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Remodeling of motor units after nerve regeneration studied by quantitative electromyography

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HIGHLIGHTS

- Reestablishing motor function after complete nerve lesion is associated with extensive remodeling, enlargement and unstable firing of motor units during nerve regeneration and muscle reinnervation.
- Force production relied on fewer and larger motor units after nerve regeneration which have implications for metabolic strain on anterior horn cells and motor fibers.
- Remodeling of motor units and recovery of force were similar after short nerve gap repair with a collagen nerve conduit and suture.

ABSTRACT

Objective: Peripheral nerve has the capacity to regenerate after nerve lesions; during reinnervation of muscle motor units are gradually reestablished. The aim of this study was to follow the time course of reestablishing and remodeling of motor units in relation to recovery of force after different types of nerve repair.
Methods: Reinnervation of muscle was compared clinically and electrophysiologically in complete median or ulnar nerve lesions with short gap lengths in the distal forearm repaired with a collagen nerve conduit (11 nerves) or nerve suture (10 nerves). Reestablishment of motor units was studied by quantitative EMG and recording of evoked compound muscle action potential (CMAP) during a 24-month observation period after nerve repair.
Results: Force recovered partially to about 80% of normal. Denervation activity gradually decreased during reinnervation though it was still increased at 24 months. Nascent motor unit potentials (MUPs) at early reinnervation were prolonged and polyphasic. During longitudinal studies, MUPs remained prolonged and their amplitudes gradually increased markedly. Firing of MUPs was unstable throughout the study. CMAPs gradually increased and the number of motor units recovered to approximately 20% of normal. There was weak evidence of CMAP amplitude recovery after suture ahead of conduit repair but without treatment related differences at 2 years.
Conclusions: Surgical repair of nerve lesions with a nerve conduit or suture supported recovery of force and of motor unit reinnervation to the same extent. Changes occurred at a higher rate during early regeneration and slower after 12 months but should be followed for at least 2 years to assess outcome. EMG changes reflected extensive remodeling of motor units from early nascent units to a mature state with greatly enlarged units due to axonal regeneration and collateral sprouting and maturation of regenerated nerve and reinnervated muscle fibers after both types of repair.
Significance: Remodeling of motor units after peripheral nerve lesions provides the basis for better recovery of force than the number of motor axons and units. There were no differences after repair with a collagen nerve conduit and nerve suture at short nerve gap lengths. The reduced number of motor units indicates that further improvement of repair procedures and nerve environment is needed.

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1. Introduction

Peripheral nerve fibers have the capacity to regenerate after Wallerian degeneration. Recovery of function after loss of peripheral nerve continuity is dependent on regeneration of nerve fibers and on reinnervation of appropriate target organs (Stoll et al., 2002). Reinnervation of muscle fibers includes establishment of neuromuscular connections and formation of motor units, which are essential for force development and control of movements. In normal muscle, the fibers of individual motor units are scattered diffusely throughout their territories (Brandstater et al., 1973; Buchthal et al., 1973). Recording with multi-lead electrodes in different normal human muscles of the upper extremity, the diameters of individual motor units ranged from 5 to 7 mm allowing space for about 25 motor units each having 500–2000 muscle fibers (Buchthal et al., 1959), and multi-lead single fiber electrodes confirmed that individual fibers are scattered across the motor unit (Stålberg et al., 1976).

In chronic partial denervation muscle fibers are reinnervated by collateral sprouting from surviving motor nerve fibers (Wohlfart, 1958) and in contrast to the scattered muscle fibers in a normal motor unit, this results in an abnormal adjacent grouping of muscle fibers belonging to the same motor unit (Morris et al., 1970). In contrast to partial denervation, recovery in complete nerve lesions is dependent on regrowth of nerve fibers from the proximal nerve stump initially incorporating a small number of muscle fibers. Nevertheless, Kugelberg et al. (1970) found grouping of muscle fibers within the same motor unit in experimental complete nerve lesions in rat. The formation of new motor units (so called "nascent" units (Weddell, 1943; Weddell et al., 1943)) is followed by remodeling and incorporation of additional muscle fibers that acquire uniform biochemical signatures (Kugelberg, 1973). Thus, type grouping, defined in human muscle as more than 50 fibers with the same biochemical signature being grouped together, occurs after both partial denervation and during regeneration after complete nerve lesions indicating that collateral sprouting occurs in both conditions (Karpati et al., 1968).

Electromyography (EMG) is an essential tool in the diagnosis and follow-up of peripheral nerve lesions. Nascent motor unit potentials (MUPs) reflect inclusion of few muscle fibers innervated by immature nerve sprouts (Weddell et al., 1944; Buchthal et al., 1979; Borenstein et al., 1980). MUPs subsequently change during partial and complete denervation and regeneration reflecting maturation of nerve fibers and reorganization of muscle fibers within the motor unit (Erminio et al., 1959; Buchthal et al., 1979).

Standardized and quantified studies of changes in MUPs in groups of patients with defined nerve and complete nerve lesions are rare (Donoso and Ballantyne, 1979), and the purpose of the present study was to examine the time course of EMG parameters during nerve regeneration and reinnervation. Furthermore, it is unknown to which extent remodeling of motor units is related to the type of repair of complete nerve lesions.

Nerve lesions with little or no tissue loss are conventionally treated by direct suture of the nerve stumps or by insertion of a short nerve graft. Studies have, however, indicated that such lesions may equally well be treated by insertion of an empty silicone (Lundborg et al., 2004) or collagen nerve conduit (Krarup et al., 2002; Boeckstyns et al., 2013). In the present study, recovery was followed over a 2-year period to compare treatment related changes in motor unit remodeling after surgical repair with a collagen nerve conduit or nerve suture. The findings supported extensive remodeling of motor units during gradual, almost complete recovery of force during the observation period, with little difference between the treatment procedures.

2. Material and methods

The 20 patients, aged 20–64 years, 5 females and 15 males (Table 1) included in the study is a subgroup of 43 subjects with completely severed ulnar or median nerves located in the distal forearm treated in Denmark or Spain. The patients were randomly assigned to nerve repair by either an empty collagen conduit (NeuraGen Nerve Guide Collagen Conduit, Integra LifeSciences, Plainsboro, NJ, USA) or suture of the nerve stumps located in the distal forearm (Boeckstyns et al., 2013). The patients were selected due to the standardized quantitative EMG methods used at the Danish department. Repair was carried out in 13 median and 8 ulnar nerves (one subject had nerve conduit repair of both the median and ulnar nerves). Eleven nerves were repaired with an empty collagen conduit leaving a short gap of maximally 6 mm between the proximal and distal stumps and 10 nerves were repaired with conventional suture of the nerve stumps (a short sural nerve auto-cable graft was used in one nerve). The regeneration distances were classified according to the distance from the tip of digit 3 to the site of the lesion measured at surgery. The patients gave informed consent, and the local ethics committees approved the study protocol. Repair of the nerve lesion was initiated within 72 h of injury. Exclusion criteria were, (1) known allergy to bovine-derived products, (2) disorders known to affect the peripheral nervous system, (3) serious systemic disease, (4) patients with complete amputation or grossly contaminated wounds, (5) pregnant women, and (6) patients that were considered uncooperative or unsuitable for completion of the study. Nerve tissue loss of more than 20 mm was an exclusion criterion, but tendon or vessel lesions or partial lacerations of other nerves were not.

2.1. Follow-up evaluation

Evaluation of recovery was planned at 1, 3, 6, 12, 18, and 24 months after repair and the actual follow-up studies did not differ significantly between the repair procedures (Table 2). Two patients with nerve conduit repair and one with suture were lost to follow-up; there were no major adverse effects of the treatments. The clinical and electrophysiological examiners were blinded to the treatment procedure.

2.2. Clinical evaluation

The force of the denervated abductor pollicis brevis (APB) or abductor digiti minimi (ADM) muscles was graded according to the Medical Research Council (MRC) (Medical Research Council, 1976) and the Rosén (Rosén and Lundborg, 2000) scales after nerve repair. The Rosén scale included measurements of force using the MRC scale of the APB in patients with median nerve lesions and of the ADM and of abduction of the second digit and adduction of the fifth digit in ulnar nerve lesions. In addition grip strength was assessed using a Jamar dynamometer. An average motor quotient, which is 1.0 in normal hands, was calculated. Atrophy was assigned on a scale of 0–3 with increasing severity.

Table 1
Distribution of nerves and patients with nerve lesions.

Number of nerves (median/ulnar)	13/8
Repair (conduit/suture)	11/10
Gender (female/male)	5/15
Age (years: average, min–max)	37, 20–64
"Regeneration distance" (mm: average, min–max)[1]	205, 170–260

One male patient had both a median and ulnar nerve repaired by nerve conduits. 1, distance measured at surgery from the tip of digit 3 to the nerve lesion.