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SCIENTIFIC ARTICLE

Comparison of Neurotization Versus Nerve Repair in an Animal Model of Chronically Denervated Muscle

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Purpose Reinnervation of chronically denervated muscle is clinically unpredictable and poorly understood. Current operative strategies include either direct nerve repair, nerve grafting, nerve transfer, or neurotization. The goal of this study is to compare muscle recovery using microneural repair versus neurotization in a rat model of chronic denervation.

Methods Fifty-eight Sprague-Dawley rats had surgical denervation of the tibialis anterior muscle by transecting the common peroneal nerve. After 0, 8, 12, or 22 weeks of denervation, animals were assigned to either a direct repair or a neurotization cohort. An additional 7 animals were used for a sham cohort, and 7 of the 58 were used as controls. After a 12-week recovery period, animals had contractile strength and EMG testing of the tibialis anterior muscle. Peak force and characteristics were compared to the unoperated, contralateral limb. Tibialis anterior muscles were then harvested for mass and histologic evaluation.

Results Sixty-two animals completed testing. Denervated controls demonstrated a significant decrease in muscle mass, contractile strength, and peak motor nerve conduction amplitude compared to sham animals. In all groups, chronicity of denervation adversely affected functional recovery. On average, repair animals performed better than neurotization animals with respect to muscle mass, contractile strength, and peak motor amplitude. Differences in contractile force, however, were significant only at the 0 week denervation group (94% ± 30 vs 50% ± 20, repair vs neurotization). Neurotized muscles processed for histologic analysis demonstrated acetylcholinesterase activity at the nerve-muscle interface, confirming the formation of motor end plates *de novo*.

Conclusions We demonstrated that neurotization is capable of reinnervating *de novo* end plates in chronically denervated muscle. Our data do not support the hypothesis that direct muscle neurotization is superior to nerve repair for functional restoration of chronically denervated muscle. However, as the duration of denervation increases, the difference between outcomes of the neurotization and repair group narrows, suggesting that neurotization may offer a viable surgical alternative in the setting of prolonged denervation. *(J Hand Surg 2008;33A: 1093–1099.*

Key words Chronic denervation, motor end plate, rat model, reinnervation.

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Reinnervation of chronically denervated muscle is clinically unpredictable and poorly understood on a biological basis. Current operative strategies include either direct nerve repair, nerve grafting, or direct implantation of a peripheral nerve into a denervated muscle (neurotization), with the expectation that the nerve will grow and reinnervate denervated motor end plates.[1] Each of these strategies has been reported to result in partial clinical restoration of muscle function that correlates inversely with the duration of denervation. Some investigators have theorized that the principal site of failure of reinnervation is the motor end plate.[2,3] Others have demonstrated that Schwann cells within the distal nerve stump deteriorate and may be unable to regain the capacity for neuronal regeneration into muscle.[4] The goal of the current study was to compare the quality of muscle recovery in microneural repair versus neurotization in a rat model of chronic denervation.[4–6]

The specific aim of this study was to compare 2 surgical strategies for reinnervation of muscle after a period of chronic denervation by assessing the quality of muscle recovery using comparative mass, electrodiagnostics, histologic differences, and muscle strength recovery. The following 2 hypotheses are proposed:

Hypothesis 1: Cohorts treated with direct implantation of a peripheral nerve graft bridging a freshly cut donor motor nerve have the ability to reinnervate muscle and establish *de novo* motor end plates in chronically denervated muscle.

Hypothesis 2: Neurotization is superior to standard nerve repair for functional restoration of chronically denervated muscle.

MATERIALS AND METHODS

Surgical denervation and repair

The relative efficacy of direct nerve repair versus neurotization was examined using a rat model of chronic denervation. Experimental groups included cohorts treated by microneural repair (repair) and cohorts treated with neurotization (neurotization) via a peripheral nerve bridge after a period of 0, 8, 12, or 22 weeks of denervation.

An animal model described by Sulaiman and Gordon using Sprague-Dawley rats was used for experimental testing.[4] Animal surgery was performed under aseptic conditions and ketamine/xylazine anesthesia in accordance with an approved protocol from the Institutional Animal Care and Use Committee, Hospital for Special Surgery. Initially, 58 animals had surgical denervation of the right tibialis anterior muscle via a posterior incision. Sciatic, tibial, and peroneal nerves were exposed.[5,7] The right common peroneal (CP) nerve was identified, transected, and ligated with a 6-0 suture (Prolene, Ethicon, Inc., Sommerville, NJ) to prevent regeneration between the proximal and distal nerve stumps.[8] The distal ligated end was tacked to the popliteal fat for later identification. Wounds were then closed with nylon sutures and surgical staples. Animals recovered in an approved housing facility with monitoring of daily weights, postoperative Buprenex Hydrochloride (Reckitt Benckiser Pharmaceuticals, Richmond, VA) analgesia, and inspection of surgical sites.

After initial denervation, animals were randomly divided into 2 cohorts: 24 animals treated with microneural repair (repair) and 24 animals treated with neurotization (neurotization). Nerve reconstruction was performed immediately after transection (time point 0 weeks) and also after 8, 12, or 22 weeks of denervation. Six animals were allotted for nerve reconstruction for each time point (0, 8, 12, and 24 weeks) for each cohort. Thus at each time point, there were 6 animals having direct repair and 6 animals having neurotization.

In the repair group, the posterior incision was used to identify the sciatic nerve and the previously transected, tagged common peroneal stump. The motor branch of the tibial nerve was identified and confirmed with an 0.5 mA nerve locator stimulator (Bovie Medical Corporation, Melville, NY). Near its origin, the tibial nerve was transected and coapted to the freshly cut distal stump of the right CP nerve. Repair was performed with the assistance of a surgical microscope using simple 10-0 nylon sutures (Ethicon, Inc.) (Fig. 1A). A second sham anterolateral incision over the tibialis anterior was then made to ensure equal treatment to both neurotization and repair cohorts.

In the neurotization group, the posterior incision was again used to expose the sciatic nerve as it courses distally into the sensory and motor branches of the tibial nerve. The sensory branch of the tibial nerve was identified and ligated proximally at its origin and distally at the level of the ankle, then set aside for use as a reversed nerve graft. The sensory nerve was harvested because this reproduced a similar clinical scenario to humans in which a sensory nerve (eg, a sural nerve) might be harvested to use as an interposition graft. In addition, it limited morbidity to the contralateral leg for later comparison and it also minimized surgical time.

At its origin, the motor branch of the tibial nerve was transected and then coapted to the peripheral nerve graft using 2 simple 10-0 nylon sutures. After this was per-

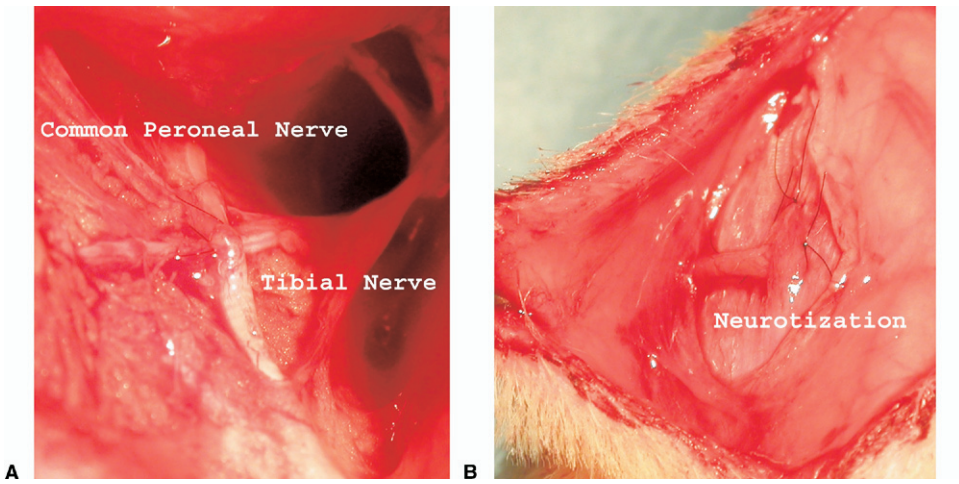

FIGURE 1: A Microneural repair of the right CP nerve to a freshly axotomized tibial nerve (repair cohort) and **B** site of neurotization of the peripheral nerve graft into the epimysium of the tibialis anterior muscle (neurotization cohort).

formed, a second incision was made anterolaterally, directly over the proximal end of the tibialis anterior muscle. The peripheral nerve graft was then passed deep to the biceps femoris muscle, and the distal end was implanted directly into the denervated tibialis anterior muscle through an incision in the epimysium (Fig. 1B). The grafted nerve was placed close to the native motor end plate of the tibialis anterior (consistently 1 to 2 mm anterior to the terminal branch of the common peroneal nerve) and secured with 2 simple 10-0 nylon sutures. Both anterior and posterior incisions were then closed. The distance from neurotomy site to the tibialis anterior was the same for both groups. In other words, the length of the sensory nerve graft was the same as that of the native peroneal nerve used for direct repair. Axonal growth required from the neurotomy site to the tibialis anterior was approximately equal in both direct repair and neurotization groups.

Similar to both treatment cohorts, animals in the denervated control group (no repair; 7 animals) had a second sham surgical incision at 8, 12, or 22 weeks, but no nerve repair or neurotization was performed. A fourth cohort, sham (7 animals), had initial skin incision but no denervation or reconstruction. At 8, 12, or 22 weeks, a second sham procedure was performed. After nerve repair or neurotization, animals were allowed to recover for 12 weeks.

Muscle function

Electrophysiologic studies were performed as described by Park and Askar.[5,8] The investigators were blinded to the treatment groups. Using general anesthesia (isoflurane), the anterior compartment of both the denervated/reconstructed leg and the contralateral leg was exposed, and fascia overlying the tibialis anterior muscle was released. Electrodiagnostics were performed using the Cadwell-Sierra LT EMG (Cadwell Inc., Kenneweck, WA). The latency and amplitude of the compound motor action potential (CMAP) of the tibialis anterior (TA) muscle were obtained by stimulating the innervating nerve of the TA muscle. A supramaximal stimulus was elicited at 1 Hz, and a response was recorded using 2 circular surface disk electrodes (active and reference) placed onto the TA muscle.

Recovery of the recipient nerve muscle strength was determined by generating a tetanic contraction and measuring the maximum force generated in the TA muscle.[9] The previous incision was used to expose the muscle belly and tendon of the TA muscle. The limb was then secured firmly to a foam board by inserting pins through the distal femur and proximal foot. After releasing its distal insertion, the TA tendon was securely fixed to a 2-kg (5-lb) load cell (MDB-5 Transducer Techniques Load Cell; Transducer Techniques Inc., Temecula, CA) using 2-0 braided polyester suture (Ethibond; Ethicon Inc.) with a locking stitch. The load cell was mounted on a post allowing adjustment of its height with respect to the tendon to ensure that the load cell was aligned with the longitudinal axis of the muscle-tendon unit. The TA muscle-tendon unit was tensioned using a worm gear stage. The innervating nerve of the TA muscle (either the right CP nerve in the repair/no repair/sham cohorts or the implanted peripheral nerve graft in the neurotization cohort) was then dissected free of surrounding tissue. Hook-shaped stimulating electrodes were placed on the nerve 1 cm from

the insertion into the TA muscle, distal to the proximal coaptation site. After a maximal response was obtained, a supramaximal stimulus was elicited at 50 Hz for a duration of 1 second to obtain a tetanic contraction. The maximum tetanic contractile force was recorded using a signal conditioner fixed to the load cell (SensoTec Inc, Columbus, OH). Initial animals were tested using a preload force of 0.05 N. A length tension curve was then established to determine the correct amount of tension needed to elicit a maximal force. This was found to require approximately 0.5 N of preload tension. Maximum contractile force was calculated subtracting the initial preload. Three repeated measures were made for each treated and untreated limb, allowing a 5-minute interval for recovery between stimulations.

The maximum force tetanic tension and mass were measured as a percentage of the unoperated contralateral side.

Histology/morphology of neuromuscular junctions

After assessment of neuromuscular recovery, the TA muscle was separated and weighed to determine differences in muscle mass between groups. The samples were then processed with hematoxylin-eosin and nicotinamide adenine dehydrogenase staining to identify the morphology and change in type of muscle fibers.[5,10] A combined bromoindoxyl acetate dye–staining for cholinesterase and silver-gold impregnation for nerve terminals was also used to identify reinnervated motor end plates.[5,6,8,11,12] The investigators were blinded to the treatment groups.

Statistical methods

Data were analyzed by 2-factor analysis of variance (ANOVA). The first factor was the type of repair, and the second factor was the period of denervation (0, 8, 12, and 22 weeks). Six animals were used per repair group, and 7 animals were used for the control and sham groups. A previous study by McNamara et al. found about a 60% difference in rabbit muscle function between the neurorrhaphy technique and neurotization at 2 months after repair.[1] With 6 specimens per group, we are able to detect such a difference in muscle function with repair type (60%) with greater than 95% power and alpha equal to .05. No previous studies have assessed the effects of delayed healing time. Therefore, power was estimated for a difference of 30% with healing time. With 6 specimens per group, we should also be able to detect a difference of 30% with 85% power. These power calculations were made using PASS 6.0 software (NCSS, Kaysville, UT) and were based on a 2-factor fixed-effects analysis of variance with a 2 by 3 design.[4,11,13]

Upon completion of the study, we ran a 2-way ANOVA with the main outcome, force ratio, as the dependent variable with time and procedure as the fixed factors. The procedure was limited to repair and neurotization. Both time ($p < .001$) and procedure ($p = .001$) were statistically significant but the interaction was not ($p = .1$). The difference at time 0 between methods is significant after a Bonferroni correction ($p < .05$) but at none of the other time periods. A logarithmic transformation of the force variable produced better equalization of the variances but did not alter the result of the analysis.

RESULTS

Sixty-two animals completed histologic and physiologic testing (48 animals had some type of nerve repair or neurotization, 7 animals were left with unrepaired nerve transection, and 7 animals had skin incision only [sham]). One animal was euthanized because of a corona virus infection, and 2 animals expired during induction of anesthesia. These animals were from the initial 58 that were denervated, leaving 55 available for testing. Self-mutilation after denervation of the limb was observed in 1 rat and was treated with a restrictive neck collar for the first 2 days after surgery. There were no significant differences observed in weight gain between treatment cohorts.

Electrodiagnostic characteristics observed demonstrated notable variability with placement of surface electrodes. This required repositioning of the recording electrode to yield an optimal CMAP with a definitive onset latency. Quantitative measurements of CMAP peak amplitude provided the most repeatable results. No muscle contraction or CMAP propagation after depolarization of the nerve was observed in 6 of 7 denervated control animals. One control animal demonstrated spontaneous axonal regeneration at the site of CP nerve transection despite use of suture ligature.

Repair and neurotization animals both demonstrated decreased peak CMAP amplitude with increasing periods of denervation. On average, neurotization animals had significantly decreased peak amplitudes compared with those of repair animals ($p = .001$). This difference was most notable at 8 weeks (8.8 mV $\pm$ 1.5 vs 7.9 mV $\pm$ 2.2, repair versus neurotization).

With respect to contractile strength, animals in both neurotization and repair groups demonstrated significantly decreased force with prolonged periods of denervation ($p < .001$). Experimental limbs demonstrated peak contractile forces ranging from 0.8 N to 13.1 N.

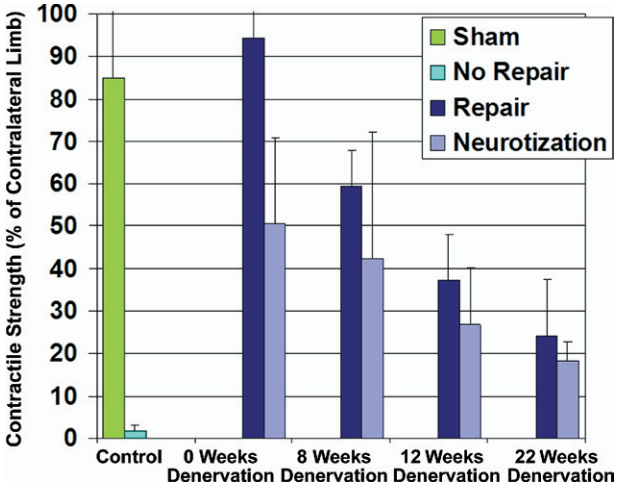

FIGURE 2: Tibialis anterior muscle strength ± SD of animals tested after denervation for 0, 8, 12, or 22 weeks and subsequent repair or neurotization. Contractile strength is expressed as a percentage of the contralateral limb. Two-factor ANOVA: procedure $p = .001$; denervation time $p < .001$; procedure × time $p = .1$ (n for each group = 5 to 7 individuals).

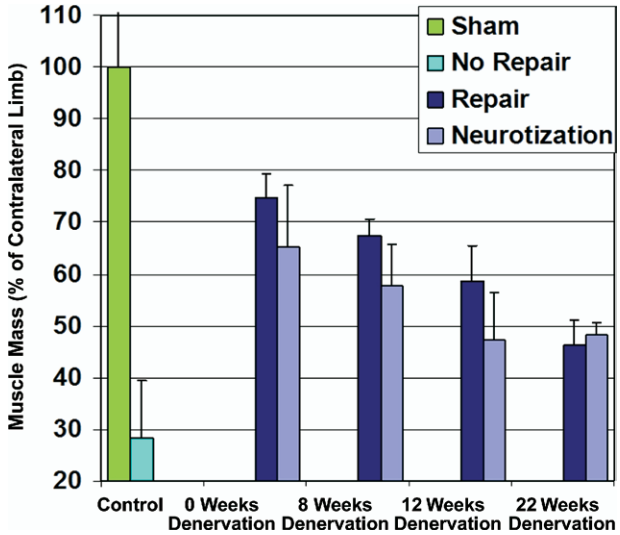

FIGURE 3: Anterior compartment mass ± SD of animals tested after denervation for 0, 8, 12, or 22 weeks and subsequent repair or neurotization. Mass is expressed as a percentage of the contralateral limb. Two-factor ANOVA: procedure $p = .001$; denervation time $p < .001$; procedure × time $p = .08$ (n for each group = 5 to 7 individuals).

REPAIR animals had significantly improved motor strength recovery at 0 weeks denervation (94% ± 30 vs 50% ± 20, repair versus neurotization, $p < .05$; Fig. 2). The distinct advantage of repair over neurotization, however, was not observed after 8, 12, or 22 weeks of denervation. There was a significant effect of treatment group favoring the direct repair ($p = .001$). A 2-factor ANOVA evaluating procedure × time, however, demonstrated only a trend (p = NS). Thus, our data suggest that both strategies have limitations, and although early direct repair appears to be more efficacious than is neurotization, this finding decreases with the chronicity of denervation. Additionally, we never encountered better than 50% muscle recovery of any of the specimens, indicating that an alternative interpretation of these results is that neither strategy is reliably or predictably effective.

Comparisons of muscle mass tended to demonstrate similar results to both nerve conduction studies and contractile strength observations. Harvested TA muscles ranged from 0.4 g to 2.4 g. Muscle mass decreased with increasing chronicity of denervation ($p < .001$). On average, neurotized animals had decreased TA muscle mass compared with that of repaired animals, and there was a significant effect of treatment group favoring repair ($p < .001$). This difference was most notable at 8 weeks (68% ± 3 versus 58% ± 8, repair versus neurotization; Fig. 3).

Muscle samples processed with hematoxylin-eosin stain revealed histologic evidence of chronic denervation in the 8-, 12-, and 22-week groups. Samples demonstrated increased fatty infiltration, decreases in sarcomere size, and increased nuclear packing. The presence of acetylcholinesterase within neurotized individuals was confirmed by antibody staining of the TA muscle near the implantation site of the peripheral nerve graft. In addition, silver-based stain was used to confirm the presence of neurofilaments and the neuromuscular junction within neurotized individuals (Fig. 4).

DISCUSSION

There are several surgical options for treating patients with chronically denervated muscles. Techniques can be divided into the categories of direct nerve repair, nerve grafting, nerve transfer, or nerve-to-muscle techniques. From a surgical standpoint, each approach has distinct advantages and disadvantages. Immediate microsurgical nerve repair is considered the most favorable type of repair, but large gaps between the divided ends can limit its effectiveness. Nerve grafting is employed when end-to-end coaptation of proximal and distal nerves is not tension-free, as can occur after segmental nerve loss. Although nerve grafting is an effective technique, its shortcomings include a second suture line, as well as the need for a dispensable donor nerve.

Neurotization is the direct implantation of a proximal divided nerve end into a denervated muscle. In the largest clinical series of nerve-to-muscle implantation

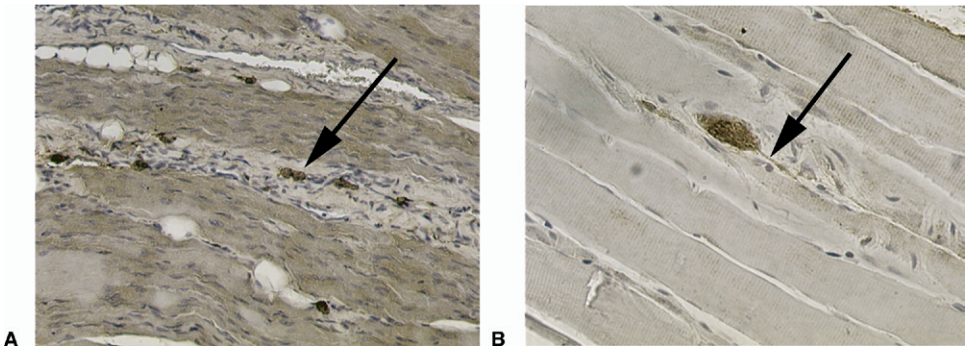

FIGURE 4: A Histologic sample of TA muscle after 12 weeks of denervation and subsequent neurotization demonstrating acetylcholine activity near the site of implantation of the nerve graft (arrow) (acetylcholinesterase antibody stain; magnification ×10). **B** Sample of TA muscle after 12 weeks of denervation and subsequent neurotization demonstrating neurofilaments (arrow) and the presence of *de novo* neuromuscular junction near the site of implantation (acetylcholinesterase antibody and silver stain; magnification ×40).

to date, Brunelli reported grade M4 or M5 return of function in 46 of 51 patients.[14] Mackinnon et al. also described recovery of gastrocnemius muscle function with nerve-to-muscle implantation in a patient with no distal nerve available for repair.[15] However, despite these sporadic reports of successful recovery of motor function, neurotization remains of experimental interest only for most reconstructive surgeons. This bias for direct nerve repair over neurotization has been based on the physiologic premise that neurotization is an inefficient means to reestablish neuromuscular reinnervation at the motor end plates. Accordingly, a procedure that relies on fostering muscle-nerve synapses *de novo* would be less favorable than a procedure that would restore previously established nerve input. In an animal study by McNamara and colleagues, immediate repair after acute nerve transection using either microsurgical neurorrhaphy, nerve grafting, or neurotization was compared.[1] Results at 6 months demonstrated less efficacy with neurotization than with either neurorrhaphy or nerve grafting. The authors concluded that neurotization could at least partially reinnervate a muscle in an animal model but suggested that nerve grafts may be preferable. Sorbie and Porter implied that the success of neurotization is likely influenced by the length of time between denervation and implantation.[16] To date, no studies have compared the efficacy of neurotization in chronically denervated muscle.

Recent experimental results have challenged the convention that muscle end-plate pathology is the underlying cause of poor results in patients with chronically denervated muscle. In their 2000 study, Sulaiman and Gordon used an animal model of chronic denervation to demonstrate profound defects in the Schwann cell environment of the distal nerve stump.[4] Short-term denervation of ≤4 weeks did not affect axonal regeneration, whereas more prolonged denervation profoundly reduced the numbers of back-labeled motor neurons and axons in the distal nerve stump. Their results demonstrated a progressive inability of chronically denervated Schwann cells to support axonal regeneration.

In a study published the same year, Emery and colleagues used a peripheral nerve bridge graft to reestablish continuity between the injured spinal cord of the marmoset and an acutely denervated biceps brachii muscle.[11] Reinnervation and regeneration of the biceps brachii muscle were documented by methods revealing axon terminals, end plates, and myofibrillary ATPase activity. These results indicate that motor neurons of the focally injured spinal cord of a small-sized primate can, following the example of the adult rat, reestablish lost motor function by extending new axons all the way through a peripheral nerve bridge connected to a denervated skeletal muscle. They noted that a significantly greater number of neurons ($p < .005$) grew axons into the denervated biceps brachii muscle via nerve-to-muscle implantation compared with such growth via nerve grafting, suggesting that neurotization may be more efficacious than nerve grafting/direct repair for muscle reinnervation.

Taken together, the results from these 2 studies provide the basis of our hypothesis that neurotization is preferable to neurorrhaphy for maximizing reinnervation in a chronically denervated muscle. Sulaiman and Gordon's[4] study demonstrated that Schwann cells in the distal nerve stump become progressively less capable of conducting axons to the motor end plates with increasing periods of denervation. Denervated muscle, however, has the potential for reinnervation and recovery from denervation atrophy. Emery and colleagues[11] demonstrated that increased numbers of motor neurons established contact with motor end plates when the

efferent nerve bridge was implanted directly into muscle than when coapted to the distal nerve stump. These findings provide the impetus for a clinical research study of neurotization in an animal model of chronic denervation.

In our experiments, we observed the most consistent recovery in animals treated immediately after nerve injury using direct nerve repair. After 12 weeks of recovery, contractile strength in repaired rats approached values of the control limbs, whereas neurotized rats recovered only 50% of their contractile strength. This confirms the work of previous authors demonstrating a preference for acute repair in the setting of a nerve injury. After 8, 12, and 22 weeks of denervation, however, the advantage of repair over neurotization was not as apparent. Our data suggest that the denervated distal stump may adversely affect recovery in the setting of chronic denervation. Evaluating the effect of procedure × time, however, demonstrated only a trend and not statistical significance. It is possible that use of a nerve graft may have impeded reinnervation. Although use of an intercalated nerve graft can be considered a limitation of our study, it was our goal to reproduce what is clinically most applicable; that is, a situation in which a nerve graft is needed to bypass a long defect in a peripheral nerve. Our data, as well as clinical data,[17] however, suggest that there is a marked decrease in muscle recovery when using a graft compared with use of direct nerve-to-muscle implantation.

We observed muscle reinnervation and recovery of muscle strength in animals after a period of chronic denervation in both neurotized and directly repaired individuals. We recognize that functional recovery may be better assessed with instruments such as the peroneal functional index, but the compound muscle action potential is an excellent objective indicator of muscle reinnervation, and determining the power of a tetanic contraction is an objective measurement of the strength associated with that degree of innervation. Although animals in the neurotization group demonstrated the ability to reinnervate a chronically denervated muscle via a peripheral nerve graft bridge, animals in the repair group tended to perform better with respect to contractile strength, muscle mass, and electrodiagnostic characteristics. In the setting of acute intervention, our work confirms previous animal and clinical studies that demonstrate direct nerve repair is superior to neurotization. Recent work has focused on the inability of Schwann cells within the chronically denervated distal stump to support axonal reinnervation. Our work suggests that as chronicity of denervation increases, the advantage of direct nerve repair over muscle neurotization becomes less profound; at some duration of denervation, there may be a role for neurotization toward our goal to improve muscle recovery. Additional clinical investigation needs to be performed to determine if neurotization is a viable treatment strategy.

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