Current Concepts Review

Pathophysiology of Nerve Compression Syndromes: Response of Peripheral Nerves to Loading*

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Nerve compression syndromes involve peripheral-nerve dysfunction that is due to localized interference of microvascular function and structural changes in the nerve or adjacent tissues. Although a well known example is compression of the median nerve at the wrist (carpal tunnel syndrome), other nerves, such as the ulnar nerve at the wrist or the elbow and the spinal nerve roots at the vertebral foramen, are vulnerable. This paper focuses on studies in which the physiological, pathophysiological, biochemical, and histological effects of biomechanical loading on the peripheral nerves were evaluated in humans and animals.

When tissues are subjected to load or pressure, they deform and pressure gradients are formed, redistributing the compressed tissue toward areas of lower pressure. Nerve compression syndromes usually occur at sites where the nerve passes through a tight tunnel formed by stiff tissue boundaries. The resultant confined space limits movement of tissue and can lead to sustained tissue pressure gradients. Space-occupying structures or lesions (for example, lumbrical muscles, tumors, and cysts) can cause nerve compression injury, as can conditions associated with accumulation of fluid (for example, pregnancy, congestive heart failure, and muscle compartment syndromes) or accumulation of extracellular matrix (for example, acromegaly, myxedema hypothyroidism, and mucopolysaccharidosis)[76]. Although nerve injuries related to vibration occur near the region of exposure, the symptoms may be manifest at another site, where the nerve may be constricted. Other conditions, such as diabetes mellitus, may increase the likelihood that a compressed nerve will undergo a pathological response. In addition, there may be an inflammatory reaction that may impair the normal gliding of the nerve. Basic knowledge of the microanatomy of peripheral nerves and neurons and of their complex reactions to compression is essential to understanding, preventing, and treating nerve compression injuries.

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Structure and Function of Peripheral Nerves

Microanatomy

The neuron consists of the nerve cell body, located in the anterior horn of the spinal cord (motor neuron) or in the dorsal root ganglia (sensory neuron), and of the axon, a long protrusion extending into the periphery that is surrounded by individual Schwann cells arranged in a longitudinal continuous chain forming myelinated nerve fibers (Fig. 1). Lying next to the myelinated nerve fibers are many nonmyelinated fibers associated with one Schwann cell. Myelinated and nonmyelinated nerve fibers are organized in bundles, called fascicles, which are surrounded by a strong membrane called the perineurial membrane, consisting of laminae of flattened cells. The fascicles usually are organized in groups, held together by a loose connective tissue called the epineurium. Between the nerve fibers and their basal membrane is an intrafascicular connective tissue known as the endoneurium. The quantity of the connective-tissue components may vary between nerves and also along the length of the same nerve. For example, nerves located superficially in the limb or parts of the nerve that cross a joint contain a greater quantity of connective tissue, possibly as a response to repeated loading[76].

The propagation of impulses in the nerve fibers as well as the communication and nutritional transport system in the neuron (axonal transport) requires an adequate energy supply. Therefore, the peripheral nerve contains a well developed microvascular system with vascular plexuses in all of its layers of connective tissue[36,38]. The vessels approach the nerve trunk segmentally and have a coiled configuration so that the vascular supply is not impaired during normal gliding or excursion of the nerve trunk. When the vessels reach the nerve trunk, they divide into branches that run longitudinally in various layers of the epineurium and they also form numerous collateral connections to vessels in the perineurial sheath. When the vessels pass through the perineurium into the endoneurium, which contains primarily capillaries, they often go through the perineurium obliquely, thereby constituting a possible valve mechanism[36,38].

The perineurial layer and the endoneurial vessels

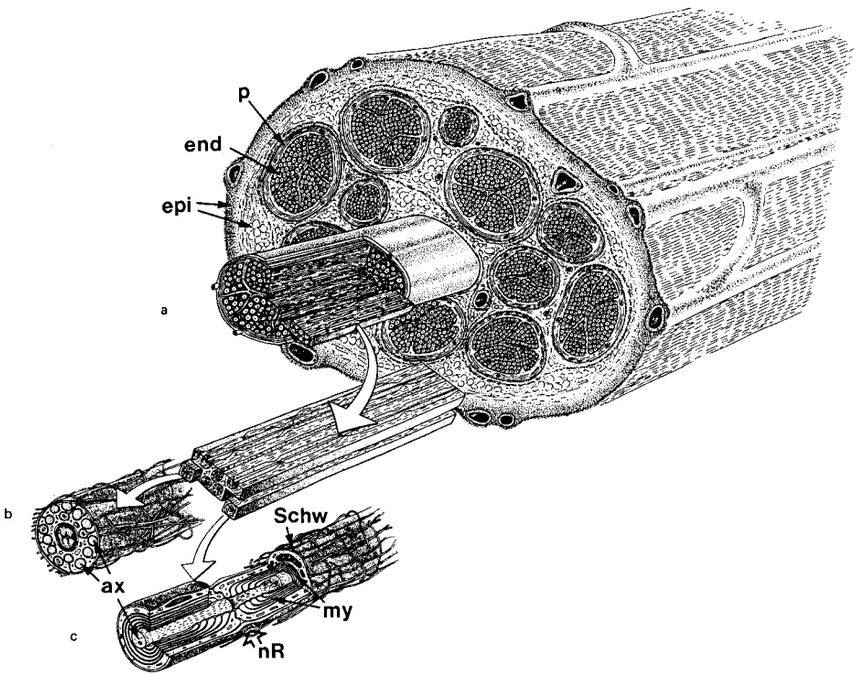

FIG. 1

Drawing showing the microanatomy of the peripheral nerve trunk and its various components.

a: Bundles of nerve fibers are surrounded by the perineurium (p), thereby creating fascicles that are embedded in loose connective tissue, called the epineurium (epi). The intrafascicular connective tissue is called the endoneurium (end).

b and *c:* The appearance of nonmyelinated *(b)* and myelinated *(c)* nerve fibers. Schw = Schwann cell, my = myelin sheath, ax = axon, and nR = node of Ranvier. (Reproduced, with modification, from: Lundborg, G.: *Nerve Injury and Repair,* p. 186. Edinburgh, Churchill Livingstone, 1988. Reprinted with permission.)

play an important role in protecting the nerve fibers in the fascicles. The endoneurial milieu is protected by a blood-nerve barrier, and the tissue pressure in the fascicle (endoneurial fluid pressure) is slightly positive[50]. This is obvious when there is injury to the perineurium; after a transection, a so-called mushrooming effect is observed. There are no lymphatic vessels in the endoneurial space; therefore, there may be problems when edema occurs in the endoneurial space. Following such edema, the pressure in the fascicle may increase and rapidly interfere with the endoneurial microcirculation[43]. The epineurial vessels are more vulnerable than the endoneurial vessels are to trauma and even to operative handling of the nerve.

As already mentioned, the neuron is a unique cell with a cell body and an axon. The length of the axon may be 10,000 to 15,000 times the diameter of the cell body. Therefore, there is a need for an intraneuronal transport system (axonal transport) whereby essential products are produced and constantly transported from the nerve cell body along the axon (antegrade transport) while disposal materials and trophic factors are transported in the opposite direction (retrograde transport)[24]. Axonal transport consists of various components. Fast axonal transport (as much as 410 millimeters per day) involves various enzymes, transmitter substance vesicles, and glycoproteins, and slow transport (as much as thirty millimeters per day) involves primarily cytoskeletal elements such as subunits of microtubules and neurofilaments. It should be noted that axonal transport is energy-dependent, and disturbances in axonal transport may be involved not only in the development of diabetic neuropathy but also in nerve compression injuries[8].

Normal Gliding of Nerve Trunks

Surrounding the nerve trunk is a conjunctiva-like adventitia that permits excursion of the nerve trunk. This extraneural gliding surface, together with the normally occurring sliding of fascicles against each other in the deeper layers (intraneural gliding surfaces), makes the normal gliding of the nerve during joint motion possible. The median and ulnar nerves may glide 7.3 and 9.8 millimeters, respectively, during full flexion and extension of the elbow, and the extent of excursion of these nerves just proximal to the wrist is even more pronounced (14.5 and 13.8 millimeters, respectively)[90]. In relation to the flexor retinaculum, the median nerve can move a maximum of 9.6 millimeters during wrist flexion and somewhat less during wrist extension; it also moves during motion of the fingers[48].

Inducement of Nerve Compression in Animals

Various methods have been used to induce acute or chronic compression of a peripheral nerve in animal

models, and each method has advantages and disadvantages. Tourniquets have been applied around the limbs of rats, rabbits, and baboons for minutes or hours. In baboons, very high pressures (range, 66.7 to 133.3 kilopascals [500 to 1000 millimeters of mercury]) have been shown to induce structural nerve changes[19,36,57]. However, it is difficult to control the precise location and pressure on the nerve with use of the tourniquet method. Using an invasive method, others have applied a miniature inflatable cuff around a mobilized nerve to achieve controlled, low-magnitude extraneural pressure for several hours[8,16,67].

In models of chronic nerve compression, mobilized nerve segments have been compressed for weeks or months by surrounding the nerve with tightly fitting arteries[87], metal spring clips[15], compression clamps[27,56], and tubes of various materials such as polyethylene[85] and silicone[11,28,29]. With these methods, it is possible to obtain a graded compression but it is not possible to relate the compression to a specific pressure level as can be done with the miniature inflatable cuff. Furthermore, the implanted foreign material also may induce an inflammatory response[28,44]. A model of normally developing chronic entrapment of the median nerve at the wrist in guinea pigs also has been used to study the structural changes of myelinated fibers[58], but, as with the other models of chronic nerve compression, neither external load nor extraneural pressure has been measured.

Acute Effects of Nerve Compression (Effects within Hours)

In animal experiments, low-magnitude extraneural compression was noted to decrease intraneural microvascular flow, impair axonal transport, and alter nerve structure and function. Extraneural pressures of 2.7 kilopascals (twenty millimeters of mercury), induced with use of miniature inflatable cuffs, reduced epineurial venule blood flow[68]. At pressures of 10.7 kilopascals (eighty millimeters of mercury), all intraneural blood flow ceased. Similarly, pressures of 4.0 kilopascals (thirty millimeters of mercury) inhibited both fast and slow antegrade as well as retrograde axonal transport[8]. Therefore, cell nutrition and the intraneuronal communication system are compromised at elevated extraneural pressures. Extraneural compression of 6.7 kilopascals (fifty millimeters of mercury), applied for two minutes, altered the shape of myelin sheaths, and at higher pressures the myelin was severely split and distorted[16].

The effect of fluctuating extraneural pressure on nerve function was investigated in a rat tibial-nerve model[79]. A fluctuating pressure (minimum, mean, and peak values of 2.7, 4.7, and 6.7 kilopascals [twenty, thirty-five, and fifty millimeters of mercury]) was applied to the nerve at one cycle per second for 20,000 cycles. The resultant decrease in nerve function was similar to that caused by a static pressure of 4.0 kilopascals (thirty millimeters of mercury). This study indicated that, when extraneural pressure fluctuates rapidly, the effects on nerve function are associated with the mean value of the pressure waveform rather than with the minimum or peak value[79].

In several studies of healthy human volunteers, the extraneural pressure in the carpal tunnel was elevated experimentally and compression was maintained for a maximum of four hours while nerve function was monitored[22,77]. The pressure was controlled precisely with a clamp that applied an adjustable external load to the palm; the extraneural pressure in the carpal tunnel was measured simultaneously with use of a fluid-filled catheter. Nerve function was blocked at 6.7 kilopascals (fifty millimeters of mercury) of pressure, whereas some function was lost at 5.3 kilopascals (forty millimeters of mercury). In subjects with different blood pressures, the critical extraneural pressure threshold above which nerve function was blocked was 4.0 kilopascals (thirty millimeters of mercury) less than the diastolic pressure. This finding, combined with the observation that carpal tunnel syndrome may manifest with the treatment of hypertension[17], provides additional support for an ischemic mechanism of acute nerve dysfunction.

Although these studies demonstrated a rapid effect of intermediate pressure on nerve function, they did not address the effects of low extraneural pressure after days or weeks. To discuss those effects, it is necessary to review the results of animal studies.

Short-Term Effects of Nerve Compression (Effects within Days)

Persistent intraneural edema has been observed in animal models after short-term compression at low pressures[67]. With use of a miniature pressure cuff, the extraneural pressure around the sciatic nerve of rats was elevated to 4.0 kilopascals (thirty millimeters of mercury) for periods of two, four, six, and eight hours[40]. In addition, a sham intervention was performed in which the cuff was applied and left in place for two to eight hours but was not inflated. The endoneurial fluid pressure was measured with a micropipette at one hour after removal of the cuff and again at twenty-four hours; the nerve then underwent histological analysis. Compression of 4.0 kilopascals led to an elevated endoneurial pressure, which persisted for twenty-four hours after release of the cuff. Furthermore, the endoneurial pressures at twenty-four hours after release of the cuff increased with increasing durations of compression. Histological examination demonstrated endoneurial edema in the nerves that had been subjected to eight hours of compression but not in those subjected to shorter durations. Eight hours of compression led to an increase of the endoneurial pressures to levels that can reduce intraneural blood flow[51]. The study demonstrated that, after low elevations of extraneural pressure for only two hours, endoneurial fluid pressures increased rapidly and the increases persisted for at least an additional twenty-

four hours[40]. These effects probably are due to the increased vascular permeability of the epineurial and endoneurial vessels after compression. Other studies have demonstrated that ischemia alters the structure of the endothelial and basement membranes over a similar time-frame[2].

Long-Term Effects of Nerve Compression (Effects within Weeks)

The same model was used to study the long-term effects of only two hours of extraneural compression applied to the sciatic nerve of rats[62]. In one group, a pressure of 10.7 kilopascals (eighty millimeters of mercury) was applied and the nerve was excised for histological analysis at intervals of four hours and one, two, seven, ten, fourteen, and twenty-eight days. In another, smaller group of animals, pressures of 1.3 and 4.0 kilopascals (ten and thirty millimeters of mercury) were applied and the follow-up intervals were five, six, and seven days. Sham procedures were also performed in the contralateral limbs: either a chamber was inserted and not inflated or an operation was done without insertion of a chamber. Edema was visible in the subperineurial space within four hours in all compression subgroups, and it persisted for the entire duration of the study. Inflammation and fibrin deposits occurred within hours after compression, followed by proliferation of endoneurial fibroblasts and capillary endothelial cells. Vigorous proliferation of fibrous tissue was noted within days, and marked fibrosis and sheets of fibrous tissue were seen extending to adjacent structures at twenty-eight days. Endoneurial invasion of mast cells and macrophages was noted, especially at twenty-eight days. Axonal degeneration was noted in the nerves subjected to 10.7 kilopascals of compression and, to a lesser extent, in those subjected to 4.0 kilopascals of compression. It rarely was seen in the nerves subjected to 1.3 kilopascals of compression. Axonal degeneration was associated with the degree of endoneurial edema. Demyelination and Schwann-cell necrosis at seven and ten days was followed by remyelination at fourteen and twenty-eight days. Demyelination was prominent in the nerves subjected to 4.0 kilopascals of compression and, to a lesser extent, in those subjected to1.3 kilopascals of compression. The sham intervention in which the cuff was applied but not inflated also led to demyelination in regions close to the surface of the cuff; this was thought to be due to the tense but uninflated rubber cuff pressing on the nerve. The sham operation in which no cuff was applied did not cause any lesions. This study[62] and another[16] demonstrated that relatively brief periods of extraneural compression result in very long-lasting subperineurial edema, which later is accompanied by degeneration and regeneration of nerve fibers and initiation of the permanent changes of the laying down of fibrous tissue. Again, there was a dose-response relationship between the amount of pressure and the severity of the effects.

Changes proximal to the nerve cell bodies also have been observed after a brief period of distal nerve compression. In a rabbit model, extraneural compression of 4.0 kilopascals (thirty millimeters of mercury) for two hours led to changes seven days later that included a decrease in nuclear volume density, an eccentric position of the nucleus in the cell, and dispersion of the Nissl substance[9]. These changes may be followed by a change in the tubulin transport in the neurons[13] as well as by functional changes in the neurons and the nerve trunk (the conditioning lesion effect)[11,14]. Such changes may be involved in conditions such as double-crush or reverse-double-crush syndrome, in which one part of the nerve trunk is compressed, thereby making other parts of the same nerve, at another level, more likely to undergo a pathological change[10].

In order to produce a model of chronic nerve compression, investigators applied loose ligatures or short silicone tubes with various internal diameters around the sciatic or sural nerve of rats and left them in place for weeks or months[46,49]. The tension of the ligatures or the inner diameter of the tube generally was selected so that blood flow was not visibly restricted. The response of nerves to compression in these studies was similar to that in the experiments involving compression with a cuff. For example, the application of loose ligatures around the sciatic nerve led to perineurial edema with proliferation of endothelial cells and demyelination within the first few days, to proliferation of fibroblasts and macrophages as well as degeneration of distal nerve fibers and the beginning of nerve sprouts within one week, to invasion by fibrous tissue and remyelination at two weeks, to regeneration of nerve fibers as well as thickening of the perineurium and the vessel walls at six weeks, and to remyelination of distal nerve segments at twelve weeks[73]. In another model, in which loose-fitting silicone tubes were used, no changes were observed at three months, whereas at five months there was epineurial and perineurial thickening along with segmental demyelination in the peripheral part of the fascicles, followed by wallerian regeneration[45]. Application of silicone tubes with a wide internal diameter can induce increased expression of interleukin-1 and transforming growth factor beta-1 in the nerve cell bodies in the dorsal root ganglia, but the relevance of this finding remains to be clarified[92]. The limitations of these models are that (1) the effects of the tissue inflammatory reaction to the device (foreign-body reaction) usually are not considered but do occur[29] and (2) it is not possible to measure or control the applied extraneural pressure. However, these observational studies provide some insight into the biological response of the nerve to chronic low-grade compression.

Similar biological responses have been observed after chronic low-grade compression of the cauda equina and the spinal nerve roots[7,84,93]. It should be noted that,

TABLE
STUDIES IN WHICH EXTRANEURAL PRESSURE WHO HAD CARPAL TUNNEL SYNDROME WAS

Study	Patients with Carpal Tunnel Syndrome					
				Pressure* *(kPa)*		
	No. of Wrists (No. of Patients)	Gender	Mean Age *(yrs.)*	Wrist in Neutral	Wrist in Flexion	Wrist in Extension
Gelberman et al. (1981)[21]†	15 (15)	11 M, 4 F	56	4.3 ± 2.0	12.5 ± 10.3	14.7 ± 11.4
Werner et al. (1983)[88]†	16 (16)	1 M, 15 F	46	4.1 ± 1.6	10.0 ± 7.9	14.0 ± 7.5
Szabo et al. (1989)[78]†	22 (22)	6 M, 16 F	51	1.3	4.3	6.8
Okutsu et al. (1989)[60]†	62 (46)	16 M, 30 F	51	5.7 ± 2.3	25.6 ± 8.5	29.7 ± 5.9
Luchetti et al. (1989)[35]	30 (26)	1 M, 25 F	51	5.9 ± 2.7	—	—
Rojviroj et al. (1990)[66]†	61 (33)	8 M, 25 F	46	1.6 ± 1.6	3.5 ± 2.6	4.4 ± 3.4
Seradge et al. (1995)[71]‡	81 (72)	18 M, 54 F	46	5.8 ± 4.3	10.6 ± 5.3	13.5 ± 6.8
Hamanaka et al. (1995)[25]	957 (647)	253 M, 394 F	54	8.0 ± 4.2	—	—

*The values are given as the mean and the standard deviation. 0.1333 kilopascal = one millimeter of mercury.
†The wrist was moved passively into three positions.
‡The wrist was moved actively into three positions.

especially at the nerve root, increased age is associated with increased degeneration and regeneration of fibers but not with changes in the number of myelinated fibers in each nerve or fascicle[33]. In addition, degeneration of the nerve in response to compression is more pronounced in older animals[84].

Histological Evaluation of Nerve Compression in Humans

A biopsy of a nerve is likely to lead to permanent nerve dysfunction; therefore, there have been few histological studies of nerves at common sites of compression in humans. In a few case reports on patients in whom a nerve segment was resected, the nerve at the site of the injury was compared with a nerve at a site proximal or distal to the injury[47,55,82]. In each instance, there was thickening of the walls of the microvessels in the endoneurium and perineurium as well as epineurial and perineurial edema, thickening, and fibrosis at the site of the injury. Thinning of the myelin also was noted, along with evidence of degeneration and regeneration of fibers. The patients in these reports had advanced stages of compression syndrome. Earlier in the course of the disease, a segment of the nerve usually is compressed with disturbance of the microcirculation, which is restored immediately after transection of the flexor retinaculum. There is usually both an immediate and a delayed return of nerve function, indicating the importance of ischemia in the early stages of compression syndrome[43].

Increased connective-tissue density has been observed along the median nerve in cadaveric wrists from individuals who died between the ages of sixty and eighty-one years[1]. The greatest density was observed at the level of the wrist crease, whereas the density decreased forty millimeters proximal and distal to the crease. Similar findings were observed in the ulnar nerve at the elbow[54]. These findings suggest that extracellular matrix is deposited in the nerve at sites of bending.

The tissues that lie next to a nerve, within a confined space (for example, synovial tissue within the carpal tunnel), are more easily obtained and can provide information on the response of these tissues to compression[18,20,32,53,61,69,70,91]. In one of the few studies that included a control group, synovial tissue from 147 patients was obtained at the time of carpal tunnel release and was compared with that from nineteen controls[20]. The important findings were increased edema and vascular sclerosis (endothelial thickening) in samples from the patients, who were between the ages of nineteen and seventy-nine years. Inflammatory cell infiltrates (lymphocytes and histiocytes) were observed in only 10 percent (seventeen) of the 177 samples. Surprisingly, the prevalence of fibrosis (3 percent [five of 177]) was much lower than the prevalences of 33 percent (fifteen of forty-five) to 100 percent (twenty-one of twenty-one) reported in the other studies. The lack of definition of histological end points in this study and the others, as well as differences in the selection of subjects, may account for the differences in the prevalences of inflammation and fibrosis. In patients who have carpal tunnel syndrome, the most consistent histological features of synovial tissue from the carpal tunnel are edema and thickening of the vascular walls. To a limited degree,

I
IN THE CARPAL TUNNEL IN PATIENTS
COMPARED WITH THAT IN CONTROL SUBJECTS

Control Subjects					
			Pressure* *(kPa)*		
No. of Wrists (No. of Controls)	Gender	Mean Age *(yrs.)*	Wrist in Neutral	Wrist in Flexion	Wrist in Extension
12 (12)	—	—	0.3 ± 0.3	4.3 ± 1.4	4.0 ± 2.0
—	—	—	—	—	—
6 (6)	6 M	32	0.7	2.1	3.6
16 (16)	10 M, 6 F	36	1.9 ± 1.3	19.2 ± 8.8	21.0 ± 8.7
4 (4)	1 M, 3 F	48	2.0 ± 2.4	—	—
32 (16)	12 M, 4 F	—	0.5 ± 0.3	1.2 ± 0.8	1.7 ± 0.8
21 (21)	10 M, 11 F	20-74	3.2 ± 2.1	10.6 ± 5.3	13.5 ± 6.8
31 (31)	19 M, 12 F	38	2.0 ± 1.4	—	—

these non-neuronal findings correspond to the biological responses of nerves (for example, edema, thickening of the vascular walls, and fibrosis) observed in the later stages of the chronic compression models.

The events taking place in peripheral nerves during compression that have been observed experimentally can be related to various clinical stages that have been observed in patients. The initial symptoms of compression of the median nerve at the wrist (carpal tunnel syndrome) usually are intermittent paresthesia and deficits of sensation that occur primarily at night (stage I). These symptoms probably are due to changes in the intraneural microcirculation that are associated with some edema, which disappears during the day. Progressive compression leads to more severe and constant symptoms that do not disappear during the day (stage II); these include paresthesia and numbness, impaired dexterity, and, possibly, muscle weakness. During this stage, the microcirculation may be altered throughout the day by edema and there may be morphological changes such as segmental demyelination. In the final stage (stage III), there are more pronounced morphological changes accompanied by degeneration of the nerve fibers; these changes manifest as constant pain with atrophy of the median-nerve-innervated thenar muscles and permanent sensory dysfunction. During stage I, use of a night splint, which prevents volar flexion of the wrist, may result in complete relief of symptoms. During stage II, operative division of the transverse carpal ligament can provide complete relief, but recovery may take days to many weeks because of the morphological changes and persistent edema. During stage III, the symptoms usually do not disappear completely even if the pressure on the nerve is relieved by operative division of the ligament. This stage usually is seen in older patients, and the wallerian degeneration and axonal regeneration may be impaired in these patients[43].

Vibration-Induced Neuropathy

Vibration is also a form of loading that can induce peripheral neuropathy. There have been histological studies of human nerves exposed to vibration as well as associated animal models. The prolonged use of handheld vibrating tools can lead to a complex of symptoms known as the hand-arm vibration syndrome, in which sensorineural disturbances are prominent[74]. The pathophysiological process associated with vibration-induced neuropathy remains to be clarified, but there is evidence that the injury may be located along the entire length of the neuron.

Animal models have been used to evaluate the events taking place in peripheral nerves following exposure to vibration. Acute vibration (eighty-two hertz at a peak-to-peak magnitude of 0.21 millimeter) with an exposure time of five hours per day for a maximum of five days was found to induce intraneural edema as well as transient structural changes in thin, nonmyelinated fibers in the nerve trunks close to the vibration exciter[41,42]. Other studies have indicated that demyelination is an early event in the process and that loss of axons may occur later[4,26]. Functional changes of both nerve fibers and non-neural cells such as Schwann cells also may occur following exposure to vibration and are part of a regenerative response following a nerve injury[3,12].

Biopsies of specimens from the fingertips of patients who had been exposed to vibrating handheld tools demonstrated nerve demyelination, loss of axons, and fibrosis in small nerve trunks[80,81]. Recently, biopsy specimens

were obtained from the dorsal interosseus nerve just proximal to the wrist of ten men who had been exposed to hand vibration at work and in twelve male age-matched cadavera (controls)[75]. All ten subjects who had been exposed to vibration and one control had pathological changes, such as breakdown of myelin and interstitial and perineurial fibrosis. These histological results suggest that, in neuropathy, demyelination may be a primary lesion that is followed by fibrosis associated with incomplete regeneration. This study demonstrated that exposure to vibration at work can induce structural changes in a peripheral nerve trunk at the wrist[75]. Such changes are likely to occur in the median nerve in the carpal tunnel of people who have been exposed to vibration. These findings may account for the poorer outcomes after carpal tunnel release in patients who have a history of exposure to vibration.

Nerve Excursion in Nerve Compression Syndromes

Longitudinal gliding of the nerve trunk occurs normally during joint motion and has been measured with use of ultrasound in humans and with markers placed in the nerve in cadavera. In a study of the ulnar nerve at the elbow, localized areas of strain (nerve-stretching) of greater than 10 percent were observed in some cadaveric arms[83]. A strain of 6 to 8 percent can limit blood flow in a nerve or can alter nerve function[5,37,59]. In a study of the cubital tunnel in cadavera, intraneural and extraneural pressures were recorded simultaneously during elbow flexion[23]. Although both types of pressure increased with flexion of greater than 70 degrees, the intraneural pressure always exceeded the extraneural pressure. Furthermore, the increase in intraneural pressure with flexion was unchanged after release of the cubital tunnel. It is therefore likely that the increase in intraneural pressure with flexion was not entirely due to an increase in extraneural pressure. Instead, it is probable that traction contributed to it.

In patients with carpal tunnel syndrome, nerve excursion during flexion and extension of the wrist or during flexion of the fingers is restricted compared with that in healthy controls[52]. The basis for this limited motion and the resultant localized strain is unknown. If it is due to adhesions to adjacent tissues and resultant traction, local regions of limited microvascular flow may occur because of nerve strain.

Extraneural Pressure in Nerve Compression Syndromes

In humans, hydrostatic pressures in the tissue next to a nerve can be measured with a small-diameter catheter filled with saline solution. A number of investigators have measured extraneural pressure in patients who had carpal tunnel syndrome and have compared it with that in healthy controls (Table I)[21,25,35,60,66,71,78,88]; the extraneural pressure has almost always been higher in the patients who had carpal tunnel syndrome. However, in one study, the mean pressure in patients who had very severe or end-stage carpal tunnel syndrome was low[78]. Differences in the selection criteria and the measurement techniques (for example, the type and location of the catheter, the inclusion of patients who had paraplegia, anesthesia, and the position of the forearm) may explain the differences in the pressures that were measured.

Taken together, these studies demonstrate that extraneural pressure is elevated in patients who have carpal tunnel syndrome compared with that in controls. The elevated pressure may be due to the formation of edema in adjacent tissues (for example, synovial tissue). However, the events leading to these tissue changes are not precisely known. One theory is that, if the repeated elevation of extraneural pressure that is associated with joint-loading is sustained, it may lead to extraneural and intraneural edema, fibrosis, and nerve fiber injury as observed in animal models.

Effects of Joint Position and Hand-Loading on Extraneural Pressure in Normal Subjects

In many of the studies mentioned earlier (Table I), extraneural pressure was measured with the wrist moved either passively or actively into full flexion or extension. In patients who had carpal tunnel syndrome, extraneural pressure increased by a factor of two to ten with flexion or extension. Although the pressures in normal subjects were of a lower magnitude, a similar response to extension and flexion was observed consistently (Table I). A similar pattern of increased extraneural pressure with increased joint flexion also was observed in the ulnar nerve at the elbow in cadavera[23,47]. In healthy subjects, the relationship between extraneural pressure and the position of the joint appears to be independent of gender or age[34].

The simultaneous recording of joint position and extraneural pressure in the carpal tunnel has been performed in healthy subjects in order to investigate the dose-response relationships between finger position[30,89], wrist extension and flexion[30,65,89], and forearm rotation[65,89] and pressure. For example, extraneural pressure was measured in seventeen healthy volunteers while they slowly and repeatedly rotated the forearm from supination to pronation[65]. The lowest pressures were recorded between 0 degrees and full pronation, while maximum pressures of 7.3 kilopascals (fifty-five millimeters of mercury) were recorded with the forearm in full supination. These studies had several limitations. First, because of the invasiveness of the procedure, the sample sizes were small, leading to difficulty in evaluating the effects of gender, age, and other factors. Second, sources of high intersubject variability were unknown. Third, the tasks that were studied are difficult to generalize to working populations. However, these studies confirmed that increasing wrist extension and, to a lesser

degree, increasing wrist flexion, increasing forearm supination, and increasing metacarpophalangeal deviation from 45 degrees of flexion all lead to increasing extraneural pressure in the carpal tunnel.

Finger-loading (for example, pinching) also increases carpal tunnel pressure in normal subjects and in cadavera. In cadavera, the extraneural pressures in the carpal tunnel increased when the flexor tendons were loaded[6,72]. Similarly, in healthy volunteers, the pressures increased during simulated holding and gripping tasks. Seradge et al.[71] found that the mean extraneural pressure increased to 10 ± 8.7 kilopascals (75 ± 65 millimeters of mercury) when subjects held a 10.5-centimeter cylinder and that it increased further to 31.2 ± 1.32 kilopascals (234 ± 10 millimeters of mercury) when they made a fist. Similar findings have been reported by others[25,60,89]. In another study, carpal tunnel pressure was measured in nineteen subjects during a task of loading and unloading 0.45-kilogram (one-pound) cans from a box at a rate of twenty cans per minute[63]. The pressures fluctuated, with peak pressures occurring during gripping. The mean pressure increased significantly ($p = 0.0003$), from 1.1 ± 0.8 kilopascals (8 ± 6 millimeters of mercury) at rest to 2.4 ± 1.7 kilopascals (18 ± 13 millimeters of mercury) during the task. In two subjects, the mean pressure was greater than 4.0 kilopascals (thirty millimeters of mercury).

In two studies of healthy volunteers, loading of the fingertips and extraneural pressure in the carpal tunnel were measured simultaneously to investigate their dose-response relationships[31,64]. In one of these studies, subjects pressed a load-cell with the index finger and pinched the load-cell between the index finger and the thumb[31]. In both positions, increasing loading of the fingertips led to increasing extraneural pressure, in a dose-response manner, with the highest mean pressure, 6.6 kilopascals (fifty millimeters of mercury), occurring during the pinching task at a force of fifteen newtons (1.5 kilograms). The pinching task led to extraneural pressures that were twice those observed during the pressing task. A limitation of this study was incomplete knowledge of the location of the catheter tip, which may have contributed to intersubject variability.

The findings that non-neutral joint positions and external load (for example, during pinch grip) can affect extraneural pressure, combined with the findings from the animal studies, can guide our understanding of the pathogenesis of nerve entrapment related to loading. On the basis of the animal studies, it appears that if elevated extraneural pressures are maintained for an adequate duration the initial injury, remodeling, and repair mechanisms, which are constantly ongoing, may be overwhelmed, leading to persistent extraneural or intraneural edema and eventually to synovial or intraneural fibrosis and loss of nerve function. However, the precise characteristics of this critical time-pressure threshold remain to be determined.

These findings also may support a rational approach to the management of patients who have entrapment neuropathies. For example, a patient who is seen early enough after the onset of carpal tunnel syndrome, when the symptoms still are occurring only at night or during exertion of the hand, may be managed with a splint, modifications of work activities, and corticosteroid injections. These interventions may be adequate to permanently reverse intraneural and synovial edema and demyelination. After the condition has progressed and the symptoms have become more frequent and severe, the underlying nerve-fiber degeneration and regeneration and the fibrosis may necessitate operative release, and there is no guarantee that nerve function will return completely. If the condition progresses even further, to the point where the symptoms are constant and there is muscle atrophy, it is unlikely that even operative release will lead to complete recovery.

Overview

The main conclusions that can be drawn from the literature regarding the role of tissue loads in the pathogenesis of peripheral-nerve entrapment are as follows.

First, elevated extraneural pressures can, within minutes or hours, inhibit intraneural microvascular blood flow, axonal transport, and nerve function and also can cause endoneurial edema with increased intrafascicular pressure and displacement of myelin, in a dose-response manner. Pressures of 2.7 kilopascals (twenty millimeters of mercury) can limit epineurial blood flow, pressures of 4.0 kilopascals (thirty millimeters of mercury) can limit axonal transport and can cause nerve dysfunction and endoneurial edema, and pressures of 6.7 kilopascals (fifty millimeters of mercury) can alter the structure of myelin sheaths.

Second, on the basis of several animal models, it is apparent that low-magnitude, short-duration extraneural pressure (for example, 4.0 kilopascals [thirty millimeters of mercury] applied for two hours) can initiate a process of nerve injury and repair and can cause structural tissue changes that persist for at least one month. While dose-response relationship effects of both pressure and duration have been observed in some studies, the critical values for pressure and duration with respect to nerve injury are unknown. The cascade of the biological response to compression includes endoneurial edema, demyelination, inflammation, distal axonal degeneration, fibrosis, growth of new axons, remyelination, and thickening of the perineurium and endothelium. The degree of axonal degeneration is associated with the amount of endoneurial edema.

Third, in healthy people, non-neutral positions of the fingers, wrist, and forearm and loading of the fingertips can elevate extraneural pressure in the carpal tunnel in a dose-response manner. For example, fingertip pinch forces of five, ten, and fifteen newtons can elevate pressures to 4.0, 5.6, and 6.6 kilopascals (thirty, forty-two,

and fifty millimeters of mercury). Extraneural pressures in healthy people performing hand-intensive tasks in the workplace or at home are unknown.

Fourth, in a rat model, exposure of the hindlimb to vibration for four to five hours per day for five days can cause intraneural edema, structural changes in myelinated and unmyelinated fibers in the sciatic nerve, and functional changes both in nerve fibers and in non-neuronal cells.

Fifth, exposure to vibrating hand tools at work can lead to permanent nerve injury with structural neuronal changes in finger nerves as well as in the nerve trunks just proximal to the wrist. The relationships between the duration of exposure, the magnitude of the vibration, and structural changes in the nerve are unknown.

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