

Entrapment neuropathies: pathophysiology and pathogenesis

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Abstract

A number of theories of pathogenesis of entrapment neuropathy, due to repeated loading, have been proposed and these theories are being actively explored with animal models. Tubes placed loosely around peripheral nerves cause delayed onset, chronic pain and changes in nerve morphology including nerve sprouting. Balloons placed around or adjacent to the nerve and inflated to low pressures, rapidly produce endoneurial edema and a persistent increase in intraneural pressure. The same models demonstrate long-term changes such as demyelination and fibrosis. The applied pressure causes a decrement in nerve function and abnormal morphology in a dose-dependent manner that appears to be linked to the amount of endoneurial edema. A new model involving involuntary, repetitive fingertip loading for 6 h per week for 4 weeks has caused slowing of nerve function at the wrist similar to that seen in patients with carpal tunnel syndrome. These models have the potential to reveal the mechanisms of injury at the cellular and biochemical level and address questions about the relative importance of various biomechanical factors (e.g. peak force, mean force, force rate, duty cycle, etc.). In addition, these models will allow us to evaluate various prevention, treatment and rehabilitation protocols.

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1. Human pathophysiology

Entrapment neuropathies usually occur near joints where the nerve passes through a fibrous tunnel as it courses from one body segment to the next. Examples are carpal tunnel syndrome, an injury to the median nerve at the wrist, and cubital tunnel syndrome, an injury to the ulnar nerve at the elbow. The diagnosis is easily made when the sensory and/or motor deficit corresponds to the tissues innervated by the nerve and a nerve conduction study documents conduction slowing [19]. The diagnosis is more difficult when the presentation is atypical.

Carpal tunnel syndrome, the most common human entrapment neuropathy, will serve as a model for this paper. Carpal tunnel syndrome involves the compression of the median nerve as it passes through the wrist within the carpal tunnel. A cross-section at the wrist reveals a tunnel tightly packed with nine tendons, the median nerve, and synovium, with tunnel walls

formed by the stiff carpal bones and flexor retinaculum. Approximately half the cross-sectional area of the tunnel is tendon and half is synovium. At the proximal and distal ends of the tunnel the synovium is gradually replaced by the muscles which are attached to the tendons.

A nerve is composed of hundreds or thousands of axons, or nerve fibers, some myelinated and the rest nonmyelinated (Fig. 1). Nerve fibers are grouped together in bundles, called fascicles, which are surrounded by a perineurial membrane. Small vessels, with a coiled appearance, supply the nerve with blood from the surrounding tissue and permit the normal gliding of the nerve within a tunnel during joint movements [12].

The median nerve from patients with carpal tunnel syndrome (in the few cases where it was possible to harvest the nerve and evaluate its histopathology) contains perineurial thickening, demyelination, and epineurial fibrosis [15]. In nerves taken at autopsy, where the status of the nerve was unknown, the amount of connective tissue in and surrounding the nerve varies by location. Where the nerve crosses a joint it contains an increased quantity of connective tissue, possibly as a response to repeated loading [1,28]. In patients with

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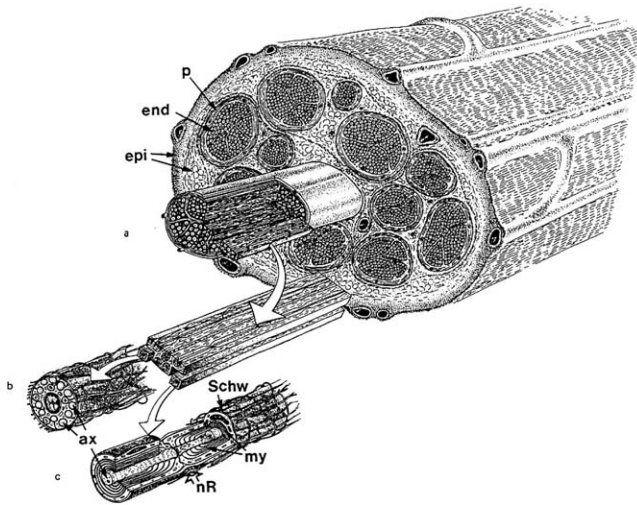


Fig. 1. Drawing of a peripheral nerve showing the various components: (a) fascicles are bundles of nerve fibers surrounded by a membrane called the perineurium (p) and are embedded in the epineurium (epi). Inside a fascicle the myelinated (c) and unmyelinated (b) axons (ax), or nerve fibers, are surrounded by the endoneurium (end). Myelinated fibers are surrounded by the myelin sheath (my) which is formed from Schwann cells (Schw) which are separated by the nodes of Ranvier (nR). (Reproduced, with modification, from: Lundborg, G.: *Nerve Injury and Repair*, p. 186. Edinburgh, Churchill Livingstone, 1988. Reprinted with permission.)

carpal tunnel syndrome, it is relatively easy to evaluate the histology of the synovium surrounding the nerve taken during carpal tunnel release surgery. The synovium from patients contains more edema and fibrosis when compared to healthy controls [9,27]. There is little evidence of inflammation.

The fluid pressure inside the tunnel is higher in patients with carpal tunnel syndrome than in healthy subjects, likely due to the edema formed in the tunnel (Fig. 2). These pressures are high enough to limit

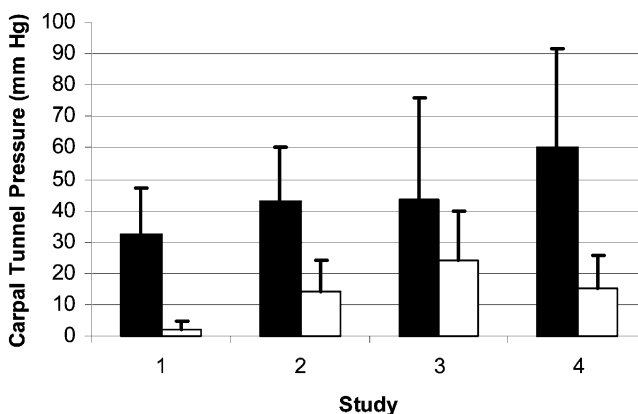


Fig. 2. Carpal tunnel pressure is elevated in patients with carpal tunnel syndrome (filled columns) in comparison to healthy controls (open columns) as demonstrated by these four studies: 1. ($n = 15, 12$) [6], 2. ($n = 46, 16$) [18], 3. [34] ($n = 72, 21$), 4. ($n = 647, 31$) [7].

microvascular blood flow. Surgical release of the flexor retinaculum leads to an immediate reduction in carpal tunnel pressure and patients report an improvement in some symptoms immediately after surgery, indicating resolution of the ischemic component due to chronic compression [18]. There is also, typically, a delayed recovery of other symptoms over the 2–12 months following surgery.

We know from studies of healthy subjects that the pressure inside the carpal tunnel is strongly influenced by pinch force and hand, wrist and forearm postures [21]. Wrist extension to 40 degrees can increase the tunnel pressures by 40 mmHg [8,31]. Independently, a static fingertip pinch to 1.2 kg force can also increase the mean pressure by approximately 40 mmHg [2,22]. The tunnel can sustain an elevated pressure, due to a sustained fingertip loading or a non-neutral wrist posture, for at least 10 min, which is as long as this has been studied. There is no mechanism for reducing these increased pressures.

The three leading theories of causation of entrapment neuropathies are (1) repeated compression leads to ischemia, edema formation in the subendoneurial space and the synovium and eventually fibrosis [23], (2) tethering of the nerve due to scar tissue leads to reduced nerve gliding and ischemia [16,30,33], and (3) localized mechanical pressure from structures such as the flexor retinaculum cause local nerve damage [17]. Elements of these theories may overlap. For example, elevated extraneural pressure may push the nerve against a stiff tissue and lead to a localized injury due to mechanical pressure.

2. Acute effects of compression

The effects of extraneural compression on microcirculation have been studied under a microscope while a balloon surrounding the nerve was inflated to different pressures [3,26]. Pressures of 20–30 mmHg interfere with venous blood flow while pressures of 35–50 mmHg reduce capillary flow. A pressure of 70 mmHg causes complete ischemia.

A brief (4 h) period of low-pressure (30 mmHg), extraneural compression of the nerve, causes increased vascular permeability leading to edema formation within the nerve, which persists for at least 24 h after the compression is completely removed [13,25]. There are no lymphatic vessels to drain the endoneurial space. When edema forms in this space the pressure in the fascicle increases, remains high, and interferes with the endoneurial microcirculation [12]. Increasing either duration of compression or compression pressure leads to greater edema formation and greater sustained intraneural pressures in a dose-response pattern.

3. Short-term compression studies

The biological effects of a brief, controlled nerve compression were studied in the rat sciatic nerve using small, inflatable cuffs [5,20]. In 91 rats, pressures of either 0, 30 or 80 mmHg were applied for 2 h to the nerve, then the cuff was removed and the incision closed. At regular intervals up to 28 days the nerves were removed and examined for evidence of injury. Within 4 h, endoneurial edema formed within all compressed nerves and persisted for the entire time of the study. Inflammation and fibrin deposits occurred within hours of compression, followed by a proliferation of endoneurial fibroblasts and capillary endothelial cells. After 2 days, vigorous proliferation of fibrous tissue was noted, with marked fibrosis observed at day 28. Demyelination and axonal degeneration were first observed a week after compression. The degree of edema formation and demyelination were related to the initial cuff pressure.

4. Chronic compression models

To model chronic nerve compression, short silicon tubes have been secured loosely around the rat sciatic or sural nerve [14,35]. Pain and nerve histologic changes occurred after 1–3 months. The biological response of the nerve was similar to that found in the cuff experiments, with early perineural edema followed by a short-term macrophage recruitment, fibrosis, demyelination, and, finally, nerve fiber degeneration.

One of the limitations of the tube models is that it is not possible to control the pressure applied to the nerve. In order to address this, Diao et al. [4] developed a nerve compression model using the rabbit. Although the rabbit paw anatomy is not the same as the human, the rabbit paw has a carpal tunnel that is bounded by a flexor retinaculum and contains four tendons and a median nerve. A small balloon catheter was inserted into the rabbit carpal tunnel with the end of the catheter protruding from the upper back in order to control the balloon pressure. Pressures of 40–80 mmHg were applied to the balloon. The rabbit nerve function was followed with weekly nerve conduction studies until the nerve conduction was prolonged. The number of days to delayed nerve function decreased with increasing pressure; at 70 mmHg, the mean number of days was 21 while at 50 mmHg it was 42 (Fig. 3). The nerve histology changes of epineurial fibrosis, demyelination, axon degeneration, and perineurial thickening were similar to those observed with the cuff and tube studies. The changes were related to the applied pressure.

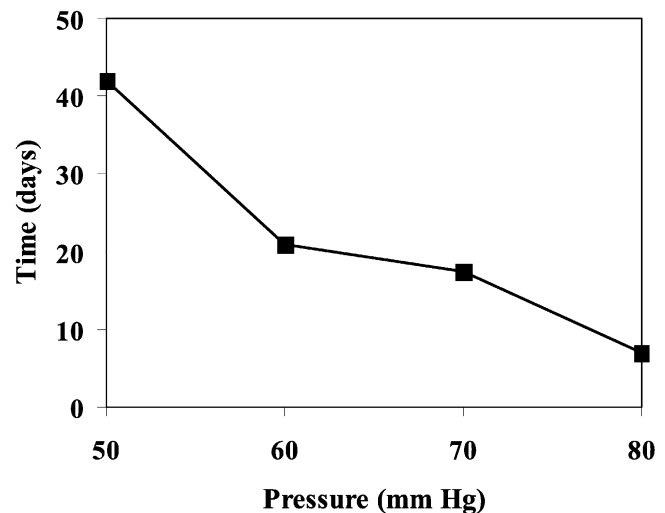


Fig. 3. Effect of pressure on the number of days to median motor nerve conduction delay. The balloon catheter is placed in the rabbit carpal tunnel and inflated to the target pressure every day [4].

5. Repetitive loading model

Recently, an entrapment neuropathy model associated with repeated loading of the digits was developed using a rabbit model [24]. The goal was to develop a model in which the finger repetition rate and applied force could be precisely controlled. The model involved stimulating the flexor digitorum profundus muscle at a controlled frequency, duty cycle, and duration. The third digit was attached to a load cell and the stimulation voltage was adjusted to achieve the desired finger twitch force. During the first experiment the peak force was adjusted to 15% of peak tetanic force. The contralateral limb served as the control. The repetition rate of 1 Hz was applied for 2 h, 3 days per week for 7 weeks (40 h of loading total). During loading the rabbits were under general anesthesia. Median nerve motor latency across the wrist was measured before and after the 7 weeks of loading. The repetitive finger loading led to a significant prolongation in motor latency when compared to the control limb in the 5 rabbits studied.

6. Summary

The critical compression pressures that alter blood flow in the nerve are known; effects on the venous flow are observed at pressures as low as 20 mmHg. A delayed nerve injury is observed after pressures as low as 30 mmHg are applied to the nerve for 2 h. These pressures initially cause capillary leakage, the accumulation of intra- and extra-neurial edema and a persistently increased intraneurial pressure. These initial changes are followed, over the next 30 days, by a brief

inflammatory reaction, fibrosis, demyelination, and axonal loss. Although the relationship between axonal degeneration and compression pressure follows a dose-response pattern, the critical injury thresholds for pressure and duration for chronic nerve compression have yet to be determined.

Studies of carpal tunnel pressure in healthy humans demonstrate fluctuations in extraneural pressure that are strongly influenced by hand activity. Tunnel pressures are altered by hand, wrist and forearm postures and fingertip loading. We do not have carpal tunnel pressure data from subjects performing their usual activities at the workplace or home. Nor do we have *in vivo* extraneural pressure data from other entrapment sites, such as the ulnar nerve at the elbow or wrist.

A recent animal model involving repetitive fingertip loading has produced a nerve injury similar to carpal tunnel syndrome. Altered nerve function occurred after 40 h of repetitive finger loading at loads of 15% of maximum force. The role of the different biomechanical factors in causing nerve injury are not well understood. This model has the potential to evaluate the relative contributions of repetition rate, peak load, mean load, loading rate, duty cycle, and duration. In addition, it may determine the time course, capacity, and mechanisms for repair and remodeling of ultrastructural damage to nerves associated with cyclical loading, including the effect of various patterns of rest and reuse after injury on the mechanisms and time course of recovery.

Finally, the molecular, cellular, and structural changes that occur during the early stages of nerve compression are not fully characterized. Knowledge of these changes would help identify the point at which the injury process becomes irreversible. This information would also be useful for planning prevention and treatment strategies.

Acknowledgements

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