Acute Improvement in Intraoperative EMG Following Common Fibular Nerve Decompression in Patients with Symptomatic Diabetic Sensorimotor Peripheral Neuropathy: 1. EMG Results

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Abstract

Background and Study Aims Electromyographic (EMG) recordings of the fibularis longus (FL) and tibialis anterior (TA) muscles were performed intraoperatively during common fibular nerve (CFN) nerve decompression (ND) in patients with symptomatic diabetic sensorimotor peripheral neuropathy (DSPN) and clinical nerve compression.

Materials and Methods Forty-six legs in 40 patients underwent surgical ND by external neurolysis; FL and TA muscles were monitored intraoperatively. Evoked EMGs were recorded just prior to and within 1 minute after ND.

Results Thirty-eight legs (82.6%) demonstrated EMG improvement 1 minute after ND. Sixty muscles (31 FL, 29 TA) were monitored, with 44 (73.3%) improving in EMG amplitude. Mean change in EMG amplitude represented a 73.6% improvement ($p < 0.0001$). Changes in EMG amplitudes correlated with visual analog scale pain improvement ($p = 0.03$).

Conclusion This is the first report of acute changes in objective EMG responses during ND of CFN in DSPN patients and demonstrates that patients with symptomatic DSPN and clinical nerve entrapment have latent but functional axons that surgical ND can improve immediately.

Keywords

- common fibular nerve decompression
- intraoperative electromyography
- motor evoked potentials
- acute objective functional improvement

Introduction

An estimated 29.1 million people in the United States have diabetes, with 1.9 million people diagnosed each year, and an additional 86 million adults are prediabetic.[1] Approximately 60 to 70% of people with diabetes have some form of neuropathy,[2] and those with diabetic neuropathy are at higher risk for disease progression leading to gangrene and amputation. Diabetic neuropathy is the leading cause of nontraumatic lower limb amputations in adults, with 60%

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of the nontraumatic amputations occurring in adults with diabetes.[1,3] Symptoms of paresthesia, pain, numbness, and signs of progressive motor weakness substantially degrade quality of life, despite aggressive medical management.

Surgical nerve decompression (ND) as a treatment for lower limb complications of diabetic sensorimotor peripheral neuropathy (DSPN) is sometimes used to treat patients who have failed other therapies. Many patients find it provides gratifying relief of pain, numbness, and weakness. However, the lack of class I clinical studies resulted in the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology rating this procedure as unproven (level U),[4] which was followed by the same rating of unproven in a Cochrane report.[5] One of the critiques in these reports was a lack of objective clinical outcome data. To address this, intraoperative nerve monitoring during ND surgery was incorporated into the clinical podiatric practice of one of the authors (J.C.A.), initially as an operative safety measure. However, the nerve monitoring provided interesting and unexpected results, namely an acute improvement in electromyographic (EMG) recordings in the target muscles of the decompressed nerves. An analysis of the EMG data was performed as a retrospective study, and the results are reported here.

Materials and Methods

This retrospective study analyzed data collected by J.C.A. at the Anderson Podiatry Center for Neuropathy. The protocol was approved by the Poudre Valley Health System institutional review board (IRB) (now the University of Colorado Health – Poudre Valley Hospital IRB). Consent was obtained for the surgery from each of the subjects, and a retrospective IRB approval was obtained for analyzing their data in this study. Forty consecutive patients with common fibular nerve (CFN) decompression surgery and intraoperative nerve monitoring from June 6, 2007, to April 13, 2011, were included in the study.

Patient Screening

DSPN was established by patient history of a diabetes diagnosis, current use of antidiabetic drugs, one-point sensibility changes, and symptoms of burning, tingling, numbness, leg weakness, or dysesthesias on the neuropathy questionnaire in the absence of other neuropathic diagnoses. As part of the presurgery assessment, patient rating of neuropathic symptoms (pain, burning, numbness, tingling, weakness, and balance) were obtained using a visual analog scale (VAS) that ranged from zero (no perceived symptoms or impairment) to 10 (worst possible symptoms or impairment).

Indications for ND surgery were diabetes with painful neuropathy, adequate circulation based on pedal pulses and capillary refill time, an abnormal neurologic sensibility examination, and a positive Tinel percussion sign on the CFN at the fibular neck suggesting entrapment.

Follow-up was at 3, 6, and 12 months. Patients were seen 4 to 7 days after surgery to remove and reapply bandages, at 2 to 4 weeks for removing sutures, and at 4 to 8 weeks to check incisions, activity levels, and evaluate progress. Any adverse events were documented at each visit, and the VAS forms were completed by the patient at the 3-month follow-up.

Surgical Procedure

The operative protocol specifies outpatient external decompression of the CFN using the methods described by Dellon[6] with the patients awake but receiving intravenous sedation (propofol) and analgesia (morphine). Subcutaneous injection of 1% xylocaine with epinephrine (0.001%) 5 cm proximal to the 3- to 4-cm skin incision generated a supplemental local field block. These injections did not affect the ability to record electromyographic (EMG) signals from the fibularis longus (FL) and tibialis anterior (TA) muscle (►**Fig. 1** shows the orientation of the CFN). Tourniquets were not used. Typically, a procedure treated two to seven nerves (CFN, tibial nerve at the tarsal tunnel, medial and lateral plantar nerves, medial calcaneal nerve, superficial and deep fibular nerves). However, only the EMG results for muscles innervated by the CFN are presented in this report.

Bilateral surgeries were staged, treating the leg with the dominant symptoms first. Six patients had both legs treated with a mean time between surgeries of 4.9 months (range: 1.5–10 months).

Intraoperative Nerve Monitoring

Electrically evoked EMG signals were recorded during the surgical procedure with the NIM-Response v.2.0 Nerve Integrity Monitor (Medtronic, Jacksonville, Florida, United States) according to its indication for use. Although this is technically a motor

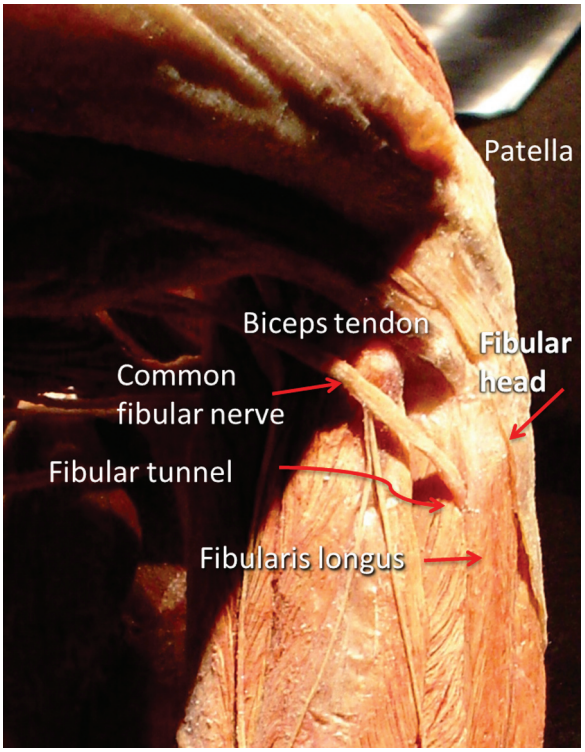

Fig. 1 The common fibular nerve of the right leg shown exiting the popliteal fossa and diving into the fibular tunnel deep to the fibularis longus muscle (with permission from Bodyworlds, (http://www.bodyworlds.com/en.html.)

evoked potential, we refer to it as EMG, which is commonly used in the intraoperative nerve monitoring literature. The CFN was stimulated with a monopolar stimulating probe (Prass, Medtronic) directly on the nerve (4Hz, monophasic, 250 µsec pulse width). For EMGs recorded prior to surgical decompression, the stimulus current was increased until at least a 1,000 µV EMG signal was evoked from the FL or TA, or until a maximum of a 30 mA stimulus current was reached.

The CFN was initially identified in the subcutaneous tissue incision by suprafascial stimulation 4 to 5 cm proximal to the fibular neck. Baseline EMGs were generated by direct application of the stimulus probe to the epineurium through a 0.5-cm fascial window. Post-decompression EMG responses were produced by direct nerve stimulation using identical stimulus parameters (current, pulse width, and frequency) applied to the same location on the nerve.

Bipolar subcutaneous needle electrodes were placed in two CFN innervated muscles, the TA lateral to the tibial shaft 8 cm distal to the tibial tuberosity and the FL posterolateral to the fibular shaft 6 cm distal to the fibular head. The ground electrode was placed between the stimulation site and stimulus return (anode) sites as shown in ►**Fig. 2**.

Baseline EMG was recorded from TA and FL muscles before ND, then again after external neurolysis by the careful division of all fascia, muscle, fibrous tissue, septal structures, and vessels impinging on the CFN nerve trunk. It is not unusual to see an indentation of the CFN immediately after decompression (►**Fig. 3**) that dissipates shortly afterward. We take this as additional evidence supporting the hypothesis by Dellon that nerve impingement was present. Careful circumferential CFN inspection at the conclusion of the ND visually verified its freedom from impingement and restrictions before the post-ND EMG was measured.

Statistical Procedures

Values from the TA and FL muscles were pooled for analysis because we did not have an a priori goal of comparing outcomes between muscles and for expediency during surgery, the muscle or muscles that displayed a reliable, good quality EMG signal (as judged intraoperatively by the surgeon) was focused on for the subsequent measures. Thus we did not choose systematically which muscle would provide the eventual EMG values for analysis.

The pre- and post-release EMG amplitude values (pre and post, respectively) were compared using the *t* test to determine statistical significance. Values are expressed as mean plus or minus standard deviation in the text and mean plus or minus standard error of the mean in the figures. The *t* tests (paired, two-tailed) were used to determine significance in EMG changes after decompression (e.g., same samples pre versus post treatment, where an improvement was being evaluated). The effect of CFN decompression on EMG was expressed two ways; *normalized EMG responses* = post/pre, and *percentage EMG change* = ((post-pre)/pre) × 100. Asterisks were used in the figures to indicate statistical significance ($p < 0.05$).

Results

Patient Data

Forty patients (18 female) underwent CFN decompression surgery on 46 lower limbs. The EMGs of 60 muscles (31 FL, 29 TA) were analyzed. ►**Table 1** lists the patient data. All patients had a history of diabetes, 7 patients with type I and 31 patients with type II diabetes. ►**Table 2** breaks down the disease distribution, duration, and A1c levels.

Overall Results

Of the 46 legs treated, 38 (82.6%) demonstrated improved EMG in at least one of the two muscles. In the 14 legs with both muscles analyzed, 6 (42.9%) showed improvement in both muscles, 7 (50.5%) had one muscle improve, and in 1 leg (7.1%) neither muscle improved. In the remaining 32 legs with one muscle analyzed, 25 (78.1%) showed an improved

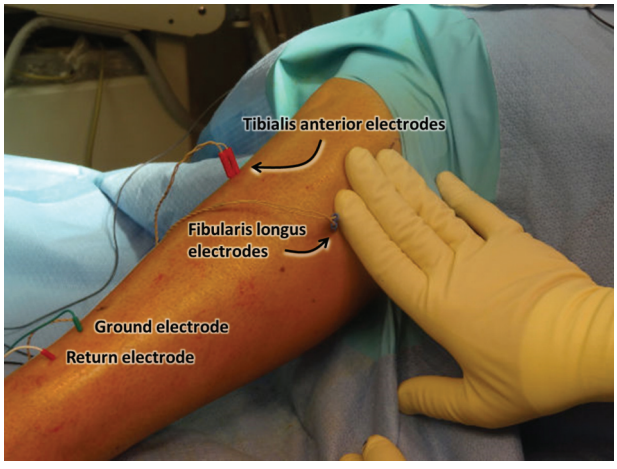

Fig. 2 Recording electrode placement. The tibialis anterior muscle electrodes were placed ~ 8 cm distal to the tibial tuberosity, and those for the fibular longus muscle ~ 6 cm distal to the fibular head. The ground was positioned between the recording and stimulus return electrodes to minimize stimulus artifact in the electromyograms.

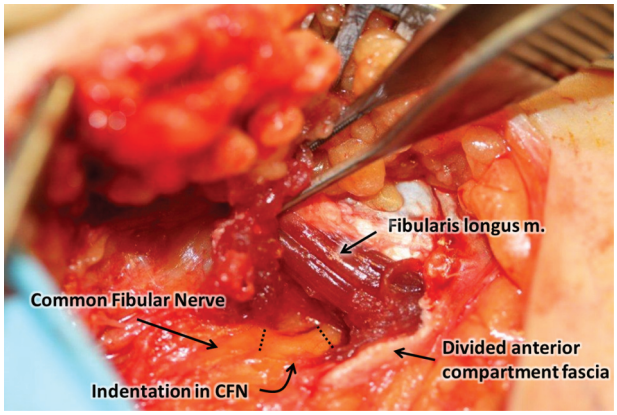

Fig. 3 Example of common fibular nerve impingement. This photograph was taken immediately after releasing the nerve. An indentation can be seen (between the dotted lines) where the nerve entered the fibular tunnel. It was being compressed by the anterior compartment fascia, whose cut collagen fibers are seen in cross section at the bottom of the figure. The free margin of this intact fascia forms the entrance to the fibular tunnel. The indentation typically dissipates within 1 minute of releasing the nerve.

Table 1 Subject data

Parameters	Value	Range
Patients	40	
Male	22	
Female	18	
Legs treated	46	
Male	26	11 right, 15 left
Female	20	6 right, 14 left
Muscles measured	60	FL 31, TA 29
Male	32	FL 17, TA 15
Female	28	FL 14, TA 14
Mean age, y	64.8 ± 9.7	44–83
Male	65.6 ± 10.2	44–82
Female	64.0 ± 9.3	48–83
Mean weight, kg	95.7 ± 24.2	54.5–163.6
Male	105.4 ± 21.0	68.2–163.6
Female	83.9 ± 22.9	54.5–131.8
Mean height, inches	68.4 ± 4.4	60–77
Male	71.2 ± 3.1	65–77
Female	64.7 ± 2.7	60–72
Mean BMI	31.4 ± 6.4	20.0–48.3
Male	31.7 ± 5.1	24.2–42.7
Female	30.9 ± 7.9	20.0–48.3
BMI levels[a]	< 30/30–39/ > 40	
All	17/19/4	
Male	7/13/2	
Female	10/6/2	

Abbreviation: BMI, body mass index; FL, fibularis longus; TA, tibialis anterior.
Averaged data are shown as mean plus or minus standard deviation.
[a]Normal, class I; overweight, class II; obesity, class III.

Table 2 Patient disease data

Parameters	Value	Range
Type I diabetes	7	
Male	6	
Female[a]	1	
Type II diabetes	31	
Male	16	
Female*	15	
Mean disease duration, y	12.6 ± 11.3	1–62
Male	13.5 ± 12.4	1–62
Female	10.9 ± 9.0	2–30
Mean A1c	7.0 ± 1.2	4.7–10.9
Male	7.1 ± 1.4	4.7–10.9
Female	6.8 ± 1.0	5.5–8.8

[a]Data on type of diabetes were missing for two female patients.

EMG. In total, 73.3% (44 of 60) of the muscles in the study showed improved EMGs. ►**Table 3** lists the results by leg and by muscle across the subject population.

There were two adverse events (AEs): one patient reported a slight loss of strength in the leg muscles, which was unconfirmed by examination. In another patient, dehiscence at one of the three incisions (CFN, deep fibular nerve, and tarsal tunnel) occurred. It was not recorded which incision was involved, but because we cannot rule out the CFN incision, we are including it as an AE. There were no serious AEs (i.e., death, myocardial infarct, or stroke), no unanticipated AEs, no AEs requiring intervention, and no AEs related to the NIM.

Pre- versus Post-Decompression EMG Results

When each muscle is plotted by its pre versus post EMG amplitudes (μV), its response to the decompression can be visualized (►**Fig. 4A**). If a muscle's pre and post EMG values are equal (i.e., no change), its value will lie on the dotted diagonal line (slope = 1.0).

Muscles that improved after the decompression lie above the diagonal, and those that declined lie below it. Forty-four muscles (73.3%) improved, and 16 (26.7%) dropped in value. The linear regression of the points shows a negative correlation, where muscles with low pre EMG values were more likely to show an improvement than those with high pre EMG values. Although the correlation coefficient (R^2) of the regression is too low to signify a good fit, the p values of the slope ($p = 0.005$) and y-intercept ($p < 0.0001$), and the F-significance ($F = 0.006$) indicate that the probability that

Table 3 Leg-centric and muscle-centric results

Parameters	*n*	Improved (%)
Legs treated	46	38 (82.6)
Legs with both muscles analyzed	14	13 (92.9)
Both muscles improved		6 (42.9)
One muscle improved		7 (50.0)
Neither improved		1 (7.1)
Legs with one muscle analyzed	32	25 (78.1)
Muscles analyzed	60	44 (73.3)
Male	32	26 (81.3)
Female	28	18 (64.3)
Fibularis longus muscle	31	24 (77.4)
Male	17	13 (76.5)
Female	14	11 (78.6)
Tibialis anterior muscle	29	20 (69.0)
Male	15	13 (86.7)
Female	14	7 (50.0)

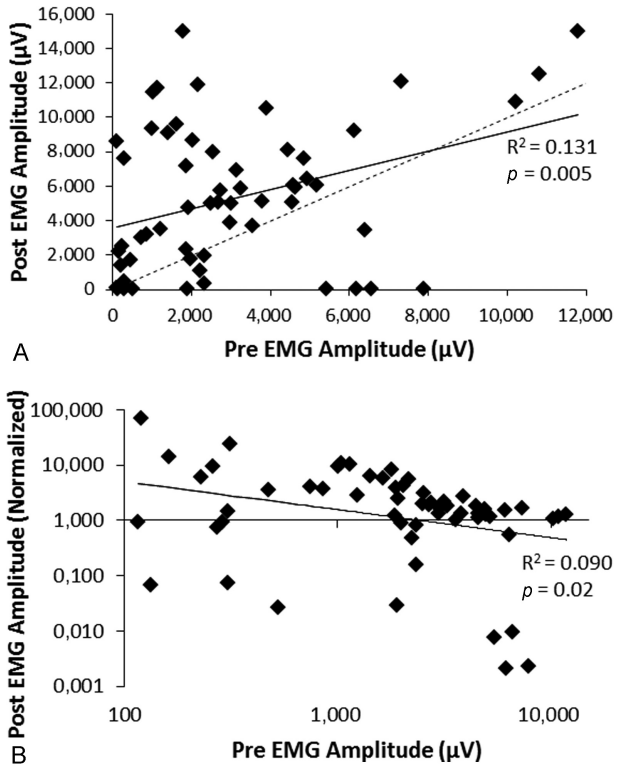

Fig. 4 Pre- versus post-decompression electromyographic (EMG) amplitudes. (A) Each muscle is plotted as its pre versus post EMG amplitude. Muscles with an increase in amplitude lie above the dotted diagonal (slope = 1.0, "No change"); those that declined lie below the diagonal. The regression suggests a negative correlation (i.e., it converges with the diagonal; slope = 0.56 versus 1.0), which can be seen more clearly in B. (B) Each muscle's pre EMG amplitude is plotted against its normalized post EMG amplitude. The horizontal line at 1.0 (null value) indicates no change in response; a value of 10 represents a 10-fold increase. Values above the null line indicate increased post EMG signals, and those below the line represent a drop in signal. Here the regression more clearly shows a negative slope, suggesting a negative correlation between the pre and post values.

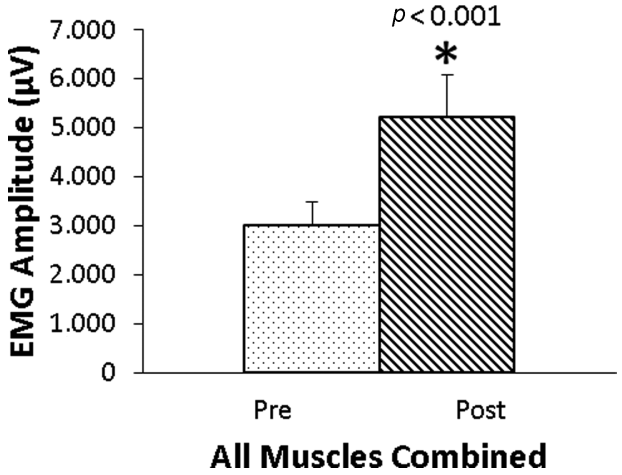

Fig. 5 Pre- versus post-decompression electromyographic (EMG) results. Pre versus post EMG amplitudes for all 60 muscles (fibularis longus [FL] and tibialis anterior [TA] muscles combined). There was a significant difference (indicated by an asterisk in this and the remaining bar graphs) when compared with the *t* test.

the regression slope was obtained by chance is low. The negative correlation can be more readily seen in ►**Fig. 4B**, where the pre EMG amplitudes are plotted against the normalized post EMG values. In the normalized plot, the null line at 1.0 on the ordinate represents no change, a value at 2.0 represents a 2-fold increase, and 0.1 indicates a 10-fold drop. A log-log plot was used to better visualize the low values across five orders of magnitude in each axis. The negative slope of the regression (− 0.51) is clearer, and the scatter plot pattern indicates that the post EMG amplitudes were greater when the pre EMG values were smaller. As in ►**Fig. 4A**, the regression fit is poor ($R^2 = 0.09$), but the *p* values for the slope ($p = 0.02$), y-intercept ($p = 0.017$), and the F-significance ($F = 0.02$) indicate that the slope was not obtained by chance.

The *t* tests were performed to determine if the improvements seen in the muscles were significant. ►**Fig. 5** shows the combined EMG results for FL and TA. There was a significant improvement. The mean post EMG amplitudes (5238μV ± 4225μV) were significantly higher than the mean pre values (3017μV ± 2739μV; $p < 0.001$) across all muscles. The mean change in EMG amplitude was 2221 ± 4120μV ranging from − 7,850 μV to + 13,216 μV. The change in amplitude represents a 73.6% increase in response.

Visual Analog Scale

The VAS survey was the only subjective data collected in this study. There was a significant drop in each of the VAS scores after the surgery except "Activity" and "Sleep" (►**Fig. 6A**). The average drop in score was − 2.3 points (range: − 0.6 to − 3.2). We selected − 2 or lower as the minimal clinically important difference based on VAS studies on rotator cuff disease, rheumatoid arthritis, and knee and hip osteoarthritis.[7–9] ►**Table 4** lists the data for the graph in ►**Fig. 6A**.

Correlations were computed between the changes in the EMG responses and changes in the VAS scores for each of the categories. The only category to show a correlation was the VAS pain scores (►**Fig. 6B**). There was a positive correlation, with greater reduction (i.e., improvements) in VAS scores associated with increasing EMG changes. The slope of the regression was − 0.07, with the slope ($p = 0.029$), y-intercept ($p = 0.003$), and significance of F ($F = 0.03$) all showing significance.

Fascicle Topography

Stimulating the different surfaces of the CFN allowed us to map the topography of the fascicles innervating the TA and FL (data not shown). The CFN is running inferoanterior at the fibular neck. The TA responded best when we stimulated the superoanterior aspect of the nerve, while the FL responded best to inferoposterior stimulation.

Effect of Surgeon Experience

Clinical studies often show an improvement over time by the investigators, either by increased familiarity of the device

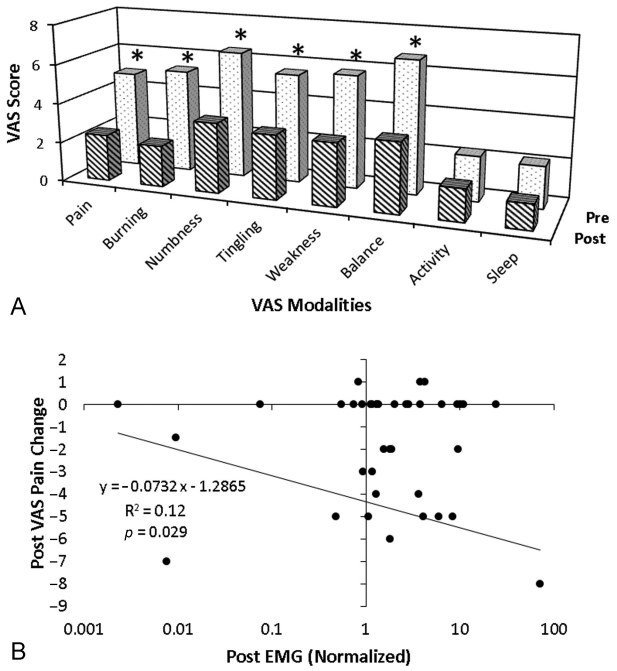

Fig. 6 Improvements in visual analog scale (VAS) scores after surgery. (A) Each VAS category shows the pre and post scores, with decreases indicating improvements. Each of the VAS categories showed clinically significant reduction of > 1.5 units, except for the "Activity" and "Sleep" categories. (B) There was a significant correlation between changes in electromyographic (EMG) amplitudes and changes in VAS pain scores. The VAS scores improved more with increasing EMG improvements.

being studied or of the surgical procedure. In this study, the surgeon (J.A.) and his staff were new to the NIM v.2.0 at the beginning of the study. Because of the high level of EMG improvement (82.6% of the treated legs showed a mean 73.6% improvement in EMG) in the study, we wanted to determine if experience with the device or surgical procedure was a factor in the results. Normalized changes in EMG were plotted chronologically over the course of the study. ►**Fig. 7** suggests little to no bias during the study period (46 months), with the slope of the regression being slightly negative and close to zero ($-$ 0.01). In ►**Fig. 7** the fit for the regression was low ($R^2 = 0.1$); however, the slope was significant at $p = 0.018$, as was the y-intercept ($p = 0.017$), and significance of F ($F = 0.018$).

Discussion

To our knowledge, this is the first report using EMG to assess the changes in neuromuscular function immediately after nerve decompression (ND) in diabetic neuropathy patients. The noteworthy finding of this study was that surgical decompression of the CFN in patients with diabetic peripheral neuropathy and nerve compression in most cases acutely increased, in some cases dramatically, the amplitude of electrically evoked EMG potentials measured intraoperatively from the FL and TA muscles. Several studies on decompression in patients with DSPN and nerve compression have reported improvements in pain reduction, sensation, balance, strength, and even reduction in skin ulcer and amputation.[10–19]

Other than the VAS scores, the results reported in this study were quantitative and objective. Both pre- and post-decompression EMG measurements were taken with the patient under sedation during the surgery. Typically, the time separating the pre and post measurements was 5 to 10 minutes. When the pre recordings were taken, the CFN was already exposed proximal to the site of impingement, so all that separated the pre and post recordings was the release of the compression (i.e., 5–10 minutes). Thus not only were the post EMG measurements taken very shortly after the decompression, but also fairly soon after the pre recordings. This suggests that the mechanism of the improvement was due not to changes in synaptic density or strength, circuitry, the target muscles, or metabolic neuropathology, but mainly to mechanical release of the compression around the nerve and its vasa nervorum. It should be noted that we do not interpret the results to mean that the metabolic pathologies are insignificant or are treated or affected in any way by the decompression. This is consistent with Dellon's hypothesis, that the symptoms of diabetic peripheral neuropathy are multifactorial and due at least in part to focal compression at specific anatomical tunnels in this subset of patients.[11]

Table 4 Summary of visual analog scale data

VAS category	*n*	Mean pre VAS	Mean post VAS	Mean point change	Meets MCID
Pain	37	4.9 ± 4.4	2.4 ± 2.9	− 2.5 ± 3.2	+
Burning	36	5.2 ± 4.0	2.1 ± 2.7	− 3.1 ± 3.5	+
Numbness	37	6.4 ± 3.3	3.5 ± 2.6	− 2.9 ± 3.2	+
Tingling	37	5.5 ± 3.5	3.2 ± 3.0	− 2.3 ± 2.9	+
Weakness	36	5.7 ± 3.8	3.2 ± 2.8	− 2.6 ± 3.2	+
Balance	35	6.7 ± 3.2	3.5 ± 3.2	− 3.2 ± 3.5	+
Activity	34	2.3 ± 0.9	1.6 ± 0.8	− 0.6 ± 0.9	−
Sleep	31	2.1 ± 1.8	1.3 ± 1.2	− 0.8 ± 1.2	−

Abbreviations: MCID, minimal clinically important difference; VAS, visual analog scale.

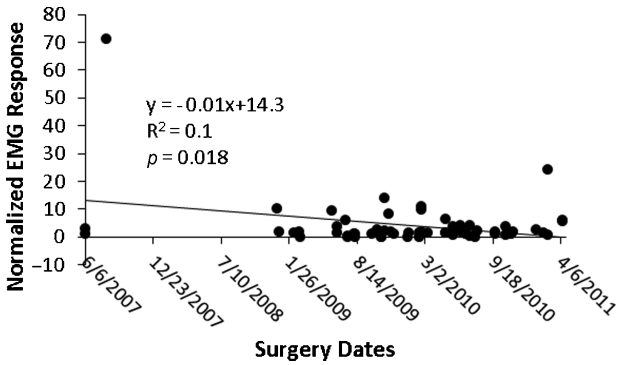

Fig. 7 Effect of surgeon experience. Normalized electromyographic (EMG) responses are plotted chronologically over the duration of the study to assess the effect of investigator experience on the study results. There was no indication that EMG outcomes improved with surgeon experience.

This report is consistent with previous studies that showed significant improvement in pain and sensibility measures in most cases.[18,20–22] Of the 46 legs treated in this study, 38 (82.6%) demonstrated improvement in EMG amplitude, with 73.3% of the muscles (44 of 60) showing significant improvement. When averaged across all muscles, the level of improvement was 73.6%, and was significant ($p < 0.001$; ►**Fig. 5**).

Because this was a retrospective study, it was not designed or powered to determine efficacy or trending. That said, the results do provide some insight to possible mechanisms of the therapy and suggest which patients would benefit most by the surgery. The negative regression lines slopes of ►**Fig. 4** suggest that patients with low pre EMG values benefit more than those with high pre EMG values. One interpretation is that patients with low pre values have more room to improve (i.e., they are not as close to the maximum level of nerve function). Alternatively, low pre values could reflect neuropathy at a more advanced stage, where acute improvement might be less likely. Although this study cannot prove either interpretation, it does suggest that in properly selected patients, even those with progressive symptomatic disease who have failed other therapies, dramatic objective improvement in neuromuscular function can occur within minutes of the release. Furthermore, in this patient sample, those with low neuromuscular function going into the surgery are likely to experience greater benefit.

Interpretation of EMG Changes

We are careful to call the EMG response *improvement* rather than *recovery* because the nerves will continue to improve to some extent over time, and the surgery does not treat diabetic metabolic neuropathy. For these patients the metabolic neuropathy remains and is likely to continue to progress. However, the EMG results are objective and consistent with the subjective improvements reported previously.[11,19,23–27]

The acute and sometimes substantial improvement in EMG amplitude shown in this study is somewhat unexpected given that these patients had both diabetic neuropathy and presumed chronic impingement. Further, the improvement was seen in all age groups and disease duration. Wallerian degeneration is well documented in the clinical and basic science literature in subjects with these conditions.[28–30] It would have been less surprising to see no immediate effect after the decompression, but rather a slow improvement over weeks, months, and years as the axons remyelinate and in some cases grow back to their targets. Although the mechanism of this rapid improvement is unknown, what this study revealed is that a portion of the axons in the CFN are latent but still viable, and they are capable of rapidly improved activity after release of the impingement. These results also indicate that at least for the rapidly improving axons, a large part of the cause for dysfunction was impingement because all that was done to elicit the improvement was to decompress the nerve.

A subjective clinical parallel has been observed. Dellon reported rapid improvement of sensibility and comfort after ND.[21] Postoperatively many of his patients have mild dysesthesia or hyperesthesia and withdraw when subjected to light touch and rubbing of the feet in the recovery room, although having been numb preoperatively.

Although 73.3% of the muscles showed varying degrees of improvement in EMG, the remaining 26.7% showed a decline in EMG amplitude. Several scenarios are consistent with a drop in function following ND including iatrogenic nerve injury, misdiagnosis, tourniquet-induced ischemia, and local anesthesia administration proximal to the treatment site.

Iatrogenic nerve injury cannot be ruled out. However, in some of the cases where EMG signals dropped, it was noted that motor and sensory improvements were seen in the recovery room as soon as the patient recovered from anesthesia. We do know that none of these patients demonstrated greater clinical weakness at first follow-up visit, even if their EMG declined $\geq$ 95% post-ND.

One explanation for this apparent dichotomy is the use of fixed bipolar needle recording electrodes. These electrodes consist of two needles separated by 2.5 mm on a fixed hub. The needles are also insulated except for the distal 5 mm. The 2.5-mm separation and 5-mm exposed tip were designed for the much smaller muscles of the head and neck where they have been used effectively for $>$ 20 years. However, these electrodes sample a small percentage of muscle fibers in the much larger TA and FL muscles. If ND affects some nerve fascicles more than others, the result will be differential improvement across the muscle fascicles in a topographic fashion that could be missed if the needles happen to be placed in the wrong portion of the muscle. Most neurophysiologic recording systems (including the NIM) use differential amplifiers that amplify the difference in voltage recorded by the two electrodes. Using noninsulated needles and increasing the interelectrode distance to 1.0–2.0 cm would sample a larger volume of the muscle and provide a better functional assessment of the entire muscle. We are now using this approach in all decompression surgeries.

Another possible cause of a small or no EMG improvement is placing the needle electrodes across the innervation zone (IZ) of the muscle (i.e., the site of the muscle's neuromuscular junctions). It is well documented that muscle action potentials propagate away from the IZ in the proximal and distal

directions. Placing bipolar electrodes across the muscle's IZ will minimize the signal because the diverging action potentials tend to cancel each other.[31–34] The IZ for each muscle varies across subjects[34] but tends to be located in the longitudinal center or belly of the muscle, which is where the needles were placed in this study. It is better to place the electrodes in either the proximal or distal one third of the muscle, which is what we currently do.

Misdiagnosis during patient screening would also explain the cases with no improvement. One of the key signs in determining who might benefit from the surgery is a positive Tinel sign.[13,26,35] A positive sign indicates both a dysfunction as well as some residual function in the tested nerve (i.e., tapping a nonfunctioning nerve will not generate paresthesia or pain). It is possible that the neuropathy and/or nerve compression was severe enough that rapid improvement was not possible or irreversible damage had occurred. However, because each of the patients in this study had a positive Tinel sign as part of their screening, it is unlikely that this was the case. Although misdiagnosis could have resulted in no improvement, it does not explain a drop in EMG.

Ischemia of the nerve or muscle due to prolonged tourniquet effect is a possible cause of a drop in EMG function. However, this can be ruled out in this study because the tourniquet was not used.

The patients were sedated but not under general anesthesia. To minimize discomfort, local anesthesia was injected 5 cm proximal to the CFN surgical field. Lidocaine diffusion to the decompression site could explain any of the three possible outcomes: a drop, an increase, or no change in post EMG, depending on when it reaches the treatment site. If it reaches the release site prior to the pre recordings, a small EMG signal would be seen along with little to no improvement after the release. If the anesthesia reached the field between the pre and post recordings, a drop in EMG would be expected. If it diffused to the treatment site prior to the pre recording and dissipated before the post recording, an increase in EMG could occur. We cannot rule out these possibilities, but it seems unlikely that lidocaine would have a differential effect at the treatment site in the 5 to 10 minutes between the pre and post recordings. Further, if the anesthetic had diffused to the site prior the pre recordings, a blocked nerve would have been more likely than a partially blocked nerve and no EMG signal would have been recorded. This has not happened in any of the cases.

Modifications of the clinical treatment protocol could resolve several issues. Using general anesthesia would eliminate the question of whether local anesthesia affects the results. Using the standard neurophysiologic procedure of 1.5 to 2 times threshold stimulus intensity would also help. The phase II study, which is currently under way, is using a "saturation" stimulus level, indicating activation of all fascicles within the nerve, for both pre and post recordings, which will help in interpreting the results.

We are aware that Macaré van Maurik et al published a report[36] concluding that, by their methods, "decompression of nerves of the lower extremity in patients with painful diabetic polyneuropathy has no beneficial effect on nerve conduction study variables 12 months after surgery." Interestingly, their subjects in this level 1 study did show significant reduction in pain.[36] Although these findings are informative to the literature in this area, a direct comparison with our present results is not appropriate. That study measured muscle response to surface stimulation and apparently used surface recordings of muscle responses, with the contralateral limb serving as a within-subject control. Their methods and time frame differ significantly from ours because the NIM protocol uses direct stimulation of nerve trunk and needle electrodes to directly record muscle evoked response during the operative procedure. Their result disagrees with our intraoperative findings using the NIM as well as those of Dellon,[11] and the significant NCV recovery found by Zhang et al at 3 months, Zhong et al at 18 months, and Liao et al at 2 years.[18,19,22] It may be that sensitivity of the Macaré van Maurik method differs enough to explain the discrepancy or that the intraoperative result we see is not maintained or measurable by their method at 12 months. This is certainly a topic of interest to be further investigated.

Much work has been reported on the changes in nerve membrane ion channel expression as a result of nerve injury. Earlier work demonstrated continuous conduction across demyelinated portions of axons,[37–40] and that there was an inward membrane current at these regions.[41] Anatomical studies provided evidence for increases in voltage-gated Na^+ (Nav) channel density in the internode regions of axons after chronic demyelination.[42–44] More recently much has been published on injury-induced expression of voltage-gated ion channels in neuropathic pain including Nav,[45–52] Ca^{2+},[53–58] and K^+ [59,60] channels. Interestingly, it has been shown that ventral root transection can cause upregulation of Nav1.3 and Nav1.8 in dorsal root ganglia neurons, bilaterally.[61] Most of this research has focused on sensory axons and pain mechanisms; while fewer studied motor fibers,[38,41,62] and none of those reports looked for injury-induced ion channel expression. We have not found any report showing changes in ion channel expression in motor fibers. However, given the strong evidence in sensory fibers, it would be interesting to suggest that similar changes occur in chronically entrapped and demyelinated motor fibers. Increased density of Nav along the demyelinated portion of the axon, decrease in demyelinated axon diameter, ischemia-induced blockage of the Na^+/K^+ ATPase, and shortening of the internodes proximal to the demyelination sites have all been reported,[44] and they could in part explain the rapid improvement in evoked EMG responses once the compression on the axon is removed.

Fascicle Topography

Our topographic observations are consistent with the results of Sunderland and Ray, and differ by 90 degrees with the results of Kudoh and Sakai and Gustafson et al, who each describe the deep fibular nerve (DFN) and superficial fibular nerve (SFN) fascicles as lateral and medial, respectively.[63–65] It is likely that the fascicles experiencing the most compression at the fibular tunnel ostium would be either adjacent to the roof of the ostium

(created by the anterior compartment fascia as shown in ►**Fig. 3**) or the neck of the fibula as shown in ►**Fig. 3**. The electrophysiologic results suggest that the SFN and DFN fascicles, being superoanterior and inferoposterior, respectively, within the CFN, would undergo similar compression at the tunnel. Although this might be the case with a static lower limb, with flexion and extension of the knee in an active subject, the posterior fascicles (i.e., the DFN fascicles) might undergo greater tension during knee extension in addition to compression at the tunnel ostium. This could explain both the differential improvement between FL and TA, and the greater improvement in FL in ►**Fig. 5A**.

Visual Analog Scale

The VAS scores were the only subjective patient-reported data analyzed in this study. The VAS data were collected at 3-month follow-up. Although these scores are subjective in nature, the amount of improvement and level of significance in each of the categories is consistent with the objective EMG results (►**Fig. 6A**). The statistically significant correlation between VAS pain scores and EMG improvement suggests that CFN impingement in these patients not only affects motor function but also contributes to small-fiber hypersensitivity. This in turn suggests that at least some of the pain in these patients is generated *and maintained* at the level of the peripheral nerves as opposed to central levels, and more importantly, it can be partially reversed, as Valdivia et al found.[36,66,67] Although central mechanisms of neuropathic pain can be initiated by peripheral lesions, their sensitization can become independent of peripheral input in some chronic pain conditions.[46,68,69] An array of molecular and cellular mechanisms have been proposed for this central sensitization including changes in membrane voltage-dependent sodium, potassium, and calcium channel expression,[52,54,55,70] phenotypic switching of large Aβ fibers,[71,72] subthreshold membrane potential oscillations,[73] activation of N-methyl-D-aspartate receptors,[74–76] and microglial-induced release of proinflammatory cytokines.[66,76–81] Interestingly, Dilley et al showed that blockage of fast axonal transport of rat sciatic nerve results in mechanical hypersensitivity but not ongoing activity of small-fiber axons (i.e., neuronal activity consistent with spontaneous pain or central sensitization).[82,83] They proposed that the mechanical hypersensitivity results from accumulation, membrane insertion, and increased density of ion channels proximal to the blockage site. Their results are consistent with ours in that decompression of the CFN led to a significant reduction of pain at follow-up, as opposed to continued centralized pain.

Effect of Surgeon Experience

Although nerve monitoring with the NIM was new to the surgeon (J.C.A.) and his surgical team at the beginning of the study period, the EMG response to decompression did not change over time (►**Fig. 7**), suggesting that experience and familiarity with the NIM was not a factor in the EMG results. An alternative interpretation is that even with increasing familiarity and experience with the NIM device, the EMG results were consistent. The surgeon had already performed > 70 cases prior to this study, so familiarity with the patient selection protocol and surgical procedure was unlikely to have affected the results.

Placebo Effects

Because there was no control group in this study, the placebo effect cannot be ruled out. However, a placebo or Hawthorne effect[84] seems unlikely because the patients were under sedation during the pre- and post-decompression recordings. Further, the post recordings were made immediately after decompression and within 10 to 15 minutes after the pre recordings.

Patient Selection

In this study, 82.6% of the treated legs showed improvement. This is consistent with previously reported success rates.[10–12,16,17,19,24,26,27,67,85] As with any treatment paradigm, the patient selection algorithm is critical for determining which patients will benefit from the procedure. This study demonstrated that in the study population, axons within the CFN are latent but still viable prior to surgery. The Tinel sign is a good indicator because it reflects both a dysfunction in and viability of at least some of the axons at the compression point, and it has been shown to correlate with good outcome with this procedure.[13,26,35,62] It has rightly been argued that electrodiagnosis is the gold standard for diagnosing nerve entrapment and demyelination, and it should play a more prominent role in patient screening.[4,86,87] There has however been a discrepancy with negative electrodiagnosis results and improved subjective outcome with this procedure. Wieman and Patel reported no consistent relationship between localized symptoms and nerve distribution with electrodiagnostic testing, and no significant difference between pre and post nerve conduction study (NCS) results in any patient.[26] In an 11-patient pilot study on ND in patients with diabetic neuropathy and entrapment of the CFN and tibial nerve, electrodiagnostic testing was performed immediately before and after surgery, and again at 3 and 6 months, and the nerves were also monitored with the Medtronic NIM as in this study.[88] The NCS was performed by a neuromuscular neurologist, board certified in electrodiagnostic medicine. The follow-up results showed improvements in NCS even at sites where no compression was demonstrated (i.e., no reduced compound motor action potential amplitudes or increased latencies) preoperatively. These results are consistent with false-positive and false-negative results of NCS for carpal tunnel syndrome.[89–91] While the mechanisms are unknown, these results suggest that NCS may not identify some patients with clinically significant nerve compression, and more studies are needed.

Study Limitations

There are several limitations in the present study. First, because this was a retrospective study, a priori inclusion/exclusion criteria and end points were not possible. In spite of this, statistical significance was shown for acute EMG responses and patient demographics in a way that provides

insight into the pathophysiology of DSPN and the mechanism of action of ND.

The results described here represent changes in EMG activity within the intraoperative monitoring period and do not necessarily indicate clinical outcome of the patient. Only the VAS surveys were captured at follow-up. This study focused on changes in EMG amplitude, but EMG latencies were not analyzed. The CFN has more sensory than motor fibers, and we did not study changes in sensory functions.[65] The clinical situation did not allow the usual laboratory procedures of eliciting a stimulus threshold and doubling stimulus intensity to ensure nerve saturation. In lieu of these limitations, care was taken to use identical parameters (nerve stimulus location, current, stimulus pulse width, and pulse shape) both pre- and post-decompression, in an attempt to stimulate the same axon populations within the nerve.

The results of this study are consistent with the marked sensory changes in the previous reports of this procedure, and suggest several hypotheses on DSPN pathophysiology. First, this demonstrates that many anterior horn motor neurons have not undergone complete Wallerian degeneration but are in a state of latent dysfunction from which they can rapidly recover to a significant degree. This is unexpected, especially in cases where the patient has experienced neuropathic symptoms and signs consistent with compression for months, years, and even decades. Second, although metabolically induced length-dependent axonopathy is a well-accepted etiology in these patients, it does not explain the rapid EMG improvements demonstrated here and may be an independent or concurrent condition.

Third, the objective electrophysiologic evidence of rapid motor nerve improvement is congruent with the subjective clinical outcomes of improved sensibility and pain relief reported previously. Fourth, the return of axoplasmic flow is an implausible explanation for the rapid functional improvements in this study. Physiologic nerve repair processes require gene expression, protein synthesis, and transport to distant action sites that seem improbable given the known rates of axoplasmic flow of up to 400 mm/day, or $<$ 1.7 cm/hour.[92] By releasing the CFN, its vasa nervorum are also decompressed, which would intuitively lead to an improvement in the nerve's microcirculation and is consistent with a rapid functional improvement. However, this retrospective clinical study was not designed to investigate this and provides no insight into blood flow or related mechanisms.

Despite its limitations, this study demonstrates that, in some DSPN cases, a large intraoperative increase in EMG of anterior and lateral compartment leg muscles can occur immediately subsequent to CFN decompression by the methods suggested by Dellon. The results provide objective electrophysiologic evidence that parallels patients' subjective reports of rapid postoperative pain relief and sensory improvement.

Conclusions

This report is the first to demonstrate intraoperative electrophysiologic improvement of neuromuscular function attributable to surgical ND in patients with combined DSPN and nerve entrapment. It is hoped that these results will lead to the design of class I clinical trials to further evaluate this surgical approach.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of Interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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References

1 Centers for Disease Control and Prevention (CDC)National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States. Available at: https://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf
2 Dyck PJ, Feldman EL, Vinik AI. Diabetic neuropathies: the nerve damage of diabetes. Available at: http://www.medhelp.org/gov/www11.htm
3 Margolis DJ, Malay DS, Hoffstad OJ, et al. Incidence of diabetic foot ulcer and lower extremity amputation among Medicare beneficiaries, 2006 to 2008: Data points #2. Available at: http://www.ncbi.nlm.nih.gov/books/NBK65149/
4 Chaudhry V, Stevens JC, Kincaid J, So YT; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Practice Advisory: utility of surgical decompression for treatment of diabetic neuropathy: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2006;66(12):1805–1808
5 Chaudhry V, Russell J, Belzberg A. Decompressive surgery of lower limbs for symmetrical diabetic peripheral neuropathy. Cochrane Database Syst Rev 2008;CD006152(3):CD006152

6 Dellon AL. Neurosurgical prevention of ulceration and amputation by decompression of lower extremity peripheral nerves in diabetic neuropathy: update 2006. Acta Neurochir Suppl (Wien) 2007; 100:149–151
7 Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken) 2011;63(Suppl 11):S240–S252
8 Tashjian RZ, Deloach J, Porucznik CA, Powell AP. Minimal clinically important differences (MCID) and patient acceptable symptomatic state (PASS) for visual analog scales (VAS) measuring pain in patients treated for rotator cuff disease. J Shoulder Elbow Surg 2009;18(6):927–932
9 Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. Ann Rheum Dis 2005;64(1):29–33
10 Aszmann OC, Kress KM, Dellon AL. Results of decompression of peripheral nerves in diabetics: a prospective, blinded study. Plast Reconstr Surg 2000;106(4):816–822
11 Dellon AL. Treatment of symptomatic diabetic neuropathy by surgical decompression of multiple peripheral nerves. Plast Reconstr Surg 1992;89(4):689–697; discussion 698–699
12 Dellon AL, Muse VL, Nickerson DS, et al. Prevention of ulceration, amputation, and reduction of hospitalization: outcomes of a prospective multicenter trial of tibial neurolysis in patients with diabetic neuropathy. J Reconstr Microsurg 2012;28(4):241–246
13 Dellon AL, Muse VL, Scott ND, et al. A positive Tinel sign as predictor of pain relief or sensory recovery after decompression of chronic tibial nerve compression in patients with diabetic neuropathy. J Reconstr Microsurg 2012;28(4):235–240
14 Ducic I, Short KW, Dellon AL. Relationship between loss of pedal sensibility, balance, and falls in patients with peripheral neuropathy. Ann Plast Surg 2004;52(6):535–540
15 Ducic I, Taylor NS, Dellon AL. Relationship between peripheral nerve decompression and gain of pedal sensibility and balance in patients with peripheral neuropathy. Ann Plast Surg 2006;56(2): 145–150
16 Hollis Caffee H. Treatment of diabetic neuropathy by decompression of the posterior tibial nerve. Plast Reconstr Surg 2000;106(4): 813–815
17 Siemionow M, Alghoul M, Molski M, Agaoglu G. Clinical outcome of peripheral nerve decompression in diabetic and nondiabetic peripheral neuropathy. Ann Plast Surg 2006;57(4):385–390
18 Zhang W, Zhong W, Yang M, Shi J, Guowei L, Ma Q. Evaluation of the clinical efficacy of multiple lower-extremity nerve decompression in diabetic peripheral neuropathy. Br J Neurosurg 2013;27(6): 795–799
19 Zhong W, Zhang W, Yang M, Li G, Ma Q, Yang X. Impact of diabetes mellitus duration on effect of lower extremity nerve decompression in 1,526 diabetic peripheral neuropathy patients. Acta Neurochir (Wien) 2014;156(7):1329–1333
20 Baltodano PA, Basdag B, Bailey CR, et al. The positive effect of neurolysis on diabetic patients with compressed nerves of the lower extremities: a systematic review and meta-analysis. Plast Reconstr Surg Glob Open 2013;1(4):e24
21 Dellon AL. The Dellon approach to neurolysis in the neuropathy patient with chronic nerve compression. Handchir Mikrochir Plast Chir 2008;40(6):351–360
22 Liao C, Zhang W, Yang M, Ma Q, Li G, Zhong W. Surgical decompression of painful diabetic peripheral neuropathy: the role of pain distribution. PLoS ONE 2014;9(10):e109827
23 Parker RG. Dorsal foot pain due to compression of the deep peroneal nerve by exostosis of the metatarsocuneiform joint. J Am Podiatr Med Assoc 2005;95(5):455–458
24 Rader AJ. Surgical decompression in lower-extremity diabetic peripheral neuropathy. J Am Podiatr Med Assoc 2005;95(5): 446–450
25 Sessions J, Nickerson DS. Biologic basis of nerve decompression surgery for focal entrapments in diabetic peripheral neuropathy. J Diabetes Sci Tech 2014;8(2):412–418
26 Wieman TJ, Patel VG. Treatment of hyperesthetic neuropathic pain in diabetics. Decompression of the tarsal tunnel. Ann Surg 1995; 221(6):660–664; discussion 664–665
27 Zhang W, Li S, Zheng X. Evaluation of the clinical efficacy of multiple lower extremity nerve decompression in diabetic peripheral neuropathy. J Neurol Surg A Cent Eur Neurosurg 2013; 74(2):96–100
28 Fazan VPS, deVasconcelos CAC, Valenca MM, et al. Diabetic peripheral neuropathies: a morphometric overview. Int J Morphol 2010;28(1):51–64
29 Malik RA. The pathology of human diabetic neuropathy. Diabetes 1997;46(Suppl 2):S50–S53
30 Yagihashi S, Matsunaga M. Ultrastructural pathology of peripheral nerves in patients with diabetic neuropathy. Tohoku J Exp Med 1979;129(4):357–366
31 Falla D, Dall'Alba P, Rainoldi A, Merletti R, Jull G. Location of innervation zones of sternocleidomastoid and scalene muscles—a basis for clinical and research electromyography applications. Clin Neurophysiol 2002;113(1):57–63
32 Guzman RA, Silvestre RA, Arriagada DA. Biceps brachii muscle innervation zone location in healthy subjects using high-density surface electromyography. int J Morphol 2011;29(2): 347–352
33 Malek MH, Coburn JW, Weir JP, Beck TW, Housh TJ. The effects of innervation zone on electromyographic amplitude and mean power frequency during incremental cycle ergometry. J Neurosci Methods 2006;155(1):126–133
34 Saitou K, Masuda T, Michikami D, Kojima R, Okada M. Innervation zones of the upper and lower limb muscles estimated by using multichannel surface EMG. J Hum Ergol (Tokyo) 2000;29(1-2): 35–52
35 Lee CH, Dellon AL. Prognostic ability of Tinel sign in determining outcome for decompression surgery in diabetic and nondiabetic neuropathy. Ann Plast Surg 2004;53(6):523–527
36 Macaré van Maurik JF, Franssen H, Millin DW, Peters EJ, Kon M. Nerve conduction studies after decompression in painful diabetic polyneuropathy. J Clin Neurophysiol 2015;32(3):247–250
37 Bostock H, Sears TA. Continuous conduction in demyelinated mammalian nerve fibers. Nature 1976;263(5580):786–787
38 Bostock H, Sears TA. The internodal axon membrane: electrical excitability and continuous conduction in segmental demyelination. J Physiol 1978;280:273–301
39 Felts PA, Baker TA, Smith KJ. Conduction in segmentally demyelinated mammalian central axons. J Neurosci 1997;17(19):7267–7277
40 Shrager P. The distribution of sodium and potassium channels in single demyelinated axons of the frog. J Physiol 1987; 392:587–602
41 Bostock H, Sears TA, Sherratt RM. The spatial distribution of excitability and membrane current in normal and demyelinated mammalian nerve fibres. J Physiol 1983;341:41–58
42 England JD, Gamboni F, Levinson SR, Finger TE. Changed distribution of sodium channels along demyelinated axons. Proc Natl Acad Sci U S A 1990;87(17):6777–6780
43 Foster RE, Whalen CC, Waxman SG. Reorganization of the axon membrane in demyelinated peripheral nerve fibers: morphological evidence. Science 1980;210(4470):661–663
44 Waxman SG, Kocsis JD, Black JA. Pathophysiology of demyelinated axons. In: Waxman SG, Kocsis JD, Stys PK eds. The Axon: Structure, Function and Pathophysiology. New York, NY: Oxford University Press; 1995:438–461
45 Black JA, Liu S, Tanaka M, Cummins TR, Waxman SG. Changes in the expression of tetrodotoxin-sensitive sodium channels within

dorsal root ganglia neurons in inflammatory pain. Pain 2004; 108(3):237–247
46 Devor M. Sodium channels and mechanisms of neuropathic pain. J Pain 2006;7(1, Suppl 1):S3–S12
47 Dib-Hajj SD, Yang Y, Black JA, Waxman SG. The Na(V)1.7 sodium channel: from molecule to man. Nat Rev Neurosci 2013;14(1):49–62
48 Rogers M, Tang L, Madge DJ, Stevens EB. The role of sodium channels in neuropathic pain. Semin Cell Dev Biol 2006;17(5):571–581
49 Waxman SG. The molecular pathophysiology of pain: abnormal expression of sodium channel genes and its contributions to hyperexcitability of primary sensory neurons. Pain 1999(Suppl 6): S133–S140
50 Waxman SG. Acquired channelopathies in nerve injury and MS. Neurology 2001;56(12):1621–1627
51 Waxman SG. Sodium channels, the electrogenisome and the electrogenistat: lessons and questions from the clinic. J Physiol 2012;590(11):2601–2612
52 Waxman SG, Dib-Hajj S, Cummins TR, Black JA. Sodium channels and pain. Proc Natl Acad Sci U S A 1999;96(14):7635–7639
53 Boroujerdi A, Zeng J, Sharp K, Kim D, Steward O, Luo ZD. Calcium channel alpha-2-delta-1 protein upregulation in dorsal spinal cord mediates spinal cord injury-induced neuropathic pain states. Pain 2011;152(3):649–655
54 Cao YQ. Voltage-gated calcium channels and pain. Pain 2006; 126(1-3):5–9
55 Gribkoff VK. The role of voltage-gated calcium channels in pain and nociception. Semin Cell Dev Biol 2006;17(5):555–564
56 Ohnami S, Tanabe M, Shinohara S, Takasu K, Kato A, Ono H. Role of voltage-dependent calcium channel subtypes in spinal long-term potentiation of C-fiber-evoked field potentials. Pain 2011;152(3): 623–631
57 Takahashi T, Aoki Y, Okubo K, et al. Upregulation of Ca(v)3.2 T-type calcium channels targeted by endogenous hydrogen sulfide contributes to maintenance of neuropathic pain. Pain 2010;150(1):183–191
58 Yaksh TL. Calcium channels as therapeutic targets in neuropathic pain. J Pain 2006;7(1, Suppl 1):S13–S30
59 Fan L, Guan X, Wang W, et al. Impaired neuropathic pain and preserved acute pain in rats overexpressing voltage-gated potassium channel subunit Kv1.2 in primary afferent neurons. Mol Pain 2014;10:8
60 Jan LY, Jan YN. Voltage-gated potassium channels and the diversity of electrical signalling. J Physiol 2012;590(11):2591–2599
61 He XH, Zang Y, Chen X, et al. TNF-α contributes to up-regulation of Nav1.3 and Nav1.8 in DRG neurons following motor fiber injury. Pain 2010;151(2):266–279
62 Bostock H, Sears TA, Sherratt RM. The effects of 4-aminopyridine and tetraethylammonium ions on normal and demyelinated mammalian nerve fibres. J Physiol 1981;313:301–315
63 Gustafson KJ, Grinberg Y, Joseph S, Triolo RJ. Human distal sciatic nerve fascicular anatomy: implications for ankle control using nerve-cuff electrodes. J Rehabil Res Dev 2012;49(2):309–321
64 Kudoh H, Sakai T. Fascicular analysis at perineurial level of the branching pattern of the human common peroneal nerve. Anat Sci Int 2007;82(4):218–226
65 Sunderland S, Ray LJ. The intraneural topography of the sciatic nerve and its popliteal divisions in man. Brain 1948;71(Pt. 3):242–273
66 Tsuda M, Masuda T, Tozaki-Saitoh H, Inoue K. Microglial regulation of neuropathic pain. J Pharmacol Sci 2013;121(2):89–94
67 Valdivia JM, Dellon AL, Weinand ME, Maloney CT Jr. Surgical treatment of peripheral neuropathy: outcomes from 100 consecutive decompressions. J Am Podiatr Med Assoc 2005;95(5):451–454
68 Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. Cell 2009;139(2):267–284
69 Jensen TS, Finnerupm NB. Neuropathic pain: peripheral and central mechanisms. Eur J Pain Suppl 2009;3(2):33–36
70 Waxman SG, Cummins TR, Dib-Hajj S, Fjell J, Black JA. Sodium channels, excitability of primary sensory neurons, and the molecular basis of pain. Muscle Nerve 1999;22(9):1177–1187
71 Devor M. Ectopic discharge in Abeta afferents as a source of neuropathic pain. Exp Brain Res 2009;196(1):115–128
72 Nitzan-Luques A, Devor M, Tal M. Genotype-selective phenotypic switch in primary afferent neurons contributes to neuropathic pain. Pain 2011;152(10):2413–2426
73 Amir R, Michaelis M, Devor M. Membrane potential oscillations in dorsal root ganglion neurons: role in normal electrogenesis and neuropathic pain. J Neurosci 1999;19(19):8589–8596
74 Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. Nature 1983;306(5944):686–688
75 Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. Pain 1991;44(3):293–299
76 Zimmermann M. Pathobiology of neuropathic pain. Eur J Pharmacol 2001;429(1–3):23–37
77 Detloff MR, Fisher LC, McGaughy V, Longbrake EE, Popovich PG, Basso DM. Remote activation of microglia and pro-inflammatory cytokines predict the onset and severity of below-level neuropathic pain after spinal cord injury in rats. Exp Neurol 2008; 212(2):337–347
78 Inoue K. The function of microglia through purinergic receptors: neuropathic pain and cytokine release. Pharmacol Ther 2006; 109(1–2):210–226
79 Lim TK, Shi XQ, Martin HC, et al. Blood-nerve barrier dysfunction contributes to the generation of neuropathic pain and allows targeting of injured nerves for pain relief. Pain 2014;155(5):954–967
80 Mika J, Zychowska M, Popiolek-Barczyk K, Rojewska E, Przewlocka B. Importance of glial activation in neuropathic pain. Eur J Pharmacol 2013;716(1–3):106–119
81 Wang D, Couture R, Hong Y. Activated microglia in the spinal cord underlies diabetic neuropathic pain. Eur J Pharmacol 2014;728:59–66
82 Dilley A, Bove GM. Disruption of axoplasmic transport induces mechanical sensitivity in intact rat C-fibre nociceptor axons. J Physiol 2008;586(2):593–604
83 Dilley A, Richards N, Pulman KG, Bove GM. Disruption of fast axonal transport in the rat induces behavioral changes consistent with neuropathic pain. J Pain 2013;14(11):1437–1449
84 McCambridge J, Witton J, Elbourne DR. Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. J Clin Epidemiol 2014;67(3):267–277
85 Biddinger KR, Amend KJ. The role of surgical decompression for diabetic neuropathy. Foot Ankle Clin 2004;9(2):239–254
86 Cornblath DR, Vinik A, Feldman E, Freeman R, Boulton AJ. Surgical decompression for diabetic sensorimotor polyneuropathy. Diabetes Care 2007;30(2):421–422
87 Vinik A, Mehrabyan A, Colen L, Boulton A. Focal entrapment neuropathies in diabetes. Diabetes Care 2004;27(7):1783–1788
88 Levine TD, Barrett S, Hank N, et al. A pilot trial of peripheral nerve decompression for painful diabetic neuropathy. In: Neurology2013:P01.125
89 Perkins BA, Olaleye D, Bril V. Carpal tunnel syndrome in patients with diabetic polyneuropathy. Diabetes Care 2002;25(3):565–569
90 Taylor-Gjevre RM, Gjevre JA, Nair B. Suspected carpal tunnel syndrome: do nerve conduction study results and symptoms match? Can Fam Physician 2010;56(7):e250–e254
91 Tetro AM, Evanoff BA, Hollstien SB, Gelberman RH. A new provocative test for carpal tunnel syndrome. Assessment of wrist flexion and nerve compression. J Bone Joint Surg Br 1998;80(3): 493–498
92 Brown A. Axonal transport of membranous and nonmembranous cargoes: a unified perspective. J Cell Biol 2003;160(6):817–821