EDITORIAL

Electrical stimulation to restore function of denervated muscles

A young female sustained lumbar spine fracture in a car accident, resulting in a complete cauda equina lesion with flaccid paraplegia from L2. Her neurologist, puzzled by the finding that the patient was continent for urine, using manual pressure to empty her bladder, referred her for urethral sphincter EMG. Two years after the injury, her urethral sphincter muscle showed massive spontaneous activity in the form of high frequency complex repetitive discharges (CRDs), with many action potentials of unusually high amplitude. Similarly, occasional patients with clinical paralysis of a muscle due to long-standing root or ventral horn lesion may present with astonishingly well preserved muscle bulk and some kind of »tone«. Again, EMG of the affected muscle shows massive high frequency CRDs of high amplitude. CRDs have been demonstrated to be based on mutual electrical stimulation of adjacent denervated muscle fibers by their neighbors' action potentials at discrete low threshold sites, often through complex intramuscular circuits [1]. The long lasting high frequency discharges apparently induce work hypertrophy, evidenced by the high action potential amplitudes and preserved muscle bulk.

Such clinical observations in chronic denervation represent a rare exception to the rule of flaccid weakness and progressive atrophy. Although based on insufficiently understood mechanisms, they nevertheless lend support to the expectation that volume of denervated muscles may be restored and some useful function regained by appropriate electrical stimulation.

In this volume, dedicated to functional electrical stimulation (FES) of denervated muscle, *Bruce Carlsson* and colleagues review the cascade of events occurring in denervated muscle. The series of changes have been well established by a number of morphological, electrophysiological and histochemical studies. Some months after denervation, the muscle starts to progressively lose its capacity to restore upon reinnervation. Although chronic electrical stimulation successfully preserved volume and force of experimentally denervated muscle, this did not appear to improve the outcome of reinnervation compared to non-stimulated denervated muscle – an observation that helps maintain controversy on the benefit of electrical stimulation.

As shown by the study of *Ronald Roy* and colleagues, the ratio between the muscle tissue and the interfibre connective tissue remained unchanged in work hypertrophy, but it decreased in denervation and inactivity atrophy, due to selective loss of muscle substance.

The paper by *Ugo Carraro* presents a comprehensive review of the present knowledge of different processes occurring in the denervated muscle, pertinent to the present clinical trial of FES. In animal models, electrical stimulation even late after denervation remarkably restored volume and muscle force, although completeness of denervation appeared questionable in some studies. Also in human patients with longstanding denervation, FES was reported to produce functionally useful limb movements. It improved trophism and function of the muscles as well as of other tissues of the affected limb. It seems that at least part of the effect is based on functional maturation of regenerated muscle fibers. If ways were found to enhance myogenesis, it should be possible to achieve functional recovery with FES considerably sooner. At any rate, both experimental and clinical evidence suggests that FES has the potential to evolve into a useful clinical method for a selected category of patients.

One of the problems with FES for denervated muscles is the need for special stimuli, bipolar pulses of long duration (several tens or hundreds of milliseconds) and rather high amplitudes (up to 100-200 mA), which may be unpleasant for patients with preserved sensation, may cause tissue damage and may present other hazards. In my own experience with intramuscular (extracellular) microstimulation in human patients (used with single fiber EMG), the threshold for direct muscle fiber stimulation was often close to that of its motor axon, i.e. 0.1-5 mA at a pulse duration of just 20-50 μs. Denervated muscle fibers needed slightly stronger stimuli, however, also their threshold is often low, especially so at discrete sites along their length [1, 2]. Proximity of the stimulating electrodes to the muscle fibers however is essential. Development of implantable electrodes – an elegant solution for nerve stimulation in normally innervated muscle – unfortunately seems difficult with present technology, if the stimulus is to reach most muscle fibers in a large muscle without unacceptable size or damaging current densities close to the electrodes.

The present state of the art regarding the technological solutions in FES for denervated muscles, mainly the requirements regarding the stimulus and the electrodes for surface and implantable stimulators, is discussed by *Winfried Mayr* and colleagues.

Thomas Mokrusch, using denervated tibialis anterior and the flexor digitorum sublimis muscles of rabbit, established MRI criteria to follow up stimulation induced changes. T2 relaxation time was seen to correlate to stimulation induced changes. MRI seems to be a promising noninvasive method to monitor the efficiency of the FES in clinical setting.

The study by *Katia Rossini* and colleagues was aimed at documenting any possible reversal of changes induced in long-term stimulated human muscle. Indeed, the biopsy study of human thigh muscles denervated for 4 years that had been stimulated over 2 years provided solid proof that atrophy is partially reversed and that generative-regenerative processes occur that have potential functional significance. The events are evident morphologically and morphometrically (in the mean size of the myofibres, in sarcomeric organization, distribution of the nuclei, mitochondrial content, and presence of activated satellite cells) as well as in molecular markers, such as the presence of embryonic myosin and myogenic transcription factors. Electrical stimulation of permanently denervated muscle was seen to increase and maintain the sarcomeres and possibly prevent apoptosis/necrosis of the myofibres.

This issue of BAM is rounded up with the paper by *Helmut Kern* and co-workers summarizing their clinical experience with the RISE project. Patients with flaccid paraplegia due to conus-cauda equina lesions could be made to stand up between parallel bars during sustained contractions of their thigh muscles achieved with electrical pulses of 30–50 ms duration, delivered at a frequency of 16–25 Hz with amplitudes of up to 250 mA through large, anatomically shaped surface electrodes. The impressive result is that with long term FES training even muscles denervated for many years could regain volume and contractile force.

Such results are certainly encouraging for patients with disabling loss of function due to permanent muscle denervation. They may be even more promising for patients waiting for regrowth of long segments of a severed peripheral nerve, such as the sciatic nerve. FES may keep the muscles in excellent condition till the newly grown axons reach them. As papers in this issue of BAM suggest, we have yet to learn how to best use the effects observed. However the way to this needed knowledge seems open.

REFERENCES:

[1]Stålberg E, Trontelj JV: *Single Fibre Electromyography. Studies in healthy and diseased muscle.* Raven Press, New York, 1994, pp 130-148.
[2]Trontelj JV, Stålberg E: Responses to electrical stimulation of denervated human muscle fibers recorded with single fibre EMG. *J Neurol Neurosurg Psychiat* 1983; 46: 305-309.

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