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Nine patients with complete denervation of the tibialis anterior were admitted to a stimulation program in order to restore dorsiflexion of the foot. Best results were obtained with pulses of 20-msec pulse width and 20-msec interval. After 3 weeks of training for 2 x 20 min/day, dorsiflexion due to stimulation was increased in all patients. In some of them, gait could be improved during the swing phase using electrical stimulation. The applied training program thus reversed the course of disuse atrophy and proved the feasibility of functional electrical stimulation for patients with denervated muscles.

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## IMPROVED MOTOR RESPONSE DUE TO CHRONIC ELECTRICAL STIMULATION OF DENERVATED TIBIALIS ANTERIOR MUSCLE IN HUMANS

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Electrical stimulation of denervated muscle is recommended to replace the function of the nerve by eliciting muscle contractions.<sup>5,7,19</sup> The therapeutic treatment by electrical stimulation limits the atrophy of denervated muscle. The assumption is based on results showing that electrically evoked contraction prevents the loss of oxidative enzymes and the atrophy associated with denervation.<sup>17</sup> By appropriate contractile activity, the oxidative enzymes and fiber diameters can be maintained at normal levels in the absence of innervation.<sup>19</sup> Recent investigations reported that electrical stimulation of denervated muscles may significantly lead to some biochemical, electrophysiologic, and biomechanical changes.<sup>1,11,22,23</sup>

Experimental findings demonstrated that stimulation significantly retarded the atrophy of

both type 1 and type 2 fibers in Wistar rats.<sup>3</sup> The atrophy that occurs in denervated muscle is invariably a progressive process.<sup>4</sup> By means of electrical stimulation, the atrophy can only be retarded, not prevented.<sup>7</sup>

It is clear from recent work that the initiation of muscle activity is a major factor in neural control of intrinsic muscle characteristic.<sup>6,13</sup> Electrical stimulation of partially deafferented ganglion cells is capable of enhancing their ability to establish contacts<sup>16</sup> and their influence on terminal sprouting.<sup>10</sup> It was reported that stimulation reduced extrajunctional acetylcholine sensitivity to normal or below normal and restored the resting membrane potential of the denervated fibers to normal.<sup>2,8,13</sup>

Direct stimulation of denervated muscle reduced the changes of twitch/tetanus ratio and prevented the slowing of contraction and relaxation that follows denervation.<sup>18</sup> The contraction became faster, but its amplitude decreased.<sup>12</sup> Electrical stimulation caused a positive effect on the regeneration and motor recovery of nerves.<sup>20</sup> Stimulated muscles are more fatigue-resistant, and fatigue-resistance is dependent on the parameters of stimulation, especially on frequency.<sup>1,19,26,31</sup> Different results were obtained by Steinberger and Smith.<sup>24</sup> After daily programmed stimulation in denervated rabbit muscle for periods of 6-18 months, relatively little change in excitability and fatigue-resistance had occurred, but contractile strength was still at a useful level after 18 months. It was also reported that appropriate impulse pat-

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tern plays a major role in muscle-nerve interaction. Effective stimulation needs a defined pattern of stimuli.<sup>5,21,25,29</sup> A frequency of 16 impulses per second most often gave the greatest increase in blood flow.<sup>30</sup>

Functional electrical stimulation of the nervous tissue has found clinical use in a wide variety of orthotic and therapeutic applications in patients with central nervous lesions.<sup>27,28</sup> Therapeutic stimulation of denervated muscle should be used only if there is strong indication that reinnervation will occur.<sup>9</sup> On the other hand, the use of denervated skeletal muscle as a source of power for functional movement has not been introduced up to now. In view of all the rather conflicting data regarding electrical stimulation of denervated muscles, we decided to explore the effects of a stimulation training program for the completely denervated tibialis anterior muscle in humans. The goals of the project were first to search for optimum stimulating parameters that would not only elicit some twitch contraction, but perhaps also restore contractile properties of denervated muscle, and second, to test the feasibility that denervated muscles might be used to perform functional movement.

#### MATERIALS AND METHODS

Nine patients from 21 to 46 years of age, with complete denervation of muscles innervated by the peroneal nerve, were selected for the program. The selection was based on clinical and neurophysiologic examinations. General muscle test, needle electromyogram (EMG), strength-duration curves, and motor response to tetanic and twitch electrical stimulation were performed in order to prove complete denervation of the pretibial muscle group. None of the patients had any volitional control of his ankle joint; there was no EMG activity, except fibrillation potentials, and the strength-duration curves were shifted to the right with increased rebase and no accommodation. No response to tetanic stimuli was observed. The times after lesion ranged from 2 to 40 months. Eight of the patients had a one-sided traumatic lesion of the sciatic nerve at the hip level, and one patient developed flaccid paralysis as result of L1 fracture.

In order to elicit smooth movements with electrical stimulation, a frequency between 15 and 30 Hz had to be used, whereas the pulse widths for denervated muscles have to be much longer than in upper motor neuron lesions. The optimum parameter combination was determined with the following procedure. The patient was seated in a

comfortable position and a lightweight goniometer was attached to the ankle joint. Two skin electrodes, 5 × 5 cm, were attached to both ends of the tibialis anterior (anterolateral side of the shank). Stimulation pulses with pulse widths between 5 and 50 msec and a pause of 20 msec were applied to the electrodes. The current amplitude was gradually increased up to 40 mA, but the initial response was usually quite small—maximally about 10° in direction of dorsal flexion. The current of 40 mA was tolerated only by three patients, who had no innervated sensory nerves (see also Fig. 3). This response varied with the pulse width, and it was consistently found that the largest response was obtained at the pulse width of 20 msec.

In the week following the initial test, only conventional physical therapy was administered in order to obtain a control level of the dorsiflexion that may be developed due to electrical stimulation without any training program. At the end of the week, the stimulation test was repeated. An averaged curve of the first and second measurements is shown in Fig. 1 and is labeled "initial state." It may be seen that pulse widths below 10 msec produce negligible responses in denervated muscles and that the largest dorsiflexion is obtained at 25 Hz, with pulse duration and pause being equal—about 20 msec each. This combination of stimulation parameters has been consistently found to be optimal in all patients, and consequently, it was applied in the training program.

For the next 3 weeks, in addition to regular physical therapy, the patients were stimulated twice daily 5 days/week for 20 minutes with the

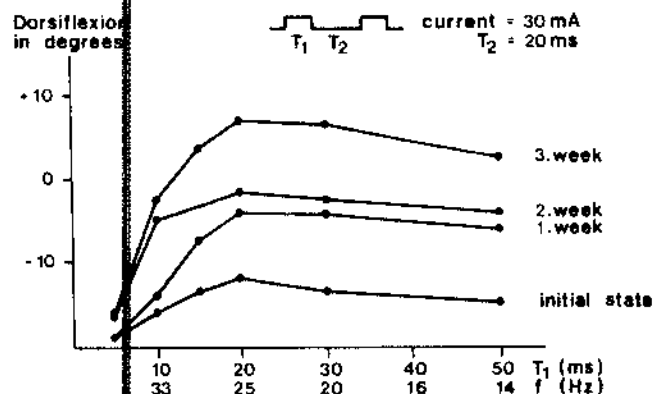


FIGURE 1. (Subject M.T.) Dependence of foot dorsiflexion on pulse width  $T_1$  or frequency  $f$  at constant pause  $T_2$ . "Initial state" curve represents the average of two tests when no stimulation program was applied for 1 week. The other three curves are responses after 1, 2, and 3 weeks of daily electrical stimulation.

same currents as the ones used for testing. Stimulation was applied rhythmically with the stimulation train on for 3 seconds, followed by a pause of equal duration. The current amplitude (15–35 mA) was adjusted for each subject individually to a level that elicited dorsiflexion of the ankle joint. At the end of the first, second, and third weeks, the same measurements were repeated as during the determination of the initial state.

## RESULTS

Effects of the training program on optimum stimulation parameters are shown for patient M.T. in Fig. 1. After each week of electrotherapy, the dorsiflexion responses increased, but the basic shapes of the curves remained similar to the initial state curve. Starting with narrow pulses ( $T_1 = 5$  msec), the response increased at longer pulse widths until 20 msec was reached. Further increases of  $T_1$  resulted in decreased dorsiflexion. Thus, the initially chosen stimulation parameters of  $T_1 = 20$  msec and  $T_2 = 20$  msec proved to be optimal after 3 weeks of training with electrical stimulation.

Typical results of the training procedure are shown in Fig. 2 for patient T.K. This patient has been tested twice weekly over a period of 5 weeks. The first 2 weeks served as control, and no significant changes in dorsiflexion could be measured during stimulation. After the second week, electrical training was started as described above. Dorsiflexion increased substantially from week to week, and at the end of the program, it was more than 100% larger than at the beginning. When the foot could be barely lifted at the start, functionally useful dorsiflexion was observed at the conclusion

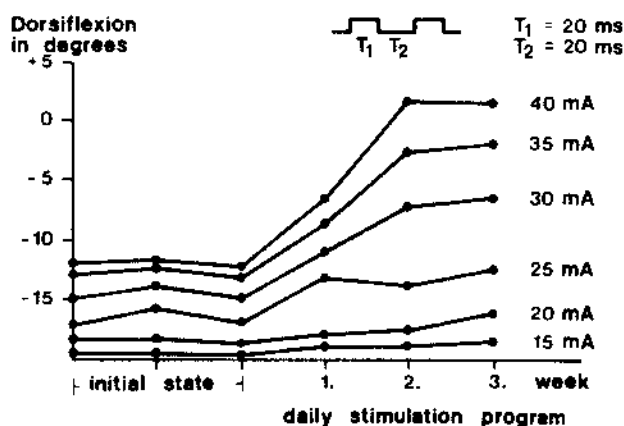


FIGURE 2. (Subject T.K.) time course of dorsiflexion at different current amplitudes before and during electrical stimulation program.

of the experiment. The amount of dorsiflexion was proportional to the current intensity. The threshold current was found to be at about 10 mA, whereas 40 mA was the upper limit because of erythema. No systematic effort was made in this study to differentiate the cause for increased dorsiflexion. Although an increased contraction of the tibialis muscle could be observed visually during the progress of the training program, reduced contractures could also affect the mobility of the joint. In a subsequent investigation, isometric measurements were performed, and the torque was found to increase in a manner similar to the increased dorsiflexion in this experiment (results not presented). Thus, it may be suggested that improved dorsiflexion was mostly due to increased muscle strength.

A summary of the results from the nine patients is shown in Fig. 3. The white column indicates the initial level of dorsiflexion that was obtained with the largest tolerable current. The solid column represents dorsiflexion that was obtained with the same currents at conclusion of the stimulation program. In all patients, the level of dorsiflexion due to electrical stimulation increased after the program. There are large individual differences. Patient E.R. had very sensitive skin and could tolerate only small currents (15 mA). Therefore, the increase after the program is only slight. Patients B.F., M.L., and M.L. either developed contractures or the activity of innervated antagonists prevented maximum dorsiflexion. The rest of the patients produced smooth functional movements when stimulated. The practical usefulness of these movements was tested on four patients during gait. They obtained a portable stimulator and were stimulated during the swing phase. As we intended primarily to prove the feasibility of performing functional movements of denervated muscles with appropriate current patterns, no quantitative gait measurements were performed. An illustration of gait without and with stimulation can be seen in Fig. 4.

On the basis of a statistical analysis of nine patients, we conclude that there was significant improvement of dorsiflexion of a mean of  $15.8^\circ$ . The mean angle of the ankle joint before the program was  $-13.3^\circ \pm 4.1^\circ$ , whereas the mean dorsiflexion after 3 weeks of the proposed stimulation program was  $2.5^\circ \pm 8.9^\circ$ . The *t*-test showed a significance of 0.003 for a one-tailed test based on a formula for correlated patterns. The correlation between the dorsiflexion before and after treatment was 0.757. The correlation was significant ( $P < 0.01$  for 7 de-

Dorsiflexion in degrees



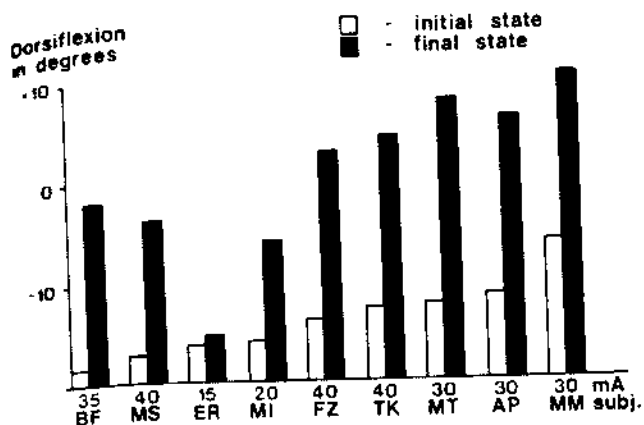
FIGURE 3. (Patients) dorsiflexion before and after stimulation program.

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## DISCUSSION

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**FIGURE 3.** Dorsiflexion at start ("initial state"—white columns) and dorsiflexion after 3 weeks of daily electrical stimulation program ("final state"—dark columns) for nine patients.

degrees of freedom). There was no significant correlation between dorsiflexion at the beginning of the program and the increase of dorsiflexion. There was also no significant correlation between the interval from the time of denervation and the response to chronic electrical stimulation.

No muscle biopsies have been performed, and consequently, we have no data regarding the mechanisms by which the contractibility was restored. There were still no signs of reinnervation at the end of the program. In patient M.T., who had denervation for over 3 years, no reinnervation could be expected.

#### DISCUSSION

Two arguments appear most frequently in the literature that question the usefulness of electrotherapy of denervated muscles. The first one is derived from animal work and claims that electrical stimulation might prevent reinnervation, and the second is based on the lack of clinical proof that electrotherapy prevents muscle atrophy. The following discussion concentrates on these topics and their relevance to our experiments.

Lomo and Westgaard<sup>15</sup> found in rats that direct stimulation of muscles with chronically implanted electrodes from the time of denervation prevented the formation of ectopic neuromuscular junctions. If stimulation began 2 or 4 days after denervation, some junctions were formed, though not as many as in the absence of stimulation. Our patients received stimulation, at the earliest, 62 days after denervation. This is well beyond the time span when electrical stimulation might prevent formation of ectopic junction.

The problem of reinnervation is a crucial question in regard to the performed experiments. Could it happen that electrical stimulation for 3 weeks, at 40 min/day would delay or prevent reinnervation in a chronically denervated muscle? It is difficult to investigate this situation, as it is virtually impossible to perform a well-controlled study on patients. To refute the assumption, let us discuss the following arguments. All subjects had lesions very proximal from the motor endplates. As the endoneurial tubes to the motor endplates are normally preserved, the regrowing axons would thus grow along the original paths and innervate the original motor endplates. The motor endplate does not lose its sensitivity to acetylcholine and is readily innervated even if artificially activated by electrical stimulation.<sup>14</sup> Thus, electrical stimulation should not prevent innervation of the original motor endplates. Let us assume now that not all axons find their way to their motor endplates and that some new motor endplates are therefore formed. This formation might then be prevented by electrical stimulation. In our program, the mus-



**FIGURE 4.** Application of functional electrical stimulator to denervated muscle. (A) Gait of patient A.P. without stimulation. (B) Patient A.P. using functional stimulator. Correction of footdrop during swing phase is evident.

cle has been stimulated less than 1.4% of a 24-hour period. Thus, for 98.6% of the day, the muscle was inactive, and sprouting to new motor plates could easily occur during that time.

Although animal experiments enable an essential insight into the mechanisms of nerve-muscle interaction and function, it seems that there are still no adequate animal models that would reflect the clinical situation found in humans. One outstanding difference between animal and human experiments is the difference in parameters used in stimulating denervated muscle. In animal work, the pulse durations are at least 10 times shorter than in humans. Reasons for these differences might be either species-related or due to the fact that human muscle may remain denervated for years, an interval very difficult to obtain in small animals. Therefore, it is quite possible that the mechanisms of denervated muscle contraction differ in animals and humans. In animal experiments, there still exist propagated muscle action potentials<sup>29</sup> that are not always observed in humans.<sup>5,25</sup> It might be that muscle contraction in chronically denervated human muscle is obtained by direct depolarization of the whole muscle membrane and, therefore, that long-lasting currents are

required. In animals, the action potential still spreads along the muscle, thus requiring much less stimulus energy.<sup>30</sup>

In any case, there seem to be some important differences between human and animal experiments that should be considered when discussing arguments for or against electrotherapy transferring from animal work to the clinical setting.

Let us finally discuss our stimulation regimen as compared to conventional electrotherapy of denervated muscles. Such therapy usually consists of single pulses of about 100-msec pulse width that are administered every 2 seconds. In a 20-minute session, the patient thus performs 600 single twitches. In our protocol, the patient was stimulated with 25 pulses per second, a frequency that is rather physiological for the fast tibialis muscle. Taking into account the 3 second on and 3 second off cycle, 15,000 impulses were delivered within the 20-minute period. As our patients had two 20-minute sessions, they received 50 times more pulses per day than in conventional electrotherapy. This might be one of the reasons for the partial restoration of contractibility that is not found in general electrotherapy.

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