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Electrical Stimulation of Denervated Muscles: First Results of a Clinical Study

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Abstract: To evaluate the effects of electrical stimulation on denervated muscles in spinal cord injured humans, the EU Project RISE was started in 2001. The aims of this project are: to design and build sufficient stimulators; to develop stimulation protocols by means of mathematical models, animal experiments, and practice in humans with denervated lower limbs; to develop examination methods and devices for evaluation of electrical stimulation training effects; and to acquire basic scientific knowledge on denervated and stimulated denervated muscle. In the clinical study 27 spinal cord injured individuals were included, furthermore 13 pilot patients participated. After a series of initial examinations they underwent an electrical stimulation program for their denervated lower limb muscles. Some of the patients have already follow up examinations. A marked increase of muscle mass and quality was observed, the trophic situation of the denervated lower limbs had improved obviously. **Key Words:** Denervated muscle—Spinal cord injury—Electrical stimulation—Computerized tomography scan—Force measurement—Human.

Spinal cord injured individuals with conus–cauda lesions and as a consequence denervation of their lower extremities suffer from severe atrophy of their lower limb muscles. After some years a lot of the muscle tissue is replaced by fat and connective tissue. The trophic situation of the paralyzed limbs worsens rapidly. Secondary problems like decubital ulcers, dysfunction of wound healing or osteoporosis occur. These changes can be reversed by a high intensity electrical stimulation therapy of the muscles (1,2).

For this kind of electrical stimulation a new protocol had to be set up. Special stimulation devices had to be developed, since there were no commercially available stimulators which could generate the high current intensities needed to stimulate denervated muscle (3).

In the EU project RISE, started in 2001, scientists and physicians from Austria, Germany, Italy, Great Britain, Slovenia, and Iceland are working together to develop a rehabilitation method for this particular kind of paraplegia, to construct a stimulation device and to acquire basic scientific knowledge concerning denervated and denervated stimulated muscle

PATIENTS AND METHODS

Forty spinal cord injured individuals were examined and started electrical stimulation training (5 women, 35 men). Twenty-seven of them took part in the EU project RISE, 13 were pilot study patients.

They had to have a conus or cauda lesion with complete denervation of the m. quadriceps femoris for at least 6–12 months. Only patients without implants, hazardous infections or disease were included, pregnant women were not allowed to participate.

Paraplegia was caused by traumatic fracture of TH 12 in 57.5%, of L1 in 12.5% and of TH 11 in 7.5%.

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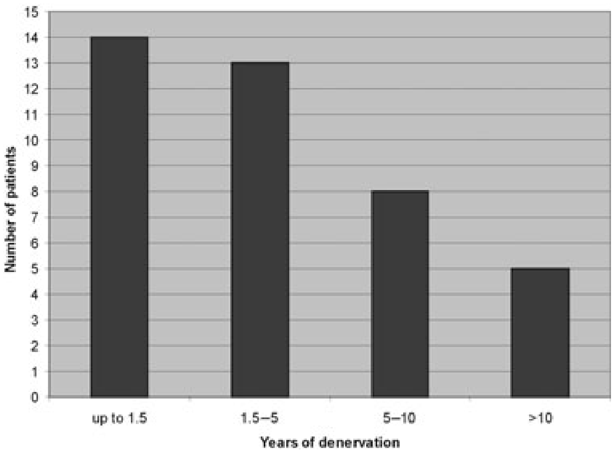

FIG. 1. Time of denervation.

In 22.5% of the patients, problems of regional blood circulation caused damage of the spinal cord over longer distances.

At the beginning of electrical stimulation the mean age was 43 years in female, 36 years in male participants. The mean time span of denervation was 5.2 years. In 14 individuals it was 0.7–1.5 years, in 13 between 1.5 and 5 years, in 8 between 5 and 10 years and in 5 cases more than 10 years (Fig. 1).

Before starting the electrical stimulation program the patients had to undergo a series of examinations to prove that they met the inclusion criteria (complete denervation of m. quadriceps femoris with absent voluntary movement, sensation, and reflexes) and to describe the status of the denervated muscles at the onset.

Test stimulation, clinical and neurological examinations, neurophysiological assessment, biopsies of skin and quadriceps muscles, computerized tomography scans (CT scans) of the thighs, bone density measurement, skin examinations, and mechanical evaluations were carried out.

For the test stimulation the patient was sitting with extended lower limbs, two pairs of large electrodes (~200 cm^2), each inside a wet sponge bag, positioned above his thighs. The quadriceps muscle was stimulated with biphasic rectangular impulses of defined durations (145, 42, 5, 2.6, and 1.3 ms) and a maximum intensity of 160 V peak to peak (Vpp). By palpating the muscle belly and the patella it was decided if a contraction of the stimulated muscle could be elicited. Only patients whose quadriceps muscles contracted by applying 5 ms or longer lasting impulses were included.

The clinical and neurological examination comprised different tests of motor and nerve function, sensibility, and of the range of movement of the joints.

The components of the neurophysiological assessment were: BMCA (brain motor control assessment), LSEP (lumbosacral somatosensory evoked potentials), SSR (sympathetic skin response), transcranial and lumbar magnetic stimulation, and needle EMG (electromyography) (4).

Biopsies were taken from the vastus lateralis of the m. quadriceps femoris and analyzed histochemically and morphologically under light and electron microscopy (5).

Transverse CT scans of both thighs were taken every 10 cm beginning at the top of trochanter major. The cross-sectional areas of m. quadriceps femoris and the hamstrings were measured in cm^2, the density of these areas was measured in Houndsfield units (2).

Force measurements were performed as soon as tetanic contractions of the thigh muscles could be elicited. Knee extension torque was measured on an isometric knee dynamometer stimulating the quadriceps muscle with a standardized program (1,2).

After passing this initial examinations, patients started their electrical stimulation training. The training was carried out at home after appropriate instruction in stimulating not only the quadriceps muscle, but also the gluteal muscle and calf bilaterally.

Electrical stimulation was applied by a specially developed stimulation device (3) with large electrodes (~200 cm^2) in sponge bags which were placed over the muscles. After 4–6 months, when the skin had adapted to electrical stimulation, the electrodes on the thighs were applied to the skin directly with gel.

Every four to eight weeks accurate check ups and appropriate adaptations of the stimulation protocol were made.

Depending on the results of the test stimulation (impulse duration necessary to elicit a muscle contraction) the electrical stimulation program was set up. Sometimes it had to be started with very long biphasic rectangular impulses lasting up to 120–150 ms. These impulses were applied with a frequency of 2 Hz in bursts of 5 s duration, 2 s pause with an intensity up to 160 Vpp. Training was performed once a day for about 15 min (in intervals) in the beginning and was than extended to 20–30 min.

After some months of regular electrical stimulation it was possible to reduce impulse duration to 70 ms (5 Hz) and subsequently to 40 ms. With 40 ms impulse duration and an impulse pause of 10 ms (20 Hz) and bursts of 2 s (2 s pause) tetanic contractions could be elicited.

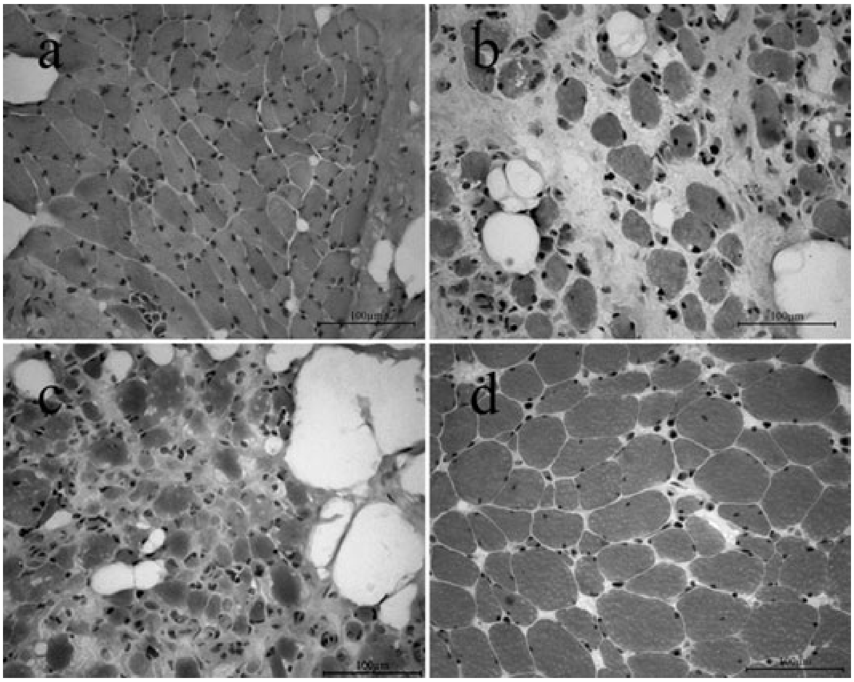

FIG. 2. Biopsies of m. quadriceps femoris, H&E stained, light microscopy: (a) 0.7 year of denervation; (b) 4 years of denervation; (c),8.7 years of denervation; (d) 2 years of denervation and 8 years of stimulation.

With increasing force of quadriceps muscle as a result of training, knee extension in a sitting position could be performed. As soon as knee extension reached 45–60° (measured from sitting position toward knee extension) additional weight around the ankle was used to increase training intensity. This resistance training was performed twice a week with 3–6 series of 12–15 repetitions of leg extension with maximum stimulation intensity, 60% of maximum possible additional weight, and pauses of 2–3 min between series (2).

Apart from the frequent assessment of the effects of the electrical stimulation training, patients were checked to assess if they still met the inclusion criteria once a year.

RESULTS

Denervation of skeletal muscle causes rapid loss of both mass as well as contractile force which is followed by severe structural changes. Figure 2 shows images of muscle biopsies at different stages of denervation after H&E (hematoxylin and eosin) staining.

In a human quadriceps muscle denervated for 0.7 years (Fig. 2a), the analyzed sections consist mainly of small, multiangular myofibers with a mean diameter of 18.6 µm (±7.4 µm SD). In the quadriceps muscle of a patient with 4 years of denervation (Fig. 2b) atrophic and severely atrophic myofibers (mean diameter 9.0 µm, ±10.5 µm SD) have been substituted by adipocytes and collagen. After 8.7 years of denervation the biopsy (Fig. 2c) demonstrates the characteristics of a typical long-term denervated and degenerated human muscle with very few muscle fibers which are severely atrophic and multiangular. The mean diameter of these myofibers is 7.9 µm (±3.7 µm SD).

In a human thigh muscle denervated 2 years and subsequently stimulated 8 years (Fig. 2d), the analyzed sections mainly consisted of large round, but still multiangular myofibers with a mean diameter of 48.2 µm (±14.8 µm SD). Adipocytes were absent.

The CT scans of the thighs 20 cm below the top of the trochanter major demonstrated the severe atrophy of the denervated muscles at the onset of stimulation. After 1–2 years of denervation the cross-sectional area of the quadriceps muscle was reduced to approximately 40% of normal values. The longer the duration of denervation was, the more pronounced was the atrophy.

Furthermore, an increase of fat occurred in the denervated muscles and subcutaneously.

After about one year of electrical stimulation a distinct increase of the cross-sectional area of the quadriceps muscle (mean: +29.74%, range from 10.45% to 58.04%) but also of the hamstrings could be observed (Fig. 3). Values of individual subjects are listed in Table 1.

At the beginning of the electrical stimulation program only single twitches could be elicited in the denervated quadriceps muscle. With the increase of

TABLE 1. *Cross-sectional area (cm²) of m. quadriceps fem. in the CT scan 20 cm below the top of trochanter major*

right			left		
1 year of electrical stimulation			1 year of electrical stimulation		
Before	After	Improvement (%)	Before	After	Improvement (%)
35.3	43.7	23.7	37.3	41.6	11.5
23.14	32.73	41.44	25.28	32.26	27.61
24.51	38.04	55.2	24.56	36.01	46.62
29.42	40.28	36.91	28.76	38.15	32.65
40.33	46.99	16.51	37.91	43.84	15.64
44.13	68.74	55.77	40.08	55.52	38.52
25.63	34.23	33.55	28.3	34.53	22.01
45.45	55.6	22.33	45.52	56.27	23.61
39.93	46.61	16.73	38.98	43.45	11.47
42.2	48.8	15.64	39.9	50.07	25.49
18.26	27.22	49.07	18.04	28.51	58.04
15.76	19.42	23.22	18.36	20.28	10.46
		mean 32.51			mean 26.97

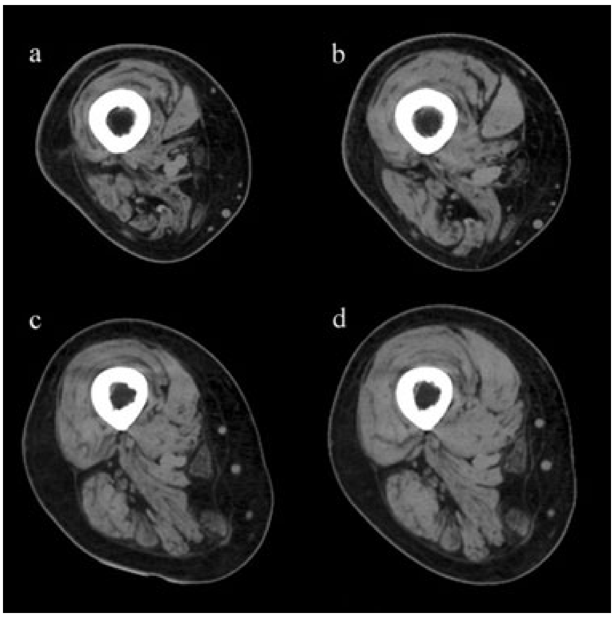

FIG. 3. CT scans of the right thighs 20 cm below trochanter major: (a) >10 years denervated; (b) same subject as (a), 1 year stimulated; (c) 1.7 years denervated; (d) same subject as (c), 1 year stimulated.

excitability of the stimulated denervated muscles the impulse duration could be reduced and the elicitation of tetanic contractions was possible. The tetanic contractions were very weak in the beginning, but after some months a force output up to 5–20 Nm could be measured.

CONCLUSIONS

This work shows that structurally and functionally denervated muscles deteriorate with increasing duration of denervation. With an adequate stimulation protocol which can only be carried out with a specially adapted stimulation device, these changes can be reversed. It is possible to increase muscle mass and to enhance the trophic situation and thereby decrease the secondary problems. Furthermore training of long-term denervated muscles is also possible, even if it takes more time to achieve similar properties.

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