The European FP5-project RISE: FES of denervated degenerated musculature

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Abstract
It was and rather commonly still is general believe that restoration of denervated degenerated musculature (DDM) or even slowing down the muscular atrophy and the degeneration process after denervation is impossible. In contrast to this believe recent experimental and clinical work gives strong evidence that functional electrical stimulation (FES) is a powerful tool for regeneration, functional restoration and maintenance of denervated muscles.

Based on these promising preliminary findings the European project RISE was established within the 5th Framework Program to develop an efficient rehabilitation method and the associated technical equipment for the treatment of flaccid paraplegia. The project started with November 2001, has a lifetime of 4 years and includes 10 primary contractors, 3 additional contractors and 6 subcontractors from Austria, UK, Italy, Germany, Slovenia and Island.

The experimental and clinical results acquired so far have confirmed the sustained regenerative and myogenetic capacity of DDM even after denervation periods of more than 10 years. Restoration of heavily degenerated musculature requires years of daily training with biphasic long duration impulses, initially with durations of up to 300 ms, later gradually reduced to 30 - 40 ms. For post denervation time spans of less than about 2 years the dominant mechanism of muscle wasting is obviously atrophy and functional restoration of the musculature is significantly easier and less time consuming. The studies within RISE are ongoing and final results will be available with the end of 2005.

1 Introduction
Practically all established clinical FES applications are based on direct excitation of neural structures and in case of muscle functions indirect activation of the muscles. For the functional activation of denervated and especially denervated degenerated muscles (DDM) the technical requirements differ substantially from those for nerve stimulation. Due to the absence of the neuromuscular junction and decomposition of motor units muscular contractions can only be elicited by depolarizing the cellular membrane of each single muscle fiber. The electrical membrane excitability strongly depends on the state of degeneration or restoration of the muscle cell, but in any case it is much lower than the excitability of a nerve cell.

As we know from preliminary experimental and clinical work, biphasic rectangular impulses with durations between 30 and 300 ms - the later in case of long term denervation and severe degeneration - have to be applied in order to achieve contractions in DDM. Consequently also the required amplitude values are significantly higher than for comparable nerve stimulation. The recruitment of a sufficient fiber population is depending on a homogeneously distributed electrical field more or less concentrated on the target muscle. The later condition is essential to minimize unwanted co-contractions of adjacent other muscles and intact neural structures in the adjacent tissue. Biphasic rectangular impulses are obviously the most efficient impulse shape for FES of DDM. In selected cases biphasic ramp-shaped impulses are advantageous that are less efficient in force development, but provide a significantly reduced excitation of neural structures lying within the stimulating electric field.
A severe problem that strongly inhibits the application of FES on denervated muscles lies in the current EU regulations for stimulators that limit the output energy to 300 mJ per impulse. This is by far not enough to elicit functionally usable contractions in denervated muscles, unless they are very small and not degenerated. To induce strong fused contractions is in addition to functional aspects not at least an important condition for an efficient muscle training.

The first real functional application on FES of denervated muscles was published by Valencic et. al. in 1986. He has demonstrated correction of dropped foot by stimulating the denervated tibialis anterior muscle in a patient study [1].

Based on the results from an extensive experimental study on sheep [2,3], where implanted electrodes were used, and very promising preliminary clinical results with surface electrode based FES [4,5] we have successfully applied for the EU-project RISE: “Use of electrical stimulation to restore standing in paraplegics with long-term denervated degenerated muscles” that started with November 2001.

2 Methods

The target patient group is the population of persons with flaccid paraplegia. This kind of paralysis is caused by a lesion in the region of the cauda equina, the lowest part of the spinal column. In this case the lowest part of the spinal cord respectively the originating spinal roots are concerned and the resulting damage of the lower motor neuron leads to a denervation of the more or less entire lower extremity musculature. Such an injury concerns about 20 persons per million EU citizens every year, about one third of all spinal cord injuries that result in paraplegia.

The objectives of RISE are

1) Development of a new efficient rehabilitation method for the target patient group, transferable to clinical practice

2) Development of the associated stimulation equipment for home based training, and test and measurement equipment for outpatient supervision, ready for transfer to industry

3) Establishing a firm scientific basis for adaptation of the EU regulation for stimulation equipment to the needs of FES of denervated musculature.

The project work is organized in 5 work packages:

Workpackages 1 is an experimental study on rabbits that aims in determination of save and efficient stimulation and training parameters first for restoring DDM and in a later phase for maintaining the restored muscle. The work is carried out by Stanley Salmons and his group in Liverpool, UK.

Workpackage 2 is a study on pigs under the responsibility of Werner Girsch in Vienna, Austria. It is dedicated to a transformation of the findings from the rabbit study to a bigger species with a musculature that is better comparable to the human one. In addition the pig provides the opportunity to test surface electrode based patient stimulation equipment under realistic conditions.

Workpackages 3 und 4 are dedicated to technical development of patient stimulation equipment for home based training respectively test and measurement equipment for patient supervision by an outpatient clinic. The development work is performed in Vienna, Austria by Winfried Mayr and colleagues.

Workpackage 5 is a patient study on application of FES in persons with a lesion in the cauda equina that results in a complete flaccid paraplegia. Helmut Kern is responsible for this study that involves 9 clinical centers in Austria, Germany, Italy and Island. Special main topics within this workpackage concern muscle physiology with research focused on muscle regeneration and myogenesis by Ugo Carraro, Padova, Italy and on metabolic capacity by Helmut Gruber, Vienna, Austria, and the development of a comprehensive neurological assessment protocol by Milan Dimitrijevic, Ljubljana Slovenia.

The project RISE is coordinated by the first author of this paper.

3 Results

After passing the Mid-term Review we are now in the second half of the RISE project. We have obtained many preliminary but in most of the tasks of course not yet the final results. Especially all three studies are still under way. Initially we had some unexpected delay in
obtaining the animal licenses due to new tightened regulations.

In the rabbit study we had a pilot study with 20 rabbits to obtain basic data for development of stimulation and measurement hardware and the experimental methodology. In addition to a bench stimulator and a dynamometer for the final assessments a battery powered single channel stimulator with a wireless control and programming link was developed. It is capable of delivering biphasic rectangular constant current impulses with up to +/- 10mA and impulse durations between 0,5 and 80ms per phase. The epifascial electrodes for the tibialis anterior muscle and cables are made of stainless steel and silicone. Meanwhile 50 stimulators were implanted. The time course of chronaxy after denervation for up to 36 weeks has been determined and several series applying different stimulation protocols have been started.

In the pig study we have denervation of the tibialis anterior in five animals and are in the phase of determining the time course of denervation with electrophysiological measurements and biopsy analysis for this model.

In the patient study 25 persons out of 93 meeting the inclusion criteria were selected for the study. Following the developed assessment protocol primary electrophysiological, biomechanical and biopsy data were obtained and therapy with a standardized stimulation protocol was started. In a pilot phase data - including biopsy data - were obtained from pre-RISE patients with different state of muscle degeneration and FES induced restoration.

Within the technology workpackages the first generation of stimulation equipment for patients was developed: It is a dual channel version programmed by a Palm PDA via infrared link and powered by rechargeable batteries. It is capable of delivering biphasic impulses of various shapes with amplitudes of up to +/-80V and lengths of up to 150ms per phase. For save and comfortable electrode application we work on electrode garments with integrated electrodes and cables that have to be made in such a way that the user is able to handle them when sitting in a wheel chair. To obtain valid data from even very far degenerated musculature new measurement techniques had to be developed. A pendulum test measures resistance data under different intensities of stimulation even if no muscle reaction is palpable. A twitch sensor applied at the patella tendon provides exact dynamic time constants of quadriceps twitches independently of unavoidable stimulus intensity dependant co-contractions of the antagonist hamstring muscles.

4 Discussion and Conclusions

The experimental and clinical results acquired so far have confirmed the sustained regenerative and myogenetic capacity of DDM even after denervation periods of more than 10 years. Restoration of heavily degenerated musculature requires years of daily training with biphasic long duration impulses, initially with durations of up to 300 ms, later gradually reduced to 30 - 40 ms. For post denervation time spans of less than about 2 years the dominant mechanism of muscle wasting is obviously atrophy and functional restoration of the musculature is significantly easier and less time consuming.

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References

Acknowledgements