBACK', hObject,eventData,handles,...) calls the local
15 % function named CALLBACK in CTAREA.M with the given input arguments.
16 %
17 % CTAREA('Property','Value',...) creates a new CTAREA or raises the
18 % existing singleton*. Starting from the left, property value pairs are
19 % applied to the GUI before ctarea_OpeningFcn gets called. An
20 % unrecognized property name or invalid value makes property application
21 % stop. All inputs are passed to ctarea_OpeningFcn via varargin.
22 %
23 % *See GUI Options on GUIDE's Tools menu. Choose "GUI allows only one
24 % instance to run (singleton)".
25 %
26 % See also: GUIDE, GUIDATA, GUIHANDLES
27
28 % Edit the above text to modify the response to help ctarea
29
30 % Last Modified by GUIDE v2.5 24-Feb-2006 10:40:50
31
32 % Begin initialization code - DO NOT EDIT
33 gui_Singleton = 1;
34 gui_State = struct('guiNames', mfilename, ...
35                 'gui_Singleton', gui_Singleton, ...
36                 'gui_OpeningFcn', @ctarea_OpeningFcn, ...
37                 'gui_OutputFcn', @ctarea_OutputFcn, ...
38                 'gui_LayoutFcn', [], ...
39                 'gui_Callback', []);
40 if nargin & isstr(varargin{1})
41     gui_State.gui_Callback = str2func(varargin{1});
42 end
43
44 if nargin
45     [varargout{1:nargout}] = gui_mainfcn(gui_State, varargin{:});
46 else
47     gui_mainfcn(gui_State, varargin{:});
48 end
49 % End initialization code - DO NOT EDIT
50
51
52 % --- Executes just before ctarea is made visible.
53 function ctarea_OpeningFcn(hObject, eventdata, handles, varargin)
54 % This function has no output args, see OutputFcn.
55 % hObject handle to figure
56 % eventdata reserved - to be defined in a future version of MATLAB
57 % handles structure with handles and user data (see GUIDATA)
58 % varargin command line arguments to ctarea (see VARARGIN)
59
60 % Choose default command line output for ctarea
61 handles.output = hObject;

```

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Printed at 21:03 on 23 Apr 2008

Page 2 of 11

```

62 % Update handles structure
63 guidata(hObject, handles);
64 guidata(hObject, handles);
65
66 set(hObject, 'Units', 'pixel');
67 set(hObject, 'Position', [ 60 60 1024-60 768-60]);
68 handles.hinit(1:120)=0;
69 handles.HU=195:101:995;
70 handles.hleftquad=handles.hinit;
71 handles.hrightquad=handles.hinit;
72 handles.hleftham=handles.hinit;
73 handles.hrightham=handles.hinit;
74 handles.fig=figure;
75 close(handles.fig);
76
77 guidata(hObject, handles);
78
79 % UIWAIT makes ctarea wait for user response (see UIRESUME)
80 % ulwait(handles.figure);
81
82
83 % --- Outputs from this function are returned to the command line.
84 function varargout = ctarea_OutputFcn(hObject, eventdata, handles)
85 % varargout cell array for returning output args (see VARARGOUT);
86 % hObject handle to figure
87 % eventdata reserved - to be defined in a future version of MATLAB
88 % handles structure with handles and user data (see GUIDATA)
89
90 % Get default command line output from handles structure
91 varargout{1} = handles.output;
92
93
94 % --- Executes on button press in pushbutton1.
95 function pushbutton1_Callback(hObject, eventdata, handles)
96 % hObject handle to pushbutton1 (see GCBO)
97 % eventdata reserved - to be defined in a future version of MATLAB
98 % handles structure with handles and user data (see GUIDATA)
99 axes(handles.axes1);
100 cla;
101 axes(handles.axes2);
102 cla;
103 axes(handles.axes3);
104 cla;
105 axes(handles.axes4);
106 cla;
107 axes(handles.axes5);
108 cla;
109 axes(handles.axes6);
110 cla;
111 axes(handles.axes7);
112 cla;
113 axes(handles.axes8);
114 cla;
115 [s1, s2] = uigetfile (*.*, 'Open File');
116 cd (s2);
117 handles.info=dircominfo (s2 s1);
118 CTScan=dircomread(handles.info);
119 handles.CTScan = double(CTScan)*handles.info.RescaleSlope + handles.info.RescaleIntercept;
120 handles.hinit(1:120)=0;
121 axes(handles.axes1);

```

```

C:\Dokumente und Einstellungen\Admin\Eigene Daten\ctarea.m          Page 4 of 11
Printed at 21:03 on 23 Apr 2008

176 handles.infotext(4)={sprintf('right thigh cross sectional area [cm2] = %6.2f', t
    higharea) , ...          sprintf('mean density [HU] = %6.2f', hr
177     lightmean) , ...
178     set(findobj(handles.text2), 'String', handles.infotext)};
180
181 guidata(hObject, handles);
182
183 % --- Executes on button press in pushbutton3.
184 function pushbutton3_Callback(hObject, eventdata, handles)
185 % hObject handle to pushbutton3 (see GCBO)
186 % eventdata reserved - to be defined in a future version of MATLAB
187 % handles structure with handles and user data (see GUIDATA)
188 axes(handles.axes3);
189 cla;
190 axes(handles.axes4);
191 cla;
192 axes(handles.axes7);
193 cla;
194 axes(handles.axes8);
195 cla;
196 axes(handles.axes4);
197 imshow(handles.CTScan, [-350 100]);
198 [x,y]=ginput(2);
199 handles.SelectedAreaLeft=handles.CTScan(y(1):y(2), x(1):x(2));
200 axes(handles.axes4);
201 imshow(handles.SelectedAreaLeft, [-350 100]);
202 imshow(handles.SelectedAreaLeft, [-125 225]);
203 axes(handles.axes3);
204 imshow(handles.SelectedAreaLeft, [-125 225]);
205 handles.SelectedAreaLeft(find(handles.SelectedAreaLeft < -200)) = NaN;
206 handles.SelectedAreaLeft(find(handles.SelectedAreaLeft > 1000)) = 1000;
207 [pixelnumber,n]=size(find(~isnan(handles.SelectedAreaLeft)));
208 thigharea = pixelnumber*handles.info.PixelSpacing(1)*handles.info.PixelSpacing(2
    )/100;
209 [pixelnumber,n]=size(find(handles.SelectedAreaLeft < 200));
210 hleftmean = mean(handles.SelectedAreaLeft(find(handles.SelectedAreaLeft < 200)))
    ;
211 hleftstd = std(handles.SelectedAreaLeft(find(handles.SelectedAreaLeft < 200)))
    ;
212 handles.infotext(5)={sprintf('left thigh cross sectional area [cm2] = %6.2f',
    thigharea) , ...
213     hleftmean) , ...          sprintf('mean density [HU] = %6.2f',
214     hleftstd) , ...          sprintf('sd = %6.2f',hleftstd)};
215 set(findobj(handles.text2), 'String', handles.infotext);
216
217 guidata(hObject, handles);
218
219 % --- Executes on button press in pushbutton4.
220 function pushbutton4_Callback(hObject, eventdata, handles)
221 % hObject handle to pushbutton4 (see GCBO)
222 % eventdata reserved - to be defined in a future version of MATLAB
223 % handles structure with handles and user data (see GUIDATA)
224 axes(handles.axes4);
225 imshow(handles.SelectedAreaRight, [-350 100]);
226 [pixelnumber,n]=size(find(handles.SelectedAreaRight, [-125 225]));
227 [x,y]=ginput(2);
228 handles.SelectedAreaRight=find(handles.SelectedAreaRight < 200)
    ;
229 [x,y]=ginput(2);
230 if x(1)<1

```

```

C:\Dokumente und Einstellungen\Admin\Eigene Daten\ctarea.m          Page 3 of 11
Printed at 21:03 on 23 Apr 2008

122 imshow(handles.CTScan, [-125 225]);
123 try handles.infotext(1) = {handles.info.PatientName.FamilyName, ' '};
124 end
125 end
126 try handles.infotext(1) = {handles.info.PatientName.FamilyName, ' ', handles.in
    fo.PatientName.GivenName(1), ' '};
127 end
128 try handles.infotext(1) = {handles.info.PatientName.FamilyName, ' '};
129 end
130 try handles.infotext(1) = {handles.info.PatientName.FamilyName, ' '};
131 end
132 try handles.infotext(1) = {handles.info.PatientName.FamilyName, ' ', handles.in
    fo.PatientName.GivenName(1), ' '};
133 end
134 end
135 handles.infotext(2) = {'date of examination: ', handles.info.AcquisitionDate(1:
    4), ', ', handles.info.AcquisitionDate(5:6), ', ', handles.info.AcquisitionDate(7:8)}
    ;
136
137 handles.infotext(4)={[]};
138 handles.infotext(5)={[]};
139 handles.infotext(7)={[]};
140 handles.infotext(8)={[]};
141 handles.infotext(10)={[]};
142 set(findobj(handles.text2), 'String', handles.infotext);
143
144 guidata(hObject, handles);
145
146
147 % --- Executes on button press in pushbutton2.
148 function pushbutton2_Callback(hObject, eventdata, handles)
149 % hObject handle to pushbutton2 (see GCBO)
150 % eventdata reserved - to be defined in a future version of MATLAB
151 % handles structure with handles and user data (see GUIDATA)
152 axes(handles.axes2);
153 cla;
154 axes(handles.axes4);
155 cla;
156 axes(handles.axes5);
157 cla;
158 axes(handles.axes6);
159 cla;
160 axes(handles.axes4);
161 imshow(handles.CTScan, [-350 100]);
162 [x,y]=ginput(2);
163 handles.SelectedAreaRight=handles.CTScan(y(1):y(2), x(1):x(2));
164 axes(handles.axes4);
165 imshow(handles.SelectedAreaRight, [-125 225]);
166 imshow(handles.SelectedAreaRight, [-125 225]);
167 axes(handles.axes2);
168 imshow(handles.SelectedAreaRight, [-125 225]);
169 handles.SelectedAreaRight(find(handles.SelectedAreaRight < -200)) = NaN;
170 handles.SelectedAreaRight(find(handles.SelectedAreaRight > 1000)) = 1000;
171 [pixelnumber,n]=size(find(~isnan(handles.SelectedAreaRight)));
172 thigharea = pixelnumber*handles.info.PixelSpacing(1)*handles.info.PixelSpacing(2
    )/100;
173 [pixelnumber,n]=size(find(handles.SelectedAreaRight < 200));
174 hrightmean = mean(handles.SelectedAreaRight(find(handles.SelectedAreaRight < 200
    )));
175 hrightstd = std(handles.SelectedAreaRight(find(handles.SelectedAreaRight < 200))
    );

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C:\Dokumente und Einstellungen\Admin\Eigene Dateien\ctarea.m
 Printed at 21:03 on 23 Apr. 2008

Page 5 of 11

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231     x(1)=1;
232 end
233 if Y(1)<1
234     Y(1)=1;
235 end
236 if x(2)>xf
237     x(2)=xf;
238 end
239 if y(2)>yf
240     y(2)=yf;
241 end
242 handles.SelectedAreaRight(y(1):y(2),x(1):x(2))=-200;
243 handles.SelectedAreaRight(find(handles.SelectedAreaRight < -199)) = NaN;
244
245 axes(handles.axes4);
246 imshow(handles.SelectedAreaRight, [-350 100]);
247 imshow(handles.SelectedAreaRight, [-125 225]);
248 axes(handles.axes2);
249 imshow(handles.SelectedAreaRight, [-125 225]);
250
251 [pixelnumber,n]=size(find(~isnan(handles.SelectedAreaRight)));
252 thigharea = pixelnumber*handles.info.PixelSpacing(1)*handles.info.PixelSpacing(2)
/100;
253 [pixelnumber,n]=size(find(handles.SelectedAreaRight < 200));
254 brightmean = mean(handles.SelectedAreaRight(find(handles.SelectedAreaRight < 200)
));
255 brightstd = std(handles.SelectedAreaRight(find(handles.SelectedAreaRight < 200)
));
256 handles.infotext(4)=[sprintf('right thigh cross sectional area [cm2] = %6.2f',b
higharea) , ...
sprintf('mean density [HU] = %6.2f',br
ightmean) , ...
sprintf('std = #%6.2f',brightstd)];
257
258
259 set(findobj(handles.text2),'String',handles.infotext);
260
261 guidata(hObject, handles);
262
263 % --- Executes on button press in pushbutton5.
264 function pushbutton5_Callback(hObject, eventdata, handles)
265 % hObject handle to pushbutton5 (see GCBO)
266 % eventdata reserved - to be defined in a future version of MATLAB
267 % handles structure with handles and user data (see GUIDATA)
268 axes(handles.axes4);
269 imshow(handles.SelectedAreaLeft, [-350 100]);
270 imshow(handles.SelectedAreaLeft, [-125 225]);
271 [yf,xf]=size(handles.SelectedAreaLeft);
272 [x,y]=ginput(2);
273 if x(1)<1
274     x(1)=1;
275 end
276 if y(1)<1
277     y(1)=1;
278 end
279 if x(2)>xf
280     x(2)=xf;
281 end
282 if y(2)>yf
283     y(2)=yf;
284 end
285 handles.SelectedAreaLeft(y(1):y(2),x(1):x(2))=-200;
286 handles.SelectedAreaLeft(find(handles.SelectedAreaLeft < -199)) = NaN;

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C:\Dokumente und Einstellungen\Admin\Eigene Dateien\ctarea.m
 Printed at 21:03 on 23 Apr. 2008

Page 6 of 11

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287 axes(handles.axes4);
288 imshow(handles.SelectedAreaLeft, [-350 100]);
289 imshow(handles.SelectedAreaLeft, [-125 225]);
290 axes(handles.axes3);
291 imshow(handles.SelectedAreaLeft, [-125 225]);
292
293 [pixelnumber,n]=size(find(~isnan(handles.SelectedAreaLeft)));
294 thigharea = pixelnumber*handles.info.PixelSpacing(1)*handles.info.PixelSpacing(2)
/100;
295 [pixelnumber,n]=size(find(handles.SelectedAreaLeft < 200));
296 hleftmean = mean(handles.SelectedAreaLeft(find(handles.SelectedAreaLeft < 200)
));
297 hleftstd = std(handles.SelectedAreaLeft(find(handles.SelectedAreaLeft < 200)
));
298 handles.infotext(5)=[sprintf('left thigh cross sectional area [cm2] = %6.2f',
thigharea) , ...
sprintf('mean density [HU] = %6.2f',
hleftmean) , ...
sprintf('sd = #%6.2f',hleftstd)];
299
300
301 set(findobj(handles.text2),'String',handles.infotext);
302
303 guidata(hObject, handles);
304
305 % --- Executes on button press in pushbutton6.
306 function pushbutton6_Callback(hObject, eventdata, handles)
307 % hObject handle to pushbutton6 (see GCBO)
308 % eventdata reserved - to be defined in a future version of MATLAB
309 % handles structure with handles and user data (see GUIDATA)
310 axes(handles.axes4);
311 handles.infotext(4)=[sprintf('right thigh cross sectional area [cm2] = %6.2f',t
higharea) , ...
sprintf('mean density [HU] = %6.2f',br
ightmean) , ...
sprintf('std = #%6.2f',brightstd)];
312
313
314 set(findobj(handles.text2),'String',handles.infotext);
315
316 guidata(hObject, handles);
317
318 % --- Executes on button press in pushbutton6.
319 function pushbutton6_Callback(hObject, eventdata, handles)
320 % hObject handle to pushbutton6 (see GCBO)
321 % eventdata reserved - to be defined in a future version of MATLAB
322 % handles structure with handles and user data (see GUIDATA)
323 axes(handles.axes4);
324 imshow(handles.SelectedAreaRight + handles.QuadricepsMaskRight*120, [-125 225]);
325
326 [pixelnumber,n]=size(find(handles.QuadricepsMaskRight == 1));
327 quadricepsarea = pixelnumber*handles.info.PixelSpacing(1)*handles.info.PixelSpac
ing(2)/100;
328 meanhu = mean(handles.SelectedAreaRight(find(handles.QuadricepsMaskRight == 1)
));
329 stdhu = std(handles.SelectedAreaRight(find(handles.QuadricepsMaskRight == 1)
));
330 handles.infotext(7)=[sprintf('right quadriceps cross sectional area [cm2] = %6.
2f',quadricepsarea) , ...
sprintf('mean density [HU] = %6.2f',
meanhu) , ...
sprintf('std = #%6.2f',stdhu)];
331
332 set(findobj(handles.text2),'String',handles.infotext);
333
334 bright = hleft(handles.SelectedAreaRight(find(handles.QuadricepsMaskRight == 1)
), handles.HU);
335 handles.HU;
336 handles.brightquad = bright/pixelnumber*100;

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C:\Dokumente und Einstellungen\Admin\Eigene Dateien\ctarea.m
 Printed at 21:03 on 23 Apr. 2008

Page 7 of 11

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337 figure(handles.fig);
338 subplot(2,1,1);
339 bar(handles.HU,[handles.hrightquad' handles.hinit'],0.8,'r');
340 hold on;
341 bar(handles.HU,[handles.hleftquad'],0.8,'b');
342 hold off;
343 axis([-150 150 0 40]);
344 xlabel('Hounsfield Units');
345 ylabel('cross sectional area [%]');
346 guidata(hObject, handles);
347
348 % --- Executes on button press in pushbutton7.
349 function pushbutton7_Callback(hObject, eventdata, handles)
350 % hObject handle to pushbutton7 (see GCBO)
351 % eventdata reserved - to be defined in a future version of MATLAB
352 % handles structure with handles and user data (see GUIDATA)
353 axes(handles.axes4);
354 cla;
355 handles.QuadriicepsMaskLeft=zeros(size(handles.SelectedAreaLeft));
356
357 imshow(handles.axes4);
358 cla;
359 handles.QuadriicepsMaskLeft=zeros(size(handles.SelectedAreaLeft));
360
361 axes(handles.axes4);
362 imshow(handles.SelectedAreaLeft,[-125 225]);
363 [x,y]=ginput(2);
364 imshow(handles.SelectedAreaLeft(y(1):y(2),x(1):x(2)),-[125 225]);
365 handles.QuadriicepsMaskLeft(y(1):y(2),x(1):x(2))=roipoly;
366 axes(handles.axes4);
367 imshow(handles.SelectedAreaLeft + handles.QuadriicepsMaskLeft*120,[-125 225]);
368 axes(handles.axes7);
369 imshow(handles.SelectedAreaLeft + handles.QuadriicepsMaskLeft*120,[-125 225]);
370
371 [pixelnumber, n]=size(find(handles.QuadriicepsMaskLeft == 1));
372 quadriicepsarea = pixelnumber*handles.info.PixelSpacing(1)*handles.info.PixelSpac
ing(2)/100;
373 meanhu = mean(handles.SelectedAreaLeft(find(handles.QuadriicepsMaskLeft == 1)));
374 stdhu = std(handles.SelectedAreaLeft(find(handles.QuadriicepsMaskLeft == 1)));
375 handles.infotext(8)=[sprintf('left quadriiceps cross sectional area [cm2] = %6
.2f',quadriicepsarea) , ...
sprintf('mean density [HU] = %6.2f',
meanhu) , ...
sprintf('sd = %6.2f',stdhu)];
376
377 set(findobj(handles.text2),'string',handles.infotext);
378
379
380 hleft = hist(handles.SelectedAreaLeft(find(handles.QuadriicepsMaskLeft == 1)),han
dles.HU);
381 handles.hleftquad = hleft/pixelnumber*100;
382
383 figure(handles.fig);
384 subplot(2,1,1);
385 bar(handles.HU,[handles.hrightquad' handles.hinit'],0.8,'r');
386 hold on;
387 bar(handles.HU,[handles.hleftquad'],0.8,'b');
388 hold off;
389 axis([-150 150 0 40]);
390 xlabel('Hounsfield Units');
391 ylabel('cross sectional area [%]');
392 guidata(hObject, handles);
393

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C:\Dokumente und Einstellungen\Admin\Eigene Dateien\ctarea.m
 Printed at 21:03 on 23 Apr. 2008

Page 8 of 11

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394
395 % --- Executes on button press in pushbutton8.
396 function pushbutton8_Callback(hObject, eventdata, handles)
397 % hObject handle to pushbutton8 (see GCBO)
398 % eventdata reserved - to be defined in a future version of MATLAB
399 % handles structure with handles and user data (see GUIDATA)
400 axes(handles.axes4);
401 cla;
402 handles.HamstringsMaskRight=zeros(size(handles.SelectedAreaRight));
403 cla;
404 handles.HamstringsMaskRight=zeros(size(handles.SelectedAreaRight));
405
406 axes(handles.axes4);
407 imshow(handles.SelectedAreaRight,[-125 225]);
408 [x,y]=ginput(2);
409 imshow(handles.SelectedAreaRight(y(1):y(2),x(1):x(2)),-[125 225]);
410 handles.HamstringsMaskRight(y(1):y(2),x(1):x(2))=roipoly;
411 axes(handles.axes4);
412 imshow(handles.SelectedAreaRight + handles.HamstringsMaskRight*120,[-125 225]);
413
413 axes(handles.axes6);
414 imshow(handles.SelectedAreaRight + handles.HamstringsMaskRight*120,[-125 225]);
415
416 [pixelnumber, n]=size(find(handles.HamstringsMaskRight == 1));
417 hamstringsarea = pixelnumber*handles.info.PixelSpacing(1)*handles.info.PixelSpac
ing(2)/100;
418 meanhu = mean(handles.SelectedAreaRight(find(handles.HamstringsMaskRight == 1)));
419 stdhu = std(handles.SelectedAreaRight(find(handles.HamstringsMaskRight == 1)));
420 handles.infotext(10)=[sprintf('right hamstrings cross sectional area [cm2] = %6
.2f',hamstringsarea) , ...
sprintf('mean density [HU] = %6.2f',
meanhu) , ...
sprintf('sd = %6.2f',stdhu)];
421
422 set(findobj(handles.text2),'string',handles.infotext);
423
424 hright = hist(handles.SelectedAreaRight(find(handles.HamstringsMaskRight == 1)),
handles.HU);
425 handles.hrightham = hright/pixelnumber*100;
426
427 figure(handles.fig);
428 subplot(2,1,2);
429 bar(handles.HU,[handles.hrightham' handles.hinit'],0.8,'r');
430 hold on;
431 bar(handles.HU,[handles.hlefttham'],0.8,'b');
432 hold off;
433 axis([-150 150 0 40]);
434 xlabel('Hounsfield Units');
435 ylabel('cross sectional area [%]');
436
437 guidata(hObject, handles);
438
439
440 % --- Executes on button press in pushbutton9.
441 function pushbutton9_Callback(hObject, eventdata, handles)
442 % hObject handle to pushbutton9 (see GCBO)
443 % eventdata reserved - to be defined in a future version of MATLAB
444 % handles structure with handles and user data (see GUIDATA)
445 axes(handles.axes4);
446 cla;
447 axes(handles.axes8);

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C:\Dokumente und Einstellungen\Admin\Eigene Dateien\ctarea.m
 Printed at 21:03 on 23 Apr. 2008

Page 9 of 11

```

448 cla;
449 handles.HamstringsMaskLeft=zeros(size(handles.SelectedAreaLeft));
450 axes(handles.axes4);
451 imshow(handles.SelectedAreaLeft, [-125 225]);
452 [x,y]=input(2);
453 [x,y]=input(2);
454 imshow(handles.SelectedAreaLeft(y(1):y(2),x(1):x(2)), [-125 225]);
455 handles.HamstringsMaskLeft(y(1):y(2),x(1):x(2))=roipoly;
456 axes(handles.axes4);
457 imshow(handles.SelectedAreaLeft + handles.HamstringsMaskLeft*120, [-125 225]);
458 axes(handles.axes8);
459 imshow(handles.SelectedAreaLeft + handles.HamstringsMaskLeft*120, [-125 225]);
460
461 [pixelnumber, n]=size(find(handles.HamstringsMaskLeft == 1));
462 hamstringsarea = pixelnumber*handles.info.PixelSpacing(1)*handles.info.PixelSpac
  ing(2)/100;
463 meanhu = mean(handles.SelectedAreaLeft(find(handles.HamstringsMaskLeft == 1)));
464 stdhu = std(handles.SelectedAreaLeft(find(handles.HamstringsMaskLeft == 1)));
465 handles.infoText(11)=[sprintf('left hamstrings cross sectional area [cm2] = %
  6.2f', hamstringsarea), ...
466 meanhu), ...
  sprintf('mean density [HU] = %6.2f',
467 stdhu), ...
  sprintf('sd = %6.2f',stdhu)];
468 set(findobj(handles.text2), 'String', handles.infoText);
469 left = hist(handles.SelectedAreaLeft(find(handles.HamstringsMaskLeft == 1)),han
  dles.HU);
470 handles.hlefttham = hleft/pixelnumber*100;
471
472 figure(handles.fig);
473 subplot(2,1,2);
474 bar(handles.HU, [handles.hrighttham handles.hinit], 0.8, 'r');
475 hold on;
476 bar(handles.HU, [handles.hrighttham handles.hlefttham], 0.8, 'b');
477 hold off;
478 axis([-150 150 0 40]);
479 xlabel('Hounsfield Units');
480 ylabel('cross sectional area [%]');
481
482 guidata(hObject, handles);
483
484
485 % --- Executes on button press in pushbutton0.
486 function pushbutton0_Callback(hObject, eventdata, handles)
487 % hObject handle to pushbutton0 (see GCBO)
488 % eventdata reserved - to be defined in a future version of MATLAB
489 % handles structure with handles and user data (see GUIDATA)
490 print;
491
492
493 % --- Executes on button press in pushbutton1.
494 function pushbutton1_Callback(hObject, eventdata, handles)
495 % hObject handle to pushbutton1 (see GCBO)
496 % eventdata reserved - to be defined in a future version of MATLAB
497 % handles structure with handles and user data (see GUIDATA)
498
499 [pixelnumber, n]=size(find(handles.HamstringsMaskRight == 1));
500 right = hist(handles.SelectedAreaRight(find(handles.HamstringsMaskRight == 1)),
  handles.HU);
501 handles.hrighttham = hright/pixelnumber*100;
502
503 [pixelnumber, n]=size(find(handles.HamstringsMaskLeft == 1));

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C:\Dokumente und Einstellungen\Admin\Eigene Dateien\ctarea.m

Page 10 of 11

```

504 hleft = hist(handles.SelectedAreaLeft(find(handles.HamstringsMaskLeft == 1)),han
  dles.HU);
505 handles.hlefttham = hleft/pixelnumber*100;
506
507 data = [handles.HU, handles.hleftquad, handles.hrightquad', ...
  handles.hlefttham handles.hrighttham'];
508
509 guidata(hObject, handles);
510
511 [s1,s2] = uiputfile('*.','Save File');
512 dlmwrite ([s2 s1 '.dat'], data, '\t');
514 saveas(gcf, [s2 s1], 'jpg');
515 saveas(gcf, [s2 s1], 'm');
516
517
518 % --- Executes on button press in pushbutton2.
519 function pushbutton2_Callback(hObject, eventdata, handles)
520 % hObject handle to pushbutton2 (see GCBO)
521 % eventdata reserved - to be defined in a future version of MATLAB
522 % handles structure with handles and user data (see GUIDATA)
523
524 figure(handles.fig);
525 subplot(2,1,1);
526 bar(handles.HU, [handles.hrightquad handles.hinit], 0.8, 'r');
527 bar(handles.HU, handles.hrightquad', 0.8, 'r');
528 hold on;
529 bar(handles.HU, [handles.hinit handles.hleftquad'], 0.8, 'b');
530 hold off;
531 axis([-150 150 0 40]);
532 xlabel('Hounsfield Units');
533 ylabel('cross sectional area [%]');
534 subplot(2,1,2);
535 bar(handles.HU, [handles.hrighttham handles.hinit], 0.8, 'r');
536 bar(handles.HU, handles.hrighttham', 0.8, 'r');
537 hold on;
538 bar(handles.HU, [handles.hinit handles.hlefttham'], 0.8, 'b');
539 hold off;
540 axis([-150 150 0 40]);
541 xlabel('Hounsfield Units');
542 ylabel('cross sectional area [%]');
543
544 axes(handles.axes4);
545 imshow(handles.SelectedAreaRight + handles.HamstringsMaskRight*120 + handles.Q
  uadriicepsMaskRight*120, [-125 225]);
546 imshow(handles.SelectedAreaRight + handles.QuadriicepsMaskRight*120, [-125 225])
  ;
547
548 % --- Executes on button press in pushbutton3.
549 function pushbutton3_Callback(hObject, eventdata, handles)
550 % hObject handle to pushbutton3 (see GCBO)
551 % eventdata reserved - to be defined in a future version of MATLAB
552 % handles structure with handles and user data (see GUIDATA)
553
554 figure(handles.fig);
555 subplot(2,1,1);
556 bar(handles.HU, [handles.hrightquad handles.hinit], 0.8, 'r');
557 hold on;
558 bar(handles.HU, [handles.hrightquad handles.hleftquad'], 0.8, 'b');
559 hold off;
560 axis([-150 150 0 40]);
561
562 xlabel('Hounsfield Units');

```

C:\Dokumente und Einstellungen\Admin\Eigene Dateien\area.m
Printed at 21:03 on 23 Apr 2008 Page 11 of 11

```
562 xlabel('cross sectional area [%]');  
563 subplot(2,1,2);  
564 bar(handles.HU, [handles.hrightham' handles.hinit'],0.8, 'r');  
565 hold on;  
566 bar(handles.HU, [handles.hinit' handles.hleftham'],0.8, 'b');  
567 hold off;  
568 axis([-150 150 0 40]);  
569 xlabel('Hounsfield Units');  
570 ylabel('cross sectional area [%]');  
571  
572 axes(handles.axes4);  
573 imshow((handles.SelectedAreaLeft + handles.HamstringsMaskLeft*120 + handles.QuadricepsMaskLeft*120), [-125 225]);  
574 imshow((handles.SelectedAreaLeft + handles.QuadricepsMaskLeft*120), [-125 225]);
```

C:\Programme\FifeID\Pulse edited.M
Printed at 20:45 on 23 Apr. 2008

Page 1 of 3

```

1  % Dpulse mfile for analysing stimulation needle EMG measurements
2  % by Christian Hofer
3
4  clear all;
5  % importing the data measured with DasyLab into Matlab
6  [s1,s2] = uigetfile ('*.ASC', 'Open File');
7  cd (s2);
8  A=dlmread (s1,'\t',10,0);
9
10 A=A(:, [1 2]) *1000;
11 O=A;
12 % filtering data
13
14 % 4th order butterworth low pass filter at 10KHz
15 [Num,Den] = butter(4,10000/50000);
16 A=filter(Num,Den,A);
17 % 4th order butterworth high pass filter at 20Hz
18 [Num,Den] = butter(4,20/50000,'high');
19 % 2nd order butterworth high pass filter at 500Hz
20 [Num,Den] = butter(2,500/50000,'high');
21 A=filter(Num,Den,A);
22
23 % searching for the stimulation artefacts and extracting the data to a separate
    matrix
24 i = 1;
25 n = 1;
26 height = 5; % window height in mV
27 width = 120; % window width in ms
28 width = 150; % window width in ms
29 pre = 4; % pretigger in ms
30 P = pre/1000*50000;
31 w = width*(1/1000*50000)-p; % Schreibweise wegen Darstellung von w als Integ
32 sz=length(A(:,1));
33 while n < (K-w)
34     if (A(n,1)>0.5 | A(n,1)<-0.5)
35         if 0 < (n - p)
36             C(:,1)=A(n-p:n+w,1);
37             if i==1
38                 O1=O(n-p:n+w,1);
39             end
40             i=i+1;
41             n=n+w;
42         else
43             n=n+w;
44         end
45     else
46         n=n+1;
47     end
48 end
49
50 if (i > 18)
51     i = i-18;
52 end;
53
54 B=1:length(C(:,1));
55 B=B/50000*1000-pre;
56
57 figure;
58 orient landscape;
59 set (gcf, 'Name', s1);

```

C:\Programme\FifeID\Pulse edited.M
Printed at 20:45 on 23 Apr. 2008

Page 2 of 3

```

60 title([s2,s1], 'FontSize', 12);
61 hold on;
62 plot (B(1,:), C(:,1));
63 set (findobj('Type','line'), 'LineWidth', 0.8);
64 plot (B(1,:), O1,'r');
65 set (findobj('Type','line'), 'LineWidth', 0.5);
66 hold off;
67 axis([-pre 40 -height height]);
68 grid on;
69 xlabel('Time [ms]');
70 ylabel('Amplitude [mV]');
71 pause (0.1);
72 height=input('Wave max. Amplitude [mV]=');
73 axis([-pre 40 -height height]);
74
75 impd=input('Impulsdauer [ms]=');
76 da=75;
77 dauer=da * (50000 / 1000);
78 de=15;
79 delay = (de + impd) * (50000 / 1000);
80 height=input('Wave max. Amplitude [mV]=');
81
82 close; %close figure after setting height and width according to actual signal
83
84 k = find (C > height);
85 C(k) = height;
86 k = find (C < -height);
87 C(k) = -height;
88
89 S=zeros(size(C));
90 D=zeros(size(C));
91 M=zeros(size(C));
92
93 % Delaywerte die zur Impulsdauer addiert werden
94
95 for s=3:i:l
96     S(l+dauer+4:dauer+delay+4,s)=C(l:dauer,l); %Wert 4 zu delay addiert wg. Sti
97     S(:,s)=S(:,s)+C(:,l);
98     D(:,s)=C(:,s)-C(:,l);
99     D(:,s)=C(:,s)-C(:,2); %Versuchweise 2. Antwort subtrahiert von Doppelpulsa
100     M(l:dauer,s)=D(l+dauer+4:dauer+delay+4,s); %Wert 4 zu delay addiert wg. Sti
101     delay=delay-50;
102 end
103
104 figure;
105 orient tall;
106 grid on;
107 set (gcf, 'Name', s1);
108 title('2nd Impulse EMG', 'FontSize', 14);
109 xlabel('Time [ms]');
110 ylabel('Amplitude [mV]');
111 ylabel([s2 s1]);
112 axis([-i, 3 da -height height*16]);
113 hold on;
114 for n=2:16;
115     plot(B(1,:), (D(:,19-n) + height*(n-1)));
116     set (findobj('Type','line'), 'LineWidth', 0.8);
117 end;

```

C:\Programme\FreID\Pulse edited.M
 Printed at 20:45 on 23 Apr 2008 Page 3 of 3

```

118 plot(B(L,:),C(:,1),'r');
119 set (findobj ('Type','line'),'LineWidth',0.8);
120 plot(B(L,:),C(:,2));
121 set (findobj ('Type','line'),'LineWidth',0.8);
122 &axis([-pre da -height 4]);
123 hold off;
124
125 figure;
126 orient 'tall;
127 grid on;
128 set (gcf,'Name','s1');
129 title('Double-Pulse EMG','FontSize',14);
130 xlabel('Time [ms]');
131 ylabel('Amplitude [mV]');
132 ylabel('s2 s1');
133 axis([-1.3 da -height height*1.6]);
134 hold on;
135 for n=2:16;
136   plot(B(L,:),C(:,n+1) + height*(17-n));
137   set (findobj ('Type','line'),'LineWidth',.5);
138   % pause;
139 end;
140 plot(B(L,:),C(:,2));
141 set (findobj ('Type','line'),'LineWidth',.5);
142 &pause;
143 plot(B(L,:),C(:,1),'r');
144 set (findobj ('Type','line'),'LineWidth',.5);
145 &pause;
146 &axis([-pre da -height 4]);
147 hold off;
148
149 &print
150 &cd c:\programme\matlab\work

```

C Operating and programming manual for the developed stimulation equipment (in German)

Inhaltsverzeichnis:

BESCHREIBUNG DES GERÄTES	3
ALLGEMEINE BESCHREIBUNG	3
STIMULATIONSPROGRAMME	3
BESCHREIBUNG DER BEDIENELEMENTE	4
BEHANDLUNG (DURCHFÜHRUNG DER STIMULATION)	7
ELEKTRODENANLAGE	7
GUMMIELEKTRODEN MIT ELEKTRODENTASCHEN	7
WEICHGUMMIELEKTRODEN MIT ELEKTRODENGEL	7
FIXIERUNG DER ELEKTRODEN	8
WAHL DES STIMULATIONSPROGRAMMS	8
BEHANDLUNGSENDE	8
LADEN DES ELEKTROSTIMULATIONSGERÄTES	9
PFEGE, WARTUNG VON ELEKTROSTIMULATIONSGERÄT UND ZUBEHÖR	10
WARTUNG DES ELEKTROSTIMULATIONSGERÄTES	10
REINIGUNG DES ELEKTROSTIMULATIONSGERÄTES	10
PFEGE DER ELEKTRODEN	10
PFEGE DER ELEKTRODENTASCHEN (SCHWAMMITUCH)	10
PFEGE DER BANDAGEN UND DER FIXIERGURTE	10
ELEKTRODENKABEL	10
ELEKTRODENKLEMMEN	10
PROBLEME, LÖSUNGSVORSCHLÄGE	11
RÖTUNGEN:	11
VERBRENNUNGEN:	11
SCHWACHE MUSKELKONTRAKTION:	11
KEINE BZW. UNREGELMÄßIGE MUSKELKONTRAKTION BEI VOLLER STIMULATION:	11
STROMGEFÜHL IM BAUCH-, BECKENBEREICH:	12
STIMULATIONSGERÄT LÄSST SICH NICHT EINSCHALTEN:	12
SUMMTON WÄHREND DER STIMULATION:	12
GERÄT FUNKTIONIERT NICHT:	12
ÜBERSICHT PROBLEME, LÖSUNGSVORSCHLÄGE	13



Bedienungsanleitung

Bedienungsanleitung

Seite 2 von 13

Beschreibung des Gerätes

Allgemeine Beschreibung

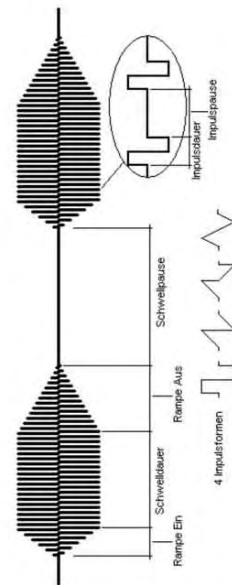
Das speziell für die Therapie denervierter Muskulatur entwickelte Elektrostimulationsgerät wird durch einen Akkumulator mit Energie versorgt. Zwei getrennte Stimulationskanäle erlauben gleichzeitiges Training von 2 verschiedenen Muskeln bzw. Muskelgruppen und damit eine Verkürzung der Gesamttherapiezeit.

Bis zu 9 verschiedene, freiprogrammierbare Stimulationsprogramme können mittels eines PDA (Personal Digital Assistant) in das Stimulationsgerät geladen werden. Ein Mikrocontroller übernimmt die Speicherung der Programme, Steuerung des Gerätes sowie die Kommunikation mit dem PDA über Infrarot-Schnittstelle (IrDA) und sorgt somit für größtmöglichen Bedienkomfort und einfache Bedienbarkeit.

Stimulationsprogramme

Nach Bedarf können bis zu 9 verschiedene Stimulationsprogramme auf den Speicherplätzen P1 – P9 abgelegt werden. Folgende Parameter können dabei entsprechend dem gewünschten Stimulationsprogramm innerhalb der angegebenen Grenzen eingestellt werden:

- Anfangsintensität Kanal 1 bei Start des Programms: 0 – 99%
- Anfangsintensität Kanal 2 bei Start des Programms: 0 – 99%
- Impulsdauer des biphasischen Stimulationsimpulses: 1,3 – 327,1ms
- Impulspause zwischen den Einzelimpulsen: 1 – 2000ms
- Impulsform: 4 verschiedene biphasische Stromformen sind möglich
- Schwelldauer: 1 – 10s
- Schwellpause: 0 – 10s
- Rampe Ein: 0 – 500ms
- Rampe Aus: 0 – 2000ms
- Programm- bzw. Stimulationsdauer: 3 – 40min



Bedienungsanleitung

Seite 3 von 13

Beschreibung der Bedienelemente

Vorderseite des Gerätes:



Rückseite des Gerätes:



- ① EIN/AUS - Schalter
- ② Sicherung
- ③ Ladebuchse
- ④ LED - Anzeige für Programm, Intensität Kanal 1 und Kanal 2, verbleibende Programmlaufzeit
- ⑤ Intensitätsregler Kanal 1 und Anschlussbuchsen Kanal 1
- ⑥ Intensitätsregler Kanal 2 und Anschlussbuchsen Kanal 2
- ⑦ Programmwahltasten
- ⑧ Taste für Programm - Neustart bzw. -Wiederaufruf
- ⑨ START/STOPP - Taste zum Aktivieren, vorübergehenden Anhalten bzw. vorzeitigen Beenden des gewählten Therapieprogramms

Bedienungsanleitung

Seite 4 von 13

Die Buchsen dienen zum Anschluss der Elektrodenkabel an den Kanal 1 des Stimulationsgerätes.

Achtung: Vor dem Start des Stimulationsprogramms immer die Zuordnung der Kabel zu den Stimulationskanälen überprüfen, um ein irrtümliches „kreuzweises“ Stimulieren zu verhindern.

⑦ Programmwahltasten

Mit den Programmwahltasten kann entsprechend der Pfeilrichtung das gewünschte Stimulationsprogramm gewählt werden. Deaktivierte Stimulationsprogramme bzw. deren Speicherplätze werden übersprungen, die Anzeige springt z.B. bei Wahl der nächsthöheren Programmnummer von „P2“ auf „P6“.

⑧ Programm – Neustart bzw. - Wiederaufruf

Mit dieser Taste kann das Stimulationsprogramm nach Ablauf der Therapiezeit neugestartet werden. Intensität und Programmdauer springen auf die programmierten Ausgangswerte zurück.

⑨ START/STOPP - Taste

Nach der Wahl des Stimulationsprogramms wird mit dieser Taste das Programm gestartet. Nochmaliges Drücken der Taste stoppt die Stimulation. Die eingestellte Stimulationsamplitude und verbleibende Restdauer bleiben gespeichert, sodass die Stimulation nach der Unterbrechung mit den vorher eingestellten Werten fortgesetzt wird.

① EIN/AUS - Schalter

In der Stellung „0“ wird das Stimulationsgerät allpolig über ein Relais vom eingebauten Akkumulator getrennt. Durch Kippen des Schalters in die Position „1“ wird das Gerät eingeschaltet. Auf der LED - Anzeige an der Vorderseite des Gerätes erscheint dann automatisch das Programm „P1“ und die programmierte Stimulationsdauer.

② Sicherung

Sollte sich das Stimulationsgerät nicht einschalten lassen und das Ladegerät nicht an der Ladebuchse des Stimulationsgerätes angeschlossen sein, kann die Ursache eine defekte Sicherung sein. In diesem Fall kann die Sicherung durch eine in Nennwert und Ausbsecharakteristik gleichwertige getauscht werden.

③ Ladebuchse

Während des Ladevorgangs kann das Elektrostimulationsgerät nicht verwendet werden, da aus Sicherheitsgründen der Akkumulator mit dem angeschlossenen Ladegerät vom Stimulationsgerät über ein Relais allpolig getrennt wird. Erst nach dem Enternen des Ladegerät-Steckers aus der Ladebuchse des Stimulationsgerätes kann die Therapie durchgeführt werden.

④ LED - Anzeige

Die LED - Anzeige zeigt je nach Betriebszustand folgende Informationen an:

- Programmnummer
- Programmdauer bzw. verbleibende Restdauer
- Intensität Kanal 1 und Kanal 2

⑤ Intensitätsregler und Anschlussbuchsen Kanal 1

Nachdem das gewünschte Stimulationsprogramm gewählt und gestartet wurde, kann mit dem Intensitätsregler die gewünschte Stimulationsamplitude für den Kanal 1 eingestellt werden. Ist das Programm angehalten oder noch nicht gestartet, hat der Regler keine Funktion. Die Buchsen dienen zum Anschluss der Elektrodenkabel an den Kanal 1 des Stimulationsgerätes.

Achtung: Vor dem Start des Stimulationsprogramms immer die Zuordnung der Kabel zu den Stimulationskanälen überprüfen, um ein irrtümliches „kreuzweises“ Stimulieren zu verhindern.

⑥ Intensitätsregler und Anschlussbuchsen Kanal 2

Nachdem das gewünschte Stimulationsprogramm gewählt und gestartet wurde, kann mit dem Intensitätsregler die gewünschte Stimulationsamplitude für den Kanal 2 eingestellt werden. Ist das Programm angehalten oder noch nicht gestartet, hat der Regler keine Funktion.

Bedienungsanleitung

Seite 5 von 13

Bedienungsanleitung

Seite 6 von 13

Behandlung (Durchführung der Stimulation)

Elektrodenanlage

Gummielektroden mit Elektrodenentaschen

Die Elektrodenaschen aus Schwamm Tuch sollen beinahe tropfnass mit der dicken Schicht (mehrjährige Seite) auf die Haut gelegt werden. Dabei ist zu beachten, dass die Öffnungen für die Elektrodenplatten voneinander abgewandt sind. Dies gewährleistet eine möglichst großflächige Verteilung des elektrischen Feldes. Die Gummielektroden vollständig in die Elektrodenaschen einschieben. Die Elektrode an den Ecken nicht knicken, da an den umgebogenen Ecken durch die erhöhte Stromdichte Verbrennungen auftreten können.



- beinahe tropfnass
- mit dicker Seite auf die Haut
- Öffnung der Elektrodenaschen möglichst weit auseinander
- vollständig in die Elektrodenasche einschieben
- keine umgebogenen Ecken oder Kanten

Weichgummielektroden mit Elektrodengel

Elektrodengel gleichmäßig über die gesamte Fläche der Elektrode auftragen und diese auf die Haut auflegen. Danach möglichst nicht mehr auf der Haut verschieben und mittels Bandagen oder elastischer Fixiergurte befestigen.



- ausreichend Elektrodengel auftragen
- gesamte Fläche der Elektrode bestreichen

Bedienungsanleitung

Seite 7 von 13

Fixierung der Elektroden

Jede Elektrode einzeln mit einer Bandage oder einem elastischen Fixiergurt mit Klettverschluss, welcher die gesamte Elektrodenfläche bedeckt, befestigen. Dabei auf einen möglichst gleichmäßigen Anlegedruck achten. Einzelne deshalb, damit ein elektrischer Nebenschluss durch feuchte Bandagen ausgeschlossen wird (Verminderung der Wirksamkeit der Therapie!).



Achtung: in der Bandage dürfen keine metallischen Fäden mitverwoben sein – Verbrennungsgefahr!

- Elektroden einzeln befestigen
- gleichmäßiger Anlegedruck

Wahl des Stimulationsprogramms

Nachdem die Elektroden angelegt und an das Stimulationsgerät angeschlossen wurden, kann das entsprechende Stimulationsprogramm mit den Programmwahltasten gewählt werden. Mit der START/STOPP - Taste wird danach das Programm aktiviert und die gewünschte Behandlungsintensität mit den Reglern für Kanal 1 und Kanal 2 eingestellt. Die Stimulation kann jederzeit durch nochmaliges Drücken der START/STOPP - Taste unterbrochen werden. Die vorher eingestellte Stimulationsamplitude und die verbleibende restliche Behandlungsdauer bleiben dabei gespeichert. Soll die Stimulation komplett neu gestartet werden, ist dies mit der Taste für Programm - Neustart bzw. -Wiederaufruf möglich.

Behandlungsende

Nach Ablauf der voreingestellten Programmdauer wird das Stimulationsprogramm gestoppt. Ist ein vorzeitiges Ende der Therapie gewünscht, so kann das laufende Programm jederzeit mit der START/STOPP - Taste angehalten werden.

Bedienungsanleitung

Seite 8 von 13

Laden des Elektrostimulationsgerätes

Je nach verordnetem Trainingsprogramm können mit dem Stimulationsgerät 1 – 2 (max. 3) Trainingseinheiten durchgeführt werden. Ein Summtot signalisiert die zu Ende gehende Kapazität des Akkumulators. Zum Laden wird das mitgelieferte Ladegerät an die Ladebuchse auf der Rückseite des Stimulationsgerätes angeschlossen. Eine zuerst blinkende, dann dauernd rot leuchtende LED (Leuchtdiode) auf dem Ladegerät zeigt den Ladevorgang an. Nach Abschluss des Ladevorgangs schaltet das Ladegerät automatisch auf Erhaltungsladung um (grüne Leuchtdiode). Ein Überladen des Elektrotherapiegeräts ist mit dem mitgelieferten Ladegerät nicht möglich. Ungefähr einmal pro Monat sollte der Akkumulator vor dem Wiederaufladen vollständig entleert werden. Dazu muss die rote Taste am Ladegerät gedrückt und solange gehalten werden bis die rote LED zu blinken beginnt. Nach der vollständigen Entladung des Akkumulators wird der Ladevorgang automatisch gestartet.

Achtung: Während des Ladevorgangs kann das Elektrostimulationsgerät nicht verwendet werden!

Pflege, Wartung von Elektrostimulationsgerät und Zubehör

Wartung des Elektrostimulationsgerätes

Das Gerät hat keine durch den Anwender zu wartende Teile. Im Falle von Fehlfunktionen ist die Wartung oder Reparatur nur durch das zuständige Fachpersonal zulässig.

Reinigung des Elektrostimulationsgerätes

Das Gerät wird mit einem trockenen oder leicht feuchten Tuch außen abgewischt. Keinesfalls nass abwaschen oder Reinigungsmittel verwenden.

Achtung: Eingedrungenes Wasser kann einen Kurzschluss verursachen.

Pflege der Elektroden

Die Gummielektroden werden nach Gebrauch mit lauwarmem Wasser abgespült, ohne daran zu reiben (Graphitverlust bedeutet erhöhten Widerstand). Danach diese zum Trocknen auflegen oder mit einem Tuch bzw. einer Küchenrolle abtupfen.

Pflege der Elektrodentaschen (Schwammtuch)

Die Elektrodentaschen werden nach jedem Gebrauch ebenfalls in warmem Wasser ausgespült. Einmal pro Woche sollten diese bei 60° C in der Waschmaschine mit etwas Waschpulver gereinigt werden.

Pflege der Bandagen und der Fixiergurte

Die Bandagen oder Fixiergurte ebenfalls zumindest einmal pro Woche ausspülen oder waschen und regelmäßig austauschen.

Elektrodenkabel

Elektrodenkabel nie knicken, nicht dehnen und nach Gebrauch nicht zu straff bzw. über scharfe Kanten aufwickeln. Regelmäßige Kontrolle, ob Schäden an der Isolation der Kabel vorhanden sind. Ist dies der Fall, Kabel durch neue ersetzen.

Elektrodenklemmen

Die Klemmen sollten regelmäßig gereinigt werden, da verschmutzte Elektrodenklemmen den Übergangswiderstand dramatisch erhöhen. Dies führt zu einer Reduktion der Wirksamkeit der Therapie (sehr schwache Muskelkontraktion). Bei starker, hartnäckiger Verschmutzung (dunkler Belag durch Gelereste etc.) auf den Metallteilen der Elektrodenklemmen, diese mit Stahlwolle oder ähnlichem entfernen.

Probleme, Lösungsvorschläge

Rötungen:

Eine gleichmäßige Rötung der Haut unter den Elektroden ist normal (gesteigerte Durchblutung) und verschwindet nach einigen Stunden wieder. Tritt die Rötung unregelmäßig (z.B. punktförmig) auf, muss sie im weiteren Verlauf genau beobachtet werden. Bleiben die Hautveränderungen bestehen, sollte Kontakt mit dem betreuenden Arzt aufgenommen werden.

Verbrennungen:

Auf Grund der fehlenden Sensibilität in den Beinen kann eine unsachgemäße Elektrodenanlage zu hohen lokalen Stromdichten führen und eine Verbrennung der Haut hervorrufen.

Punktförmige Verbrennungen werden trocken behandelt. Damit eine weitere Stimulation möglich ist, wird die betroffene Stelle während jeder Strombehandlung mit Zinkpaste und kleinen Silikon-Gummiplättchen isoliert. Erst nach völliger Abheilung (nach ca. 2 - 4 Wochen) kann wieder ohne Isolierung stimuliert werden.

Größere Verbrennungen müssen vom Arzt behandelt werden. Die Stimulation muss in diesem Fall ausgesetzt werden.

Mit zunehmender Stimulationsdauer (2 - 3 Monate) adaptiert sich die Haut an die Elektrostimulation und das Risiko einer Verbrennung nimmt in der Regel deutlich ab. Nach ca. 4 - 5 Monaten treten solche Verbrennungen nur mehr bei unsachgemäßer Handhabung der Stimulationselektroden auf.

Schwache Muskelkontraktion:

Bei zu starker Muskelermüdung bzw. Überbeanspruchung kann es zu einem Abnehmen der Muskelkontraktionsstärke kommen. Grund dafür können zu hohe Wiederholungszahlen oder Serienzahlen, zu hohe Zusatzgewichte, zu kurze Serienpausen oder zu intensives Wochentrainingsprogramm sein. Eine ungünstige Körperhaltung während der Stimulation kann Ursache für schwache Kontraktion der stimulierten Muskulatur sein. In all diesen Fällen muss Kontakt mit dem betreuenden Arzt aufgenommen werden, der eine Adaptierung des Stimulationstrainings vornimmt.

Bei Auftreten von Krankheiten, die das allgemeine Wohlbefinden deutlich beeinträchtigen (z. B. grippaler Infekt), soll die Elektrostimulation ausgesetzt werden und Kontakt mit dem betreuenden Arzt aufgenommen werden.

Keine bzw. unregelmäßige Muskelkontraktion bei voller Stimulation:

Bei voller Stimulation erfolgt keine oder nur schwache Muskelreaktion, wenn in der Kabelverbindung ein Fehler aufgetreten ist. D. h., es kann entweder das Kabel am Stimulationsgerät nicht richtig angesteckt sein oder an der Elektrode nicht richtig angeklebmt sein bzw. kann ein Kabelbruch (Wackelkontakt) vorliegen.

Wenn sich die Elektroden oder die Elektrodenaschen berühren, kann es zu einem Kurzschluss kommen. Vor Simulationsbeginn muss daher auf die korrekte Positionierung der Elektroden oder der Elektrodenaschen geachtet werden.

Bedienungsanleitung

Seite 11 von 13

Eine weitere Ursache für eine schwache Muskelkontraktion kann ein zu hoher Übergangswiderstand sein. Dieser kann durch eine Verschmutzung der Elektrodenklammern (Elektrodenabrieb und Gelereste) bedingt sein, aber auch durch eine Verunreinigung des Schwammtuches durch Hautschuppen, Fett und die mikrobielle Flora der Haut sowie durch einen Verschluss der Elektrodenaschen.

Der Übergangswiderstand kann auch durch mangelnde Feuchtigkeit der Elektrodenaschen oder Verwendung von zu wenig Elektrodengel erhöht werden. Auch die Anwendung einer fetthaltigen Creme vor der Elektrostimulation steigert den Hautwiderstand.

Diese Probleme können vermieden werden, wenn folgendes beachtet wird:

Die Klemmen sollen regelmäßig kontrolliert werden und bei Bedarf mit Stahlwolle oder ähnlichem gereinigt werden.

Eine Verschmutzung des Schwammtuches kann durch Ausspülen nach der Stimulation sowie regelmäßiges Waschen in der Waschmaschine vermieden werden. Weiters sollen die Elektrodenaschen in regelmäßigen Abständen erneuert werden. Die Elektrodenaschen müssen ausreichend befeuchtet werden (tropfnaß), bei Verwendung von Gelelektroden muss genügend Gel aufgetragen werden.

Die Haut über der zu stimulierenden Muskulatur soll vor dem Training gereinigt und entfettet werden.

Stromgefühl im Bauch-, Beckenbereich:

Kommt es zu einem Auftreten von Stromgefühl im Bauch-, Beckenbereich während der Stimulation ist es zu einem „gekreuzten“ Anstecken der Elektrodenkabel am Stimulationsgerät gekommen.

Vor Beginn der Stimulation soll daher immer die korrekte Zuordnung der Kabel zu den Stimulationskanälen überprüft werden.

Stimulationsgerät lässt sich nicht einschalten:

Dieses Problem kann auftreten, wenn das Ladegerät noch an der Leadebuchse angesteckt ist, die Sicherung defekt ist oder der Akkumulator vollständig entladen ist. Je nach Ursache muss das Ladegerät vom Stimulationsgerät abgesteckt werden, die Sicherung getauscht werden oder das Gerät aufgeladen werden.

Sumnton während der Stimulation:

In diesem Fall ist der Akkumulator fast vollständig entladen und muss mittels Ladegerät aufgeladen werden.

Gerät funktioniert nicht:

Sollte das Gerät aus einem für den Anwender nicht ersichtlichen Grund nicht ordnungsgemäß funktionieren (alle oben angeführten möglichen Fehlerursachen ausgeschlossen), so muss Kontakt mit dem technischen Fachpersonal aufgenommen werden.

Bedienungsanleitung

Seite 12 von 13

Übersicht Probleme, Lösungsvorschläge

PROBLEM	MÖGLICHE URSACHEN	LÖSUNG
Verbrennungen	unsachgemäße Elektrodenanlage	Elektrodenplatten ganz in die Elektrodenaschen einschieben Elektrodenaschen ausreichend befeuchten (Tropfpass) ausreichend Elektrodengel auftragen gleichmäßiger Anlagerück der gesamten Elektrode Kontrolle der Elektroden in den Elektrodenaschen Bandagen ohne metallische Fäden verwenden bei größeren Verbrennungen Kontrolle durch den Betreuenden Arzt regelmäßiges Austausche der Elektrodenaschen
keine, schwache bzw. unregelmäßige Muskelkontraktion bei voller Stimulation	zu dünne, verschlissene Elektrodenaschen zu starke Muskelermüdung bzw. Überbeanspruchung ungünstige Körperhaltung während der Stimulation Krankheiten (Grippe, sonstige Infektionen, ...) Fehler bei Kabelverbindungen Elektrodenaschen berühren sich stark verschmutzte Elektrodenklemme Elektrodenaschen sind stark verschmutzt Elektrodenaschen sind verschlissen Elektrodenaschen zu wenig feucht zu wenig Elektrodengel verbrauchte Gummielektroden Haut vor der Therapie zu fett eingecremt	Rücksprache mit dem betreuenden Arzt Rücksprache mit dem betreuenden Arzt Aussetzen der Elektrostimulation, Kontaktaufnahme mit dem betreuenden Arzt Kontrolle der Kabelverbindung mit dem Stimulationsgerät bzw. den Elektroden Kabelbruch Kontrolle der Elektrodenanlage vor Start des Stimulationsprogramms regelmäßige Kontrolle der Klemmen bei Bedarf Reinigung mit Stahlwolle oder ähnlichem Auspülen der Taschen nach der Stimulation, 1x wöchentlich waschen regelmäßiges Austauschen der Elektrodenaschen Elektrodenaschen beinahe tropfpass verwenden ausreichend Elektrodengel auftragen Elektroden gegen neue austauschen Elektroden auf gereinigte, entfettete Haut legen
Stromgefühl im Bauch-, Beckenbereich Stimulationsgerät lässt sich nicht einschalten Summton während der Stimulation Gerät funktioniert nicht	falsche "gekreuzte" Zuordnung der Stimulationskanäle Ladegerät an der Ladebuchse angesteckt Sicherung defekt Akkumulator vollständig entladen Akkumulator fast leer technisches Problem im Gerät	Kontrolle der Zuordnung der Kabel zu den Stimulationskanälen Ladegerät vom Stimulationsgerät abstecken Sicherung tauschen Akkumulator aufladen Stimulationsgerät vor dem Training aufladen Rücksprache mit techn. Fachpersonal

Bedienungsanleitung

Seite 13 von 13

Inhaltsverzeichnis:

BESCHREIBUNG DES KONZEPTS	3
DIE STIMULATIONSPARAMETER IM ÜBERBLICK	3
PROGRAMMIERUNG DES ELEKTROSTIMULATIONSGERÄTES	4
LESEN DER IM ELEKTROSTIMULATIONSGERÄT GESPEICHERTEN PROGRAMME	7
ZUSÄTZLICHE FUNKTIONEN: DATUM, UHRZEIT, PROTOKOLL	8
LESEN UND SETZEN DES DATUMS UND DER UHRZEIT IM STIMULATIONSGERÄT	8
ABRUFEN UND LÖSCHEN DES STIMULATIONSPROTOKOLLS	9
FEHLERMELDUNGEN	10



Programmieranleitung

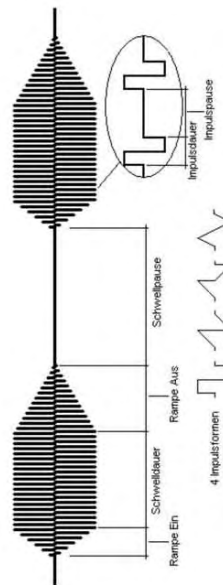
Programmieranleitung

Seite 2 von 10

Beschreibung des Konzepts

Die Programmierung der Elektrostimulationsgeräte erfolgt mit Hilfe einer auf dem Palm-OS Betriebssystem basierenden Software. Der Vorteil ist die einfache, intuitiv zu bedienende Benutzeroberfläche und die hohe Mobilität, da kein Personal-Computer oder Notebook für die Programmierung der Geräte notwendig ist. Durch die Kommunikation mittels Infrarot-Schnittstelle ist zwischen dem PDA (Personal Digital Assistant) und dem Elektrotherapiegerät keine elektrisch leitende Verbindung notwendig.

Die Stimulationsparameter im Überblick



Programmierung des Elektrostimulationsgerätes

1. Elektrostimulationsgerät einschalten (Kippschalter auf der Rückseite). Sollte sich das Gerät nicht einschalten lassen, kontrollieren, ob das Ladegerät angesteckt oder die Sicherung defekt ist.
2. Zur Aktivierung der Infrarot-Schnittstelle im Elektrostimulationsgerät den Stabmagneten über der Anzeige für das Stimulationsprogramm auf das Gerät legen.

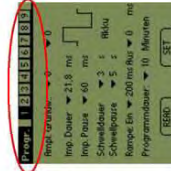


3. PDA Einschalten



4. Programm „DenStim“ auf dem PDA starten

5. In der Benutzeroberfläche des Programms den gewünschten Programmspeicherplatz für das zu speichernde Programm wählen (1-9)



6. Die Parameter des Programms einstellen:

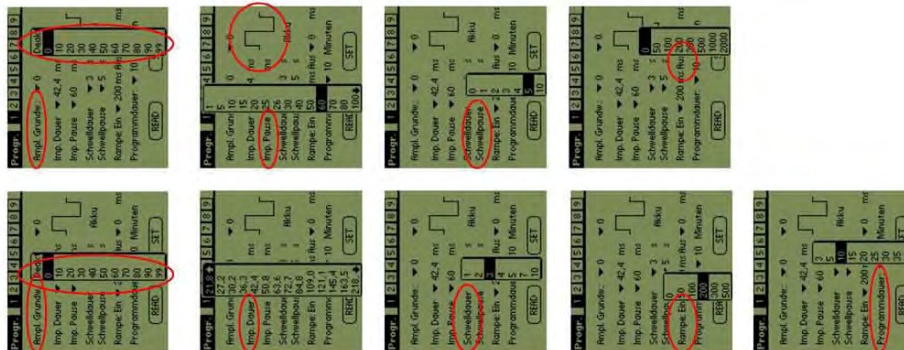
Grundwert der Amplitude für Kanal 1 und Kanal 2 einstellen bzw. den Stimulationskanal deaktivieren, wenn nur 1 Kanal verwendet werden soll oder beide Kanäle deaktivieren, um das gewählte Programm am Stimulationsgerät zu deaktivieren.

Impulsdauer und Impulspause wählen und durch mehrmaliges Tippen auf die grafische Darstellung des Stimulationsimpulses die Impulsform festlegen.

Die Schwelldauer („Burst-Dauer“) und die Schwellpause (Zeitdauer zwischen den Bursts) einstellen.

Die Rampe am Anfang („Rampe Ein“) und am Ende der Schwellung („Rampe Aus“) wählen.

Die Simulationszeit („Programmdauer“) einstellen.



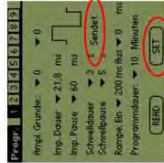
Seite 5 von 10

Programmieranleitung

7. Programm auf das Elektrostimulationsgerät übertragen
Die Schaltfläche „SET“ auf der Benutzeroberfläche des Programms antippen und den PDA in Richtung der Anzeige des Programmspeicherplatzes halten.

Achtung: Es muss eine Sichtverbindung zwischen den Infrarot-Schnittstellen auf dem PDA und dem Stimulationsgerät bestehen.

Auf dem Bildschirm des PDA erscheint statt dem Stimulationsgerättyp („Akku“ oder „Netz“) die Meldung „Sendet“ und die Anzahl der Übertragungsversuche (max. 3 Versuche). Nachdem das Programm gespeichert wurde, springt die Anzeige (am PDA) wieder zurück und zeigt den Typ des Stimulationsgerät an. Ist die Übertragung nicht erfolgreich, so erscheint eine Fehlermeldung.



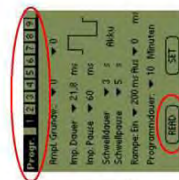
Nach erfolgreicher Übertragung des Programms erscheint am Stimulationsgerät der entsprechende Programmspeicherplatz und die gewählte Simulationsdauer. Wird ein Programm übertragen während der Patient stimuliert, wird das laufende Programm angehalten und das soeben gespeicherte Programm auf der LED-Anzeige angezeigt.

Programmieranleitung

Seite 6 von 10

Lesen der im Elektrostimulationsgerät gespeicherten Programme

1. Elektrostimulationsgerät einschalten (Kippschalter auf der Rückseite). Sollte sich das Gerät nicht einschalten lassen, kontrollieren, ob das Ladegerät angesteckt oder die Sicherung defekt ist.
2. Zur Aktivierung der Infrarot-Schnittstelle im Elektrostimulationsgerät den Stabmagneten über der Anzeige für das Stimulationsprogramm auf das Gerät legen.
3. PDA Einschalten
4. Programm „DenStim“ auf dem PDA starten
5. In der Benutzeroberfläche der Anwendung den gewünschten Programmspeicherplatz für das zu lesende Programm wählen (1-9)
6. Programm lesen
Die Schaltfläche „READ“ auf der Benutzeroberfläche des Programms antippen und den PDA in Richtung der Anzeige des Programmspeicherplatzes halten.

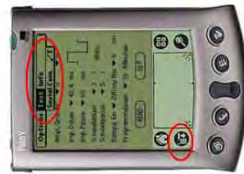


Achtung: Es muss eine Sichtverbindung zwischen den Infrarot-Schnittstellen auf dem PDA und dem Stimulationsgerät bestehen.

Nachdem das Programm gelesen wurde, springt die Anzeige (am PDA) um und zeigt die im Elektrostimulationsgerät gespeicherten Parameter des ausgelesenen Programmspeicherplatzes an. Ist die Übertragung nicht erfolgreich, so erscheint eine Fehlermeldung.

Nachdem das Programm ausgelesen wurde, erscheint am Stimulationsgerät der entsprechende Programmspeicherplatz und die Stimulationsdauer für dieses Programm. Wird ein Programm gelesen während der Patient stimuliert, wird das laufende Programm angehalten und das soeben ausgelesene Programm auf der LED-Anzeige angezeigt.

Zusätzliche Funktionen: Datum, Uhrzeit, Protokoll



Benutzeroberfläche für die zusätzlichen Funktionen im Stimulationsgerät über das Menü „Test“ aufrufen. Auswählen der Schaltleiste „Serial Com.“ im Display erscheint dann eine Zeile zur Eingabe der Befehle und ein mehrzeiliges Textfeld für die Anzeige der vom Stimulationsgerät gesendeten Daten.



Lesen und Setzen des Datums und der Uhrzeit im Stimulationsgerät

In der Befehlszeile den Kleinbuchstaben „u“ für Uhrzeit eingeben und auf die Schaltfläche „SEND“ tippen. Im Testfeld erscheint nach erfolgreicher Übertragung des Befehles das im Stimulationsgerät eingestellte Datum und die Uhrzeit.



Anzeigeformat: MM/TT hh:mm:ss

Zum Setzen des Datums und der Uhrzeit in der Befehlszeile den Großbuchstaben „U“ gefolgt vom zu setzenden Datum und der Uhrzeit (z.B.: U0721135700 für den 21. Juli Uhrzeit: 13:57:00). Hier erfolgt keine Rückmeldung vom Stimulationsgerät nach dem Übertragen der Daten mit der Schaltfläche „SEND“, um das gesetzte Datum und die Uhrzeit zu kontrollieren, müssen die Daten wie oben beschrieben gelesen werden.



Abrufen und Löschen des Stimulationsprotokolls

Zum Abrufen des im Stimulationsgerät gespeicherten Stimulationsprotokolls den Großbuchstaben „R“ in der Befehlszeile eingeben und auf die Schaltflächen „SEND“ tippen. Im Textfeld erscheint dann das im Stimulationsgerät gespeicherte Protokoll.

Achtung: Die Übertragung kann je nach Umfang des gespeicherten Protokolls lange dauern. Während dieser Zeit können keine weiteren Befehle zum Stimulationsgerät gesendet werden.



Soll das Protokoll im Stimulationsgerät gelöscht werden den Großbuchstaben „S“ in der Befehlszeile eingeben und auf die Schaltflächen „SEND“ tippen. Im Textfeld erscheint hier keine Rückmeldung vom Stimulationsgerät. Zur Bestätigung der Löschung des Protokolls, Daten wie oben beschrieben auslesen.



Anzeigeformat der Protokollmeldungen

Einschalten des Elektrostimulationsgerätes:

MM/TT hh:mm:ss RESET

Start des Stimulationsprogramms mit der Nr. „X“ (1-9):

MM/TT hh:mm:ss PROGRAMM X

Anhalten bzw. Beenden des Stimulationsprogramms:

MM/TT hh:mm:ss STOP

Neu Programmierung eines Stimulationsprogrammes:

MM/TT hh:mm:ss NEU PROGRAMMIERUNG

Programmieranleitung

Seite 9 von 10

Fehlermeldungen

Ist keine Übertragung über die Infrarot-Schnittstelle möglich bzw. sind die übertragenen Daten nicht vollständig, so erscheint am Display des PDA die Fehlermeldung „Data not transmitted!“.

Sichtverbindung zwischen den Infrarot-Schnittstellen muss bestehen. Optimale Distanz (ca. 30 – 50cm) für die Datenübertragung zwischen PDA und Stimulationsgerät einhalten.



Wenn nach 3 Versuchen das Stimulationsprogramm nicht fehlerfrei zum Elektrostimulationsgerät übertragen wurde, erscheint am Display des PDA die Fehlermeldung „Program was not correct transmitted! Please try again“. In diesem Fall ist die Kommunikation zwischen PDA und Elektrostimulationsgerät möglich, doch wird die Datenübertragung durch eine andere Infrarotstrahlung emittierende Quelle gestört.

Versuch, die Übertragungsstrecke zwischen PDA und Stimulationsgerät gegen die Störstrahlung abzuschirmen.



Achtung: Bei den zusätzlichen Funktionen, welche über die Benutzeroberfläche „SerialCom Test“ aufgerufen werden, erfolgt keine Kontrolle der Datenübertragung.

Programmieranleitung

Seite 10 von 10

Curriculum vitae

- **Personal data**

Christian Hofer

Born: July 18th, 1968, Vienna, Austria

Citizenship: Austria

- **Education, academic and professional background**

Polytechnical College (HTBLVA Wien 20, TGM), 1982-1987.

Civil Service, 1987 –1988.

Studies of Electrical Engineering and Electronics, University of Technology Vienna, 1988 – 1995.

Diploma Thesis at the Institute of Control and Industrial Electronics in cooperation with the Institute of Biomedical Engineering and Physics of the Medical University of Vienna, 1995.

Title: „Entwicklung eines Stimulators zur funktionellen Elektrostimulation der gelähmten Hand“

Graduation (passed with distinction): 1995.

Research collaborator at the Ludwig Boltzmann Institute for Electrical Stimulation and Physical Rehabilitation, Institute of Physical Medicine and Rehabilitation, Wilhelminenspital Vienna, since 1995.

Participated in the design and execution of several national and international research projects among 3 projects funded by the European Commission.

Reviewer for Artificial Organs, since 2005.

- **Scientific publications**

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