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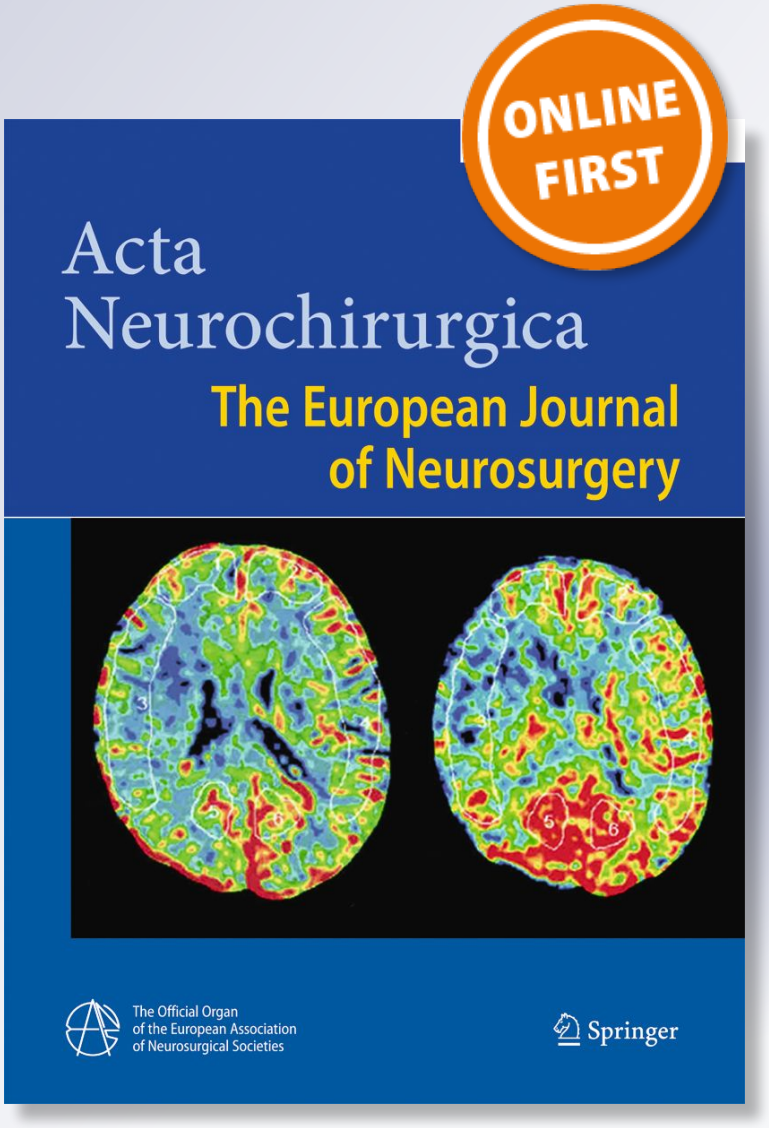

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REVIEW ARTICLE

An update on addressing important peripheral nerve problems: challenges and potential solutions

Wilson Z. Ray[1] · **Mark A. Mahan**[2] · **Danzhu Guo**[3] · **Danqing Guo**[3] · **Michel Kliot**[4]

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Abstract From time to time it is thoughtful and productive to review a medical field and reflect upon what are the major issues that need to be addressed and what is being done to do so. This review article is not meant to be all-inclusive but rather focuses on four evolving areas in the field of peripheral nerve disorders and treatments: (1) nerve surgery under ultrasound guidance using a new ultra-minimally invasive thread technique; (2) evolving magnetic resonance imaging (MRI) and ultrasound imaging techniques that are helping to both diagnose and treat a variety of peripheral nerve problems including entrapment neuropathies, traumatic nerve injuries, and masses arising from nerves; (3) promoting recovery after nerve injury using electrical stimulation; and (4) developing animal models to reproduce a severe nerve injury (neurotmetic grade in continuity) that requires a surgical intervention and repair. In each area we first describe the current challenges and then discuss new and emerging techniques and approaches. It is our hope that this article will bring added attention and resources to help better address peripheral nerve problems that remain a challenge for both patients and physicians.

Keywords Peripheral nerve · Carpal tunnel · Regeneration · Diffusion tensor imaging

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New surgical procedure: thread transecting technique

The thread transecting technique is an ultra-minimally invasive surgical technique for dissecting a tissue in a body, in which a piece of flexible and smooth thread is utilized as a means to divide the target [1]. This technique involves several steps: (1) encircling the structure with a smooth small diameter cutting thread through two small skin puncture sites under image guidance; (2) checking that only the structure(s) desired to be cut are encircled by the cutting thread; and (3) actually cutting the desired structure(s). The thread carpal tunnel release (TCTR) is the first clinical application of this new technique.

Procedure

The transverse carpal ligament (TCL) is looped with the dividing thread through a spinal needle under real-time ultrasound guidance. After checking the loop position, the TCL is divided by sawing the thread, leaving only two needle punctures as entry and exit points (Fig. 1). During the TCTR procedure, ultrasound provides real-time three-dimensional high-quality images (Fig. 2) which allows tracking of the course of the third common digital nerve from the median nerve, the ulnar nerve and its sensory branches to the ring finger and little fingers, as well as the Berrettini branch if it exists. The clear visualization of the needle and thread during the procedure, and the ease of making necessary adjustments, allows the risk of causing iatrogenic injuries to be minimized while preserving the superficial palmar aponeurosis [2].

During the TCTR procedure, before the final transecting step, the position of the loop of the dividing thread can be verified relative to the TCL and other anatomical structures. If an incorrect thread path is indicated, then the thread can be

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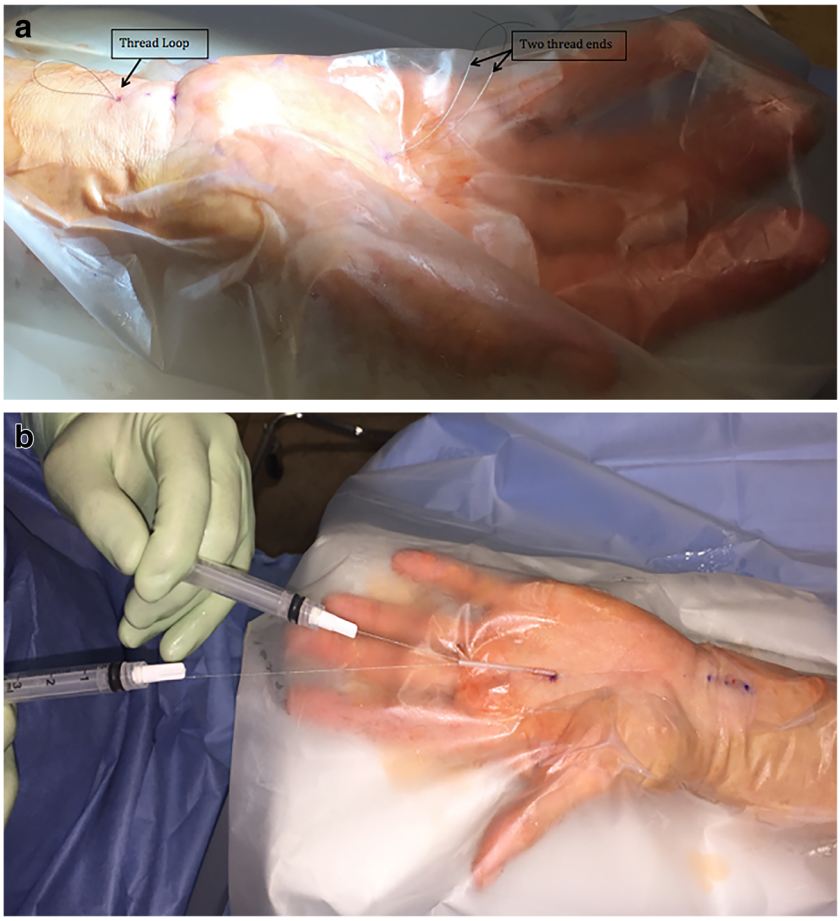

Fig. 1 Thread transecting technique. **a** Looped thread around transverse carpal ligament. **b** -A smooth thread is looped around the TCL, and the two ends are moved back and forth until the TCL has been cut

removed and immediately re-routed using the same procedure. If the surgeon encounters difficulties that require early termination of the procedure, it can be safely stopped at any step prior to the dividing of the TCL [1]. The technique ensures that the division happens only inside the loop of thread around the target without injuring adjacent tissues.

Clinical outcomes

TCTR results in improved clinical outcomes as compared to open and endoscopic approaches. To date, there have been no significant neurovascular complications in the 310 hands we have operated on. Significant relief of symptoms is observed 3 to 5 h after the procedure. Most patients use their hands the day of the procedure for simple daily activities. Patients report their sleep quality is improved on the day of surgery. Most patients with office jobs are able to return to work on postoperative day 1, and those with jobs involving more vigorous manual activities return to work in about two weeks [3]. TCTR minimizes postoperative complications, such as pillar pain, scar tenderness, and functional weakness, by avoiding unnecessary injury to the structures surrounding the TCL.

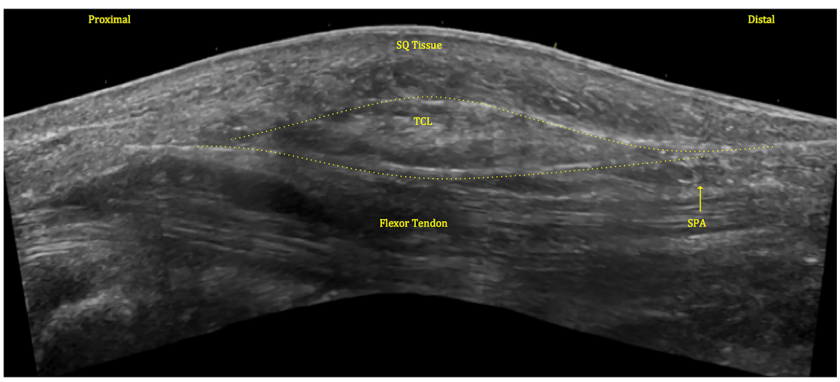

Fig. 2 Ultrasonographic panoramic view of the carpal tunnel in the long axis. *Yellow dotted line* indicates thread path. *TCL* Transcarpal ligament, *SPA* Superficial palmar artery, *SQ tissue* Subcutaneous tissue

Further studies

TCTR is available for clinical practice. The thread trigger finger release has been tested and verified in a cadaveric study, and is under clinical investigation. Further studies are planned to investigate the use of this technique for cubital tunnel release, tarsal tunnel release, plantar fascia release, release for De Quervain's tenosynovitis, common peroneal nerve release, and fascial release for compartment syndrome and plantar fasciitis.

Advanced nerve imaging techniques

Just as imaging has played a very important role in visualizing and helping to diagnose pathology in the central nervous system involving the brain and spinal cord, it is playing an increasingly important role in localizing and identifying both pathology and recovery of nerves of the peripheral nervous system throughout the body. For example, both ultrasonography and MRI have proven useful in diagnosing entrapment neuropathies ranging from common disorders, such as carpal tunnel syndrome and ulnar nerve entrapment across the elbow, to less common entrapment syndromes. Ultrasonography is proving to be particularly useful in helping surgeons localize pathological lesions, such as tumors and sites of nerve entrapment, in the operating room making it possible to perform surgery through smaller incisions more efficiently. Ultrasonography has also made it possible to develop new ultra-minimally invasive nerve surgical procedures as described in the section New surgical procedure. However, certain very important clinical problems and challenges remain, such as distinguishing severe traumatic nerve injuries that can recover on their own (e.g. an axonotmetic grade of nerve injury where the axons have been damaged but the cellular and molecular highways remain, allowing regeneration of nerve fibers) from more severe injuries that require surgical repair (e.g. a neurotmetic grade of injury in continuity where blocking intraneural scar tissue must be resected and the two ends of the nerve sutured together with or without interposition grafts). Other challenges include recognizing preoperatively the surgical resectability and grade of a peripheral nerve tumor. Progress is being made to address these challenging problems using both improving MRI and ultrasonography technology as is described in greater detail below.

Grading of severe traumatic peripheral nerve injuries: distinguishing axonotmetic from neurotmetic nerve injuries

Initial efforts at using standard MRI pulse sequences with some modifications in combination with high-resolution phased array MR coils [4] led to improvements in the ability to visualize both normal nerves and nerves with various types of pathology. For example, T1 as well as T2 and STIR sequences are able to detect focal or segmental abnormalities in nerve configuration and size as well as signal intensity in patients with nerve entrapment syndromes such as carpal tunnel syndrome and ulnar nerve entrapment across the elbow. In most cases of entrapment syndrome, the grade of nerve injury is neuropraxic and involves only a segment of nerve usually measuring no more than several centimeters. Several studies have shown a good correlation between the actual length of abnormal nerve signal and the amount of nerve conduction slowing [5, 6]. However, efforts to use these MR imaging parameters to visualize both nerve degeneration and regeneration in the setting of more severe grades of nerve injury have produced ambiguous results [7, 8].

MR diffusion tensor imaging (DTI) approaches, directed at detecting and visualizing the presence or absence of axons by virtue of their anisotropic properties, has met with some success. For example, MR DTI has shown changes in a severely damaged peroneal nerve that was surgically repaired with sural nerve grafts that correlated with the initial injury and subsequent successful regeneration of axons [9]. In addition, ultrasonography (Fig. 3) has proven useful in demonstrating whether nerves are in continuity or not, especially when clinical and electrodiagnostic evidence and standard MR imaging (Fig. 4) are equivocal. Ultrasonography combined with MR DTI (Fig. 5) can be very accurate in localizing the site of injury and disruption in axonal continuity that correlates well with intraoperative findings (Fig. 6). We also have some preliminary evidence that MR DTI may be helpful in visualizing the extent of injury in the clinical setting of severe brachial plexus injuries that involve avulsion of some of the spinal nerve roots [10]. As we collect more and more MR DTI data on intact and injured peripheral nerves, it is becoming increasingly clear that collecting specific DTI values along the intact, damaged, and recovering segments of nerve will play a critical role in distinguishing nerve segments with and without axons.

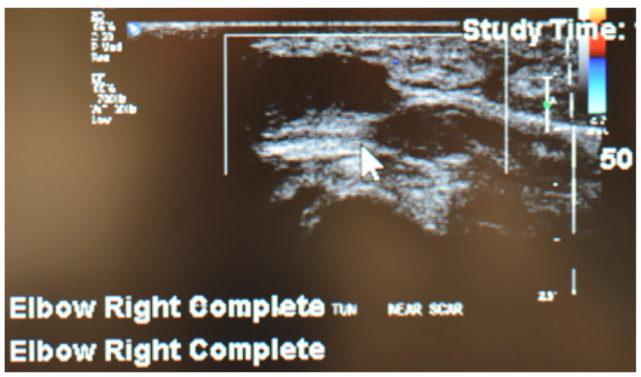

Fig. 3 Longitudinal ultrasound image showing proximal (*left*) and distal (*right*) stumps of a transected ulnar nerve with a small gap between (*arrow*)

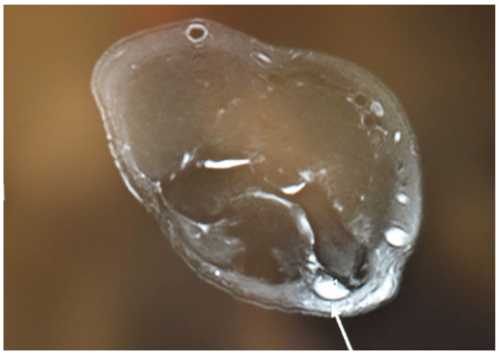

Fig. 4 Standard axial T2 MR neurographic image showing a traumatic neuroma at the site of nerve injury (*arrow*)

Determining the resectability of peripheral nerve tumors

It has been known for a while that many peripheral nerve tumors, including both schwannomas and neurofibromas, can be surgically resected with sparing of functioning nerve fibers, so that patients suffer few if any deficits [11]. However, some nerve tumors are more challenging, such as plexiform neurofibromas, and their resection often produces significant functional deficits. Standard MRI protocols have been useful in helping the surgeon to appreciate the relationship of a nerve mass to the surrounding nerve fascicles [12, 13]. More recently both MR DTI and ultrasonography have proven useful in helping the surgeon determine the relationship of nerve fascicles to the tumor proper [10].

Determining the grade of peripheral nerve tumors

Peripheral nerve tumors demonstrate a wide range of growth behaviors which is reflected in their pathology that ranges from benign to malignant. In fact, the majority of peripheral nerve tumors actually stop growing for long periods of time [14]. However, it can be challenging to distinguish malignant from benign tumors on the basis of standard imaging characteristics. Other imaging modalities, such as PET/CT which measures the metabolic activity of tissue, can be helpful

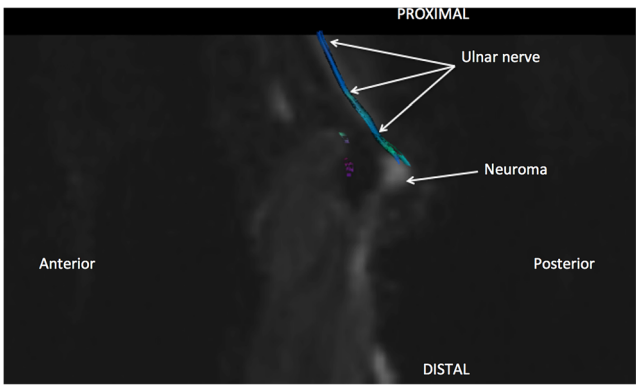

Fig. 5 Longitudinal MR neurographic DTI image showing ulnar nerve axons (blue axons) stopping at the site of a traumatic neuroma

especially in combination with clinical and MRI criteria [15]. MR diffusion is also showing promise [16, 17]. Nonetheless, at present, a definitive diagnosis can only be obtained from a biopsy obtained through either an open or a percutaneous approach. High-resolution MR neurographic techniques have increased diagnostic accuracy and success by making it possible to detect and selectively target for biopsy, via an open surgical approach, abnormal appearing fascicles within a peripheral nerve [18]. Novel approaches using a nerve biopsy device with a nerve stimulator at the tip to avoid damaging functioning nerve fibers are under development (unpublished work by senior author).

Enhancing nerve regeneration: electrical stimulation

Mechanisms to further improve functional recovery remain at the forefront of peripheral nerve research. While nerve transfers have no doubt brought about a paradigm shift in the management of peripheral nerve injuries, there remains a significant void in meaningful interventions that can enhance or accelerate axonal regeneration. Work is underway investigating the use of exogenous growth factors as well as transient immunosuppression [19–21]. While both of these techniques have demonstrated tangible benefits, their practical widespread clinical application has not been realized. A potentially more applicable adjunct is the use of electrical stimulation. Indeed, a considerable amount of work has been done investigating the use of electrical stimulation and its potential therapeutic effects in both animal and human models. Initial work largely focused on electrical stimulation of denervated muscle [22–24] or continuous stimulation of the nerve [25–28]. A significant amount of work has been done to define optimal nerve stimulation parameters [29–35]. It has clearly been demonstrated that 1 h of 20 Hz electrical stimulation upregulates the expression of proregenerative growth factors and leads to both enhanced and accelerated functional recovery following nerve injury [30]. Even in the setting of delayed repair this stimulation paradigm results in improved functional recovery [29]. Previous work has also demonstrated that more is not necessarily better, that chronic stimulation over several weeks is not beneficial [25, 36]. More recently, our own group has demonstrated that indeed while prolonged continuous stimulation may not improve regeneration, intermittent stimulation over several days may enhance functional recovery (unpublished results).

The application of 1 h of stimulation, or potentially an alternative paradigm over several days, remains challenging for the nerve surgeon given (1) the time required in the operating room to deliver 1 h of direct nerve stimulation and (2) the inability to deliver ongoing direct nerve stimulation following the index surgical procedure. Recent advances in wireless inductively powered technologies have changed the landscape

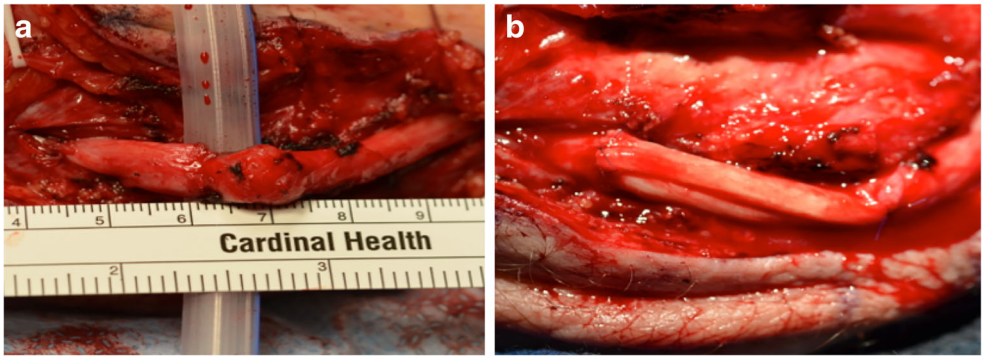

Fig. 6 Intraoperative photographs showing resection of a traumatic neuroma. *Left* The traumatic neuroma was maximally damged and showed discontinuity of the nerve at level 6 on the ruler. *Right*: Two cadaveric nerve grafts are interposed between the proximal and distal stumps of the nerve after the intervening neuroma has been resected

of implantable medical devices. Using widespread established technology we have fabricated dedicated peripheral nerve stimulation devices which can be used to both wirelessly assess functional recovery and provide direct nerve stimulation without additional surgery to access the nerve [37, 38]. These devices have been demonstrated to enhance functional recovery following cut and repair in a rodent model (Fig. 7) without the additional time required to deliver direct stimulation during the index procedure. We expect that further innovation and development of device composition will allow these devices to have practical application in a human population.

Animal models of nerve injury

Despite the fact that rapid-stretch injury is the commonest form of severe traumatic nerve injury [39], there is no generally accepted animal model for investigating this type of injury. While much attention has been given to biomechanics of peripheral nerves [40–46], there is no existing animal model to investigate the pathophysiology specific to rapid-stretch nerve injuries. Creation of a successful animal model that replicates the most common clinical presentation of acute nerve injury may provide new insights and treatment options.

Rapid stretch injuries produce a unique pathology (and pose a unique challenge)

The majority of severe nerve injuries result from rapid nerve stretch caused by the rapid deceleration that occurs during, for example, a motor vehicle collision or ejection from the vehicle, or other high-speed collisions, such as a fall from height or sustained during a sporting activity [47]. The severest injuries benefit from surgery – but most patients are left with limited strength and function of the injured limb. Even a "good" surgical outcome rating may be associated with only minimal return of strength [39].

There are specific problems unique to rapid-stretch injuries that are not recreated in animal models of focal crush or transection injuries. First, rapid-stretch injuries often heal in a pathological "neuroma-in-continuity", which creates uncertainty in clinical decision making as well as intraoperative repair [48–51]. Second, more severe nerve stretch injuries produce long regions of nerve injury. The distal nerve is often scarred and the results after repair tend to be poor, especially when long segment grafts are utilized to replace diffusely injured nerves. Third, when confronted with a stretch injury, the standard approach remains to consider surgery within 3 to 6 months of the injury [52]; however, regenerative capacity peaks within 2 weeks of injury [53]. The optimal intervention should ideally pivot on the biological response to injury, and should not be performed as a belated response to failure.

Current animal models

Overwhelmingly, experimental models to reproduce nerve injury have employed either surgical transection or crush injury

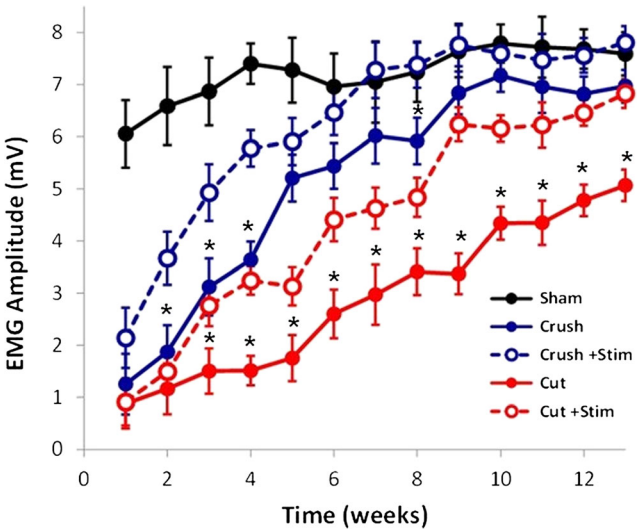

Fig. 7 Effect of electrical stimulation on functional recovery of the sciatic nerve following cut and repair in a rodent model. Maximum isometric twitch force (*top*) and maximum isometric tetanic force (*bottom*) evoked by the tibealis anterior (*TA*) and extensor digitorum longus (*EDL*) muscles upon stimulation of uninjured, crushed, and cut and repair sciatic nerve both in the presence and absence of brief electrical stimulation via an implanted wireless nerve stimulator. Mean values and standard deviations are shown. *$p < 0.05$ versus time-matched injury model without brief electrical stimulation

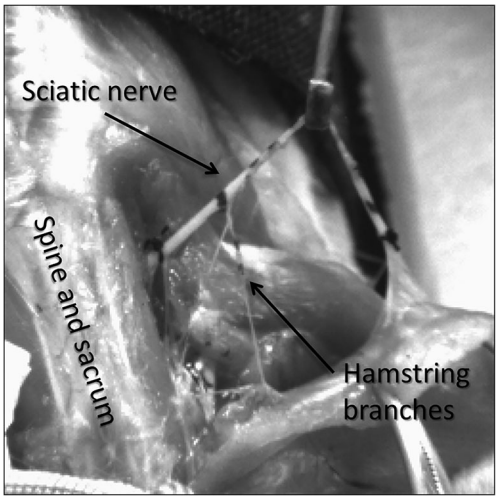

Fig. 8 Video still from ultra-high speed video during rapid stretch of a rat sciatic nerve

in the laboratory [54]. In clinical practice, however, these injuries are relatively uncommon [55]. Surgical transection and crush injury models serve to provide axonotmetic injuries, but these do not mimic the clinical situation characterized by an extensive stretch injury to nerve architecture. Neither the biomechanics nor the pathophysiology of rapid stretch has been studied experimentally in a rigorous manner. All major studies analyzing the effects of stretch on peripheral nerves have utilized slow rates of stretch [40–46]. Interestingly, while these studies showed consistent relationships among strain, function and histology, essentially all of the studies found conflicting results. For example, the maximum strain (the measurement of stretch) at biomechanical failure has ranged from 4% [56] to over 100% [57], with recent values ranging from 20% to 73% [41, 42, 44, 45] of the total length of the tested nerve.

Proposed model

Several elements are necessary for an animal model to accurately mimic rapid-stretch nerve injuries: (1) reproducibility of the injury; (2) lack of confounding injuries; (3) reproduction of the histology seen in human injuries; and (4) production of the dynamic range of injuries, including neurapraxia, axonotmesis with recovery, and neurotmesis where the nerve remains in continuity with no recovery. One of the authors (M.A.M.) has developed a system to produce rapid-stretch injuries in peripheral nerves in animals. Utilizing a vector-constrained system, the force of a defined weight drop is used to rapidly stretch a nerve in the animal (Fig. 8). An ultra-high-

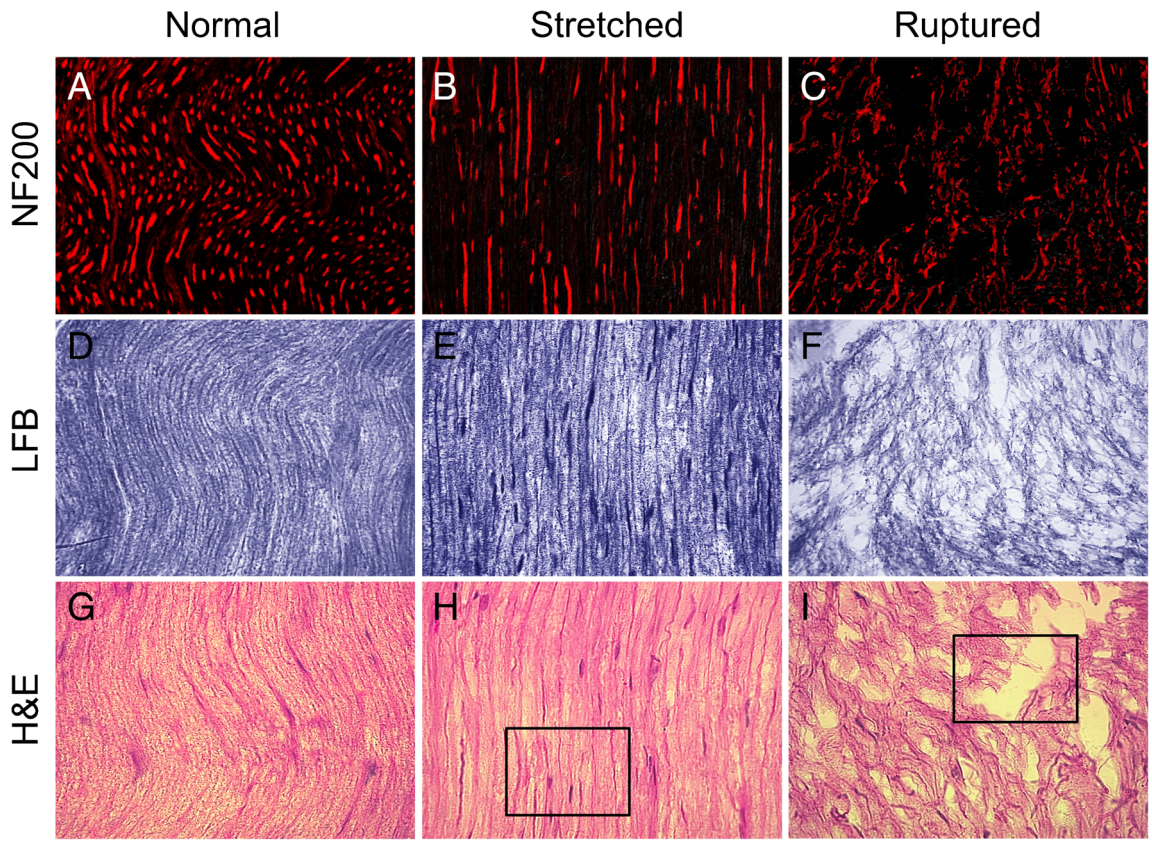

Fig. 9 Normal (**a**, **d**, **g**) and damaged (**b–c**, **e**, **f**, **h**, **i**) sciatic nerve tissues as visualized by neurofilament 200 antibody (*NF200*, **a–c**), luxol fast blue (*LFB*, **d–f**), and hematoxylin and eosin stain (*H&E*, **g–i**). Normal tissues show well-organized Schwann cells, while sections from stretched nerve show straightened axons with gaps between the Schwann cells (**b**, **e**, **h**), and severely disrupted internal architecture (**c**, **f**, **i**)

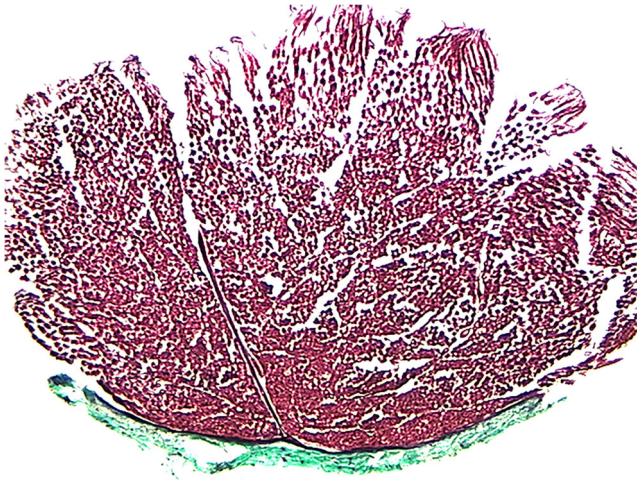

Fig. 10 Cross-sectional slice of rat sciatic nerve (modified Lillie's trichrome). The epineurium is the *green-colored tissue* at the base of the figure. Intact perineurium is the dark laminar membrane separating the epineurium from the endoneurium, as well as an intraneurial septum (vertical membrane). Endoneurial fibers are dispersed and fragmented

speed video system captures the event at 5,000 frames per second, and optical markers allow precise calculation of the strain deformation, velocity, acceleration, and regional variation of rapid-stretch injury along the nerve. The system has been used to study the biomechanical properties of nerves subjected to rapid stretch, which have not been previously studied, as well as the histological consequences of rapid stretch. Similar to prior studies into the viscoelastic properties of peripheral nerves [41, 42, 44], rapidly stretched rat nerves demonstrate transition from an elastic phase (with passive recoil to near prestretch length) to a plastic phase (loss of recoil) after stretch beyond 50% strain. Biomechanical comparison with isolated nerve preparations has demonstrated that the branching pattern of the nerve contributes to the magnitude of the failure (rupture) strain level as well as the location of the rupture site. Detailed histological analysis has demonstrated consistent injury patterns, with rupture of the epineurium occurring at low strain levels, progressive fragmentation of the endoneurium with increasing strain severity (Fig. 9), and rupture of the perineurium when the nerve is stretched beyond elastic recoil and undergoes plastic deformation (Fig. 10).

More importantly, preliminary studies in mice have demonstrated that the severity of the biomechanical force applied in our rapid-stretch nerve injury model determines the degree of recovery. Specifically, mice subjected to an injury below the elastic limit demonstrate rapid recovery consistent with a neurapraxic grade of injury. Ruptured nerves with the ends placed in continuity and thus less than the critical gap (as defined for sharp transection in rodents [58]) demonstrate no improvement in functional performance. In the middle range, mice whose nerves were stretched beyond the elastic limit (i.e. plastic deformation) demonstrated persistently worse functional performance consistent with at least a severe axonotmetic grade of injury with partial recovery of function. Thus, it appears that the degree of rapid-stretch injury can be closely correlated with the likelihood of successful regeneration and recovery. Our experimental animal model of rapid-stretch nerve injury represents significant progress towards generating in the laboratory biological grades of nerve injury that are clinically relevant, important, and currently very challenging to treat.

Conclusion

It is our hope that this update on important and challenging peripheral nerve problems will whet the appetite of the budding peripheral nerve surgeon. Although much progress has been made, to paraphrase Robert Frost's famous poem "Stopping by Woods on a Snowy Evening", we still have miles to go before we sleep, and miles to go before we sleep….

Compliance with ethical standards

Funding No funding was received for this research.

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 article.

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. For this type of study formal consent is not required. All procedures performed in studies involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted.

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