NEURAL REGENERATION RESEARCH
Volume 8, Issue 11, April 2013

www.nrronline.org

doi:10.3969/j.issn.1673-5374.2013.11.010 [http://www.nrronline.org; http://www.sjzsyj.org]
Gao YM, Weng CS, Wang XL. Changes in nerve microcirculation following peripheral nerve compression. Neural Regen Res. 2013;8(11):1041-1047.

Changes in nerve microcirculation following peripheral nerve compression☆

Yueming Gao[1], Changshui Weng[2], Xinglin Wang[1]

1 *Rehabilitation Medicine Center, General Hospital of Chinese PLA, Beijing 100853, China*
2 *Department of Rehabilitation Medicine, South Building, General Hospital of Chinese PLA, Beijing 100853, China*

Abstract

Following peripheral nerve compression, peripheral nerve microcirculation plays important roles in regulating the nerve microenvironment and neurotrophic substances, supplying blood and oxygen and maintaining neural conduction and axonal transport. This paper has retrospectively analyzed the articles published in the past 10 years that addressed the relationship between peripheral nerve compression and changes in intraneural microcirculation. In addition, we describe changes in different peripheral nerves, with the aim of providing help for further studies in peripheral nerve microcirculation and understanding its protective mechanism, and exploring new clinical methods for treating peripheral nerve compression from the perspective of neural microcirculation.

Key Words

neural regeneration; peripheral nerve injury; peripheral nerve; microcirculation; nerve compression; nerve blood flow; sciatic nerve; grants-supported paper; neuroregeneration

Research Highlights

(1) This study summarized results of changes in nerve microcirculation following peripheral nerve compression.
(2) This study reviewed some characteristics of peripheral neural microcirculation including bidirectional blood supply. The blood supply of the distal segment is significantly larger than that of the proximal segment, and the number of anastomotic branches in the middle region is considerably less than that at both the proximal and distal ends. Changes in blood flow are not directly correlated with changes in vascular density or number during neural regeneration.
(3) This study provided a new idea for treatment of peripheral nerve lesions through improved nerve microcirculation.

Yueming Gao☆, M.D.

Yueming Gao and Changshui Weng contributed equally to this work.

Corresponding author: Xinglin Wang, M.D., Chief physician, Professor, Rehabilitation Medicine Center, General Hospital of Chinese PLA, Beijing 100853, China, wxl0620@sina.com.

Received: 2012-10-12
Accepted: 2013-02-10
(N20111004001)

INTRODUCTION

Nerve regeneration is complicated following peripheral nerve injury. Current studies have mainly focused on intracellular signaling transduction, molecular biological mechanisms, neurotrophic factors and the regeneration of axonal myelin sheaths, Schwann cells and basilar membranes. In contrast, few studies have examined changes in nerve microcirculation following peripheral nerve injury. Nerve tissues and microcirculation are both damaged following nerve injury, and because inflammatory changes, axon growth, and cell regeneration require a large number of nutritive substances and oxygen[1], damaged microcirculation can hamper neural regeneration and functional recovery. The present study summarized research methods and results of changes in nerve microcirculation following peripheral nerve compression to provide a guide for further

investigations into peripheral neural microcirculation and protective mechanisms and to explore new therapeutic methods.

VASCULAR STRUCTURE AND CHARACTERISTICS OF PERIPHERAL NERVES

Peripheral nerves have both exogenous and endogenous blood-supply systems. The exogenous blood-supply system, which is located on loose connective tissues around nerves and epineurium, is composed of small arteries and veins from neighboring tissue space and muscular blood vessels. The exogenous blood-supply system serves as sources of nutrients and provide blood flow for the endogenous vascular system[2]. The endogenous blood-supply system has many anastomoses with the exogenous system, but can exert independent effects. The endogenous system contains three components detailed below: epineurial vessels, a vascular network between nerve tracts, and a vascular network within nerve tracts. (1) Epineurial vessels: distal and proximal segmental vessels anastomose to form epineurial vessels, and blood-flow direction changes depending on the metabolic requirements of different regions of the nerve trunk. Short transverse branches or oblique branches erupt and cross the surface of nerve tracts towards the inner part, forming the vascular network between nerve tracts[2]. (2) Vascular network between nerve tracts: vascular branches extend and distribute in loose connective tissue between nerve tracts, and this structure is adaptive to the changes in nerve length. When the nerve is dragged, vessels freely stretch within a certain range to ensure normal blood supply of the nerve. Peptidergic, 5-hydroxytryptamine, and adrenergic nerve plexuses in perineurial and epineurial vessels regulate the pressure in these blood vessels[2]. (3) Vascular network within nerve tracts: The vascular network between nerve tracts extends, traverses the perineurium, enters the nerve tract, and penetrates the endoneurium, forming microvascular networks that mainly contain longitudinally arranged blood capillaries. Anastomotic endoneurial vessels are abundant, composed of single-layer flat endothelial cells and simple-layer basement membrane, accompanied by adventitial cells occasionally. Endothelial cells in small arteries promote phosphorylation, which alters osmotic pressure, and thus plays an important role in local blood-flow regulation. Adventitial cells in small arteries do not differ from cells under a light microscope. The artery diameter is bigger than that of common blood capillaries. Strictly, they are separated from blood capillaries. Adjacent vascular endothelial cells and perineurial cells are tightly connected and form the blood-nerve barrier that prevents intravascular proteins and macromolecular substances from infiltrating the endoneurium, and maintains the stability of the endoneurial microenvironment[2].

CHANGES IN NERVE MICROCIRCULATION FOLLOWING PERIPHERAL NERVE COMPRESSION AT DIFFERENT REGIONS

Peripheral nerve compression is a common cause of peripheral nerve injury. Pathological, electrophysiological, functional and prognostic changes can differ depending on the degree, duration, and property of the damage. Nerve ischemia and mechanical injury are the main wounding factors of compressed nerves. Acute short-term compression results in nerve ischemia, hypoxia, edema, increases vascular permeability, and blocks axoplasmic flow. Severe, persistent compression adversely affects microcirculation, causes distal axonal disintegration and Wallerian degeneration of myelin sheaths, and even causes breakage of nerve fibers and motor function loss. Peripheral neural microcirculation, which has an important role in nerve regeneration, can affect nerve injury and regeneration, blood-oxygen supply, neurotrophic effects, maintenance of neural conduction and axonal transport[3-6]. The regulatory mechanism of blood supply in peripheral nerves remains unclear, but is probably affected by autonomic nerves, intraneural nutrients, vascular receptors, and mechanical properties[3-6]. Peripheral nerves are distributed extensively throughout the body. The anatomic structure of each region is varied, as are the corresponding diseases and pathogeneses.

Facial nerve

Wedge pressure in the facial canal and nerve microcirculation disturbances are important pathological factors in facial paralysis. Li *et al* [7] investigated changes in nerve blood flow following facial nerve compression and decompression using laser Doppler flowmetry, and showed that blood flow decreased from 1 063.1 ± 474.3 mV to 520.0 ± 226.8 mV during 10 g weight compression for 10 seconds, an average decrease of 50 ± 7%. The baseline increased within 1–2 minutes following decompression, and then recovered to pre-operation levels. Sillman *et al* [8] demonstrated that nerve blood flow decreased by 80–95% following rapid compression of distal facial nerve of the geniculate

ganglion, as measured by laser Doppler flowmetry. Yanagida[9] revealed that Evans blue was exuded from the distal end of the compression site, and the contents of gadolinium-diethylene-triamine-penta acetate were greater in the distal end compared with the proximal end. These results indicated that significant differences in blood supply are detectable between the proximal and distal ends, and the effects on neural function were variable. However, the precise anatomic and blood-supply mechanisms remain unclear. Our team has found a similar phenomenon in the sciatic nerve; the blood supply of the distal nerve exerts significant effects on that of the nerve stump[10].

Sciatic nerve

The sciatic nerve is a mixed function nerve that has several conveniently separable branches and is therefore an ideal model for studying peripheral nerves. Blood supply of the sciatic nerve is derived from vessels of the proximal buttocks and distal popliteal vessels, which can effectively restore blood flow to the ischemic nerve[10-11].

Changes in intraneural vascular permeability following sciatic nerve compression

Endoneurial vessels are not permeable under normal conditions, but the permeability increases following nerve injury. Weerasuriya[12] has confirmed that endoneurial capillary permeability and vascular space peaked at 2–3 weeks following sciatic nerve compression, which was identical to that after transverse injury. Subsequently, endoneurial vascular space returned to near-normal values, but endoneurial capillary permeability reached a second peak at 9 weeks. Nevertheless, both endoneurial capillary permeability and vascular space began to decrease 2–3 weeks after nerve transverse injury, and were close to a normal levels 6 weeks later. The increase in endoneurial capillary permeability was probably correlated with axon decomposition products, chemical signal conduction of Schwann cells, and endoneurial debris clearance. Compressed nerves differed from those with transverse injuries in having a second increase in endoneurial capillary permeability that was probably associated with homeostatic mechanisms of the endoneurium[12]. Rapid regeneration of axons and myelin sheaths increased nerve blood-exchange, resulting in the second increase in vascular permeability[12]. Sparrow and Kiernan[13] reported that endoneurial capillary permeability increased from 1–21 days following nerve compression, which was consistent with results from a previous study[12]. The permeability markedly increased in the distal part during axonal regeneration[13]. Although a rapid increase in endoneurial permeability was consistent with a rapid increase in axons, permeability did not change within 6 hours when axonal regeneration was inhibited[13]. Intraneural vascular permeability was strongly associated with axonal regeneration. Changes in vascular permeability during axonal regeneration are probably affected by vasoactive substances, which are secreted in nerve growth cones. Increases in vascular permeability can induce increases in plasma protein expression and contribute to axonal regeneration.

Changes in intraneural vascular number and density following sciatic nerve compression

Vascular regeneration has been shown to follow peripheral nerve injury[14], and plays an important role in neural regeneration and functional recovery. However, factors affecting the number and density of regenerated vessels deserve further investigation. Podhajsky and Myers[15] found that the vascular reaction of injured nerves was composed of two peak phases: the first phase appeared at 1 week following injury; vascular radius and perimeter increased, but vessel number decreased. The second phase appeared at 6 weeks following injury; vessel number and density increased. In early stages of the first phase, vascular reaction was correlated with macrophage aggregation, axon disintegration, and myelin sheath clearance when Wallerian degeneration began. In the second phase, the increase in vessel number was associated with cell proliferation, axonal extension, and myelination during neural regeneration. Nevertheless, Nukada[16] has demonstrated that endoneurial capillary number increased from 1–8 weeks following injury, and that while vessel number and density of injured nerves also increased, blood supply did not recover to normal in the late stage of neural regeneration. These inconsistent results may be associated with the degree of injury and the manner and degree of regeneration.

Changes in nerve microcirculation following sciatic nerve compression at different time points and pressures

Sciatic nerve compression of different durations and pressures has been shown to have varying effects on changes in nerve injury and microcirculation. Jacobs and Ro[17] confirmed that intraneural blood flow was stopped within 8.5 hours of compression and ischemia, motor function changes, Schwann cell necrosis, and axon injury appeared. At 48 hours, endoneurium had developed edema and severe nerve fiber degeneration.

Ju *et al* [18] showed that blood flow reduced following 30.5 mmHg compression of the sciatic nerve, and at 102.8 mmHg blood flow was further reduced to 30% of pre-compression levels. Xu *et al* [19] suggested that epineurial blood flow transiently decreased following short-distance, and especially long-distance, compression. Blood flow decreased 34% by 1 hour after long-distance compression, and endoneurial blood flow did not obviously change. Epineurial blood flow significantly diminished after epineurial blood supply was destroyed and nerves were damaged by long-distance compression. Blood flow had decreased by 16% 3 hours after injury and endoneurial blood flow had not dramatically changed. Rydevik and Lundborg[20] compressed rabbit sciatic nerves for 15 minutes and 6 hours at 50–600 mmHg, and indicated that light compression (50 mmHg, 2 hours) could induce epineurial edema and increases in vascular permeability, but endoneurial vascular permeability was not damaged. These results suggest that compared with endoneurial vessels, epineurial vessels are more sensitive to compression injury. The special structure of the vascular network between nerve tracts could protect endoneurial vessels. When the pressure was increased and compression time was prolonged, endoneurial vessels were damaged, resulting in edema in nerve tracts. The edema was extremely clear on the edge of compressed segments. Matsumoto[21] reported that blood flow decreased in nerve tracts when the pressure reached 47.2 ± 3.7 mmHg. As pressure was gradually increased, intraneural blood flow was gradually reduced. Nerve blood flow was completely blocked when the pressure reached 118.6 ± 5.9 mmHg. When the pressure lasted 75 minutes and was relieved, the blood-flow speed was slower when compared with normal intraneural blood-flow. Nerve compression for 3 weeks caused grade II injuries, and nerve blood flow decreased by 80%. With decompression, nerve blood flow increased to levels that exceeded those before compression. The most significant changes in peripheral nerves following short-period slight compression were the changes in epineurial vessels. In contrast, with prolonged compression time and increased pressure intensity, the endoneurial vascular permeability was altered leading to nerve edema and increased hydraulic pressure. There was no lymphatic drainage in the perineurium, and increased hydraulic pressure caused endoneurial vascular occlusion and aggravated ischemia, resulting in a vicious circle. Intraneural edema and microcirculation disturbances coexisted following long-period compression, with the presence of axonal injury, myelin sheath decomposition, and protein exudation that finally resulted in scar formation, nerve fibrosis, and neurofunctional deficits[21].

Cauda-equina nerve

Cauda-equina nerve lesion refers to a series of neurological deficits produced by cauda-equina nerve compression from absolute or relative lumbar spinal-canal stenosis. The blood supply comes from blood vessels branching off the spinal pia mater. It has been shown that while normally, superficial blood vessels are abundant and parallel to nerve fibers, once these blood vessels are compressed, ischemia occurs[22]. Some scholars[23-24] reported that mean arterial pressure was 150 mmHg in nerve roots, and that 127 mmHg of pressure could block intraneural arteriolar blood flow. Further, 40 mmHg obstructed capillary blood flow and 30 mm Hg blocked venular blood flow. Rapid compression of cauda-equina nerves (0.05–0.1 second) had greater effects on neurotrophic supply than slow compression (20 seconds). Cerebrospinal fluid provided some nutrition for damaged nerves, but could not compensate for compression-induced disturbances in blood supply. Delamarter *et al* [25] observed that when the cauda-equina nerve was pressed (25%) for 3 months, the seventh lumbar nerve root and dorsal root ganglion veins were slightly engorged, and histopathological changes were detectable. At 50% pressure, the nerve displayed edema and demyelination, and the seventh nerve root and dorsal root ganglia were moderately and severely engorged, respectively. At 75% pressure, the artery in the damaged region became severely narrowed and nerve root and dorsal root ganglia were obviously engorged. Axoplasmic transport in the distal nerve segment was blocked, and Wallerian degeneration was visible. Similarly, Takahashi *et al* [26] compressed two regions of the cauda-equina nerve using air bags, and measured blood-flow changes between the two compression sites. Blood flow in the middle part decreased by 64% under 10 mmHg of pressure, disappeared completely between 10 and 20 mmHg, and recovered to normal at 200 mmHg for 10 minutes. However, following 2 hours of compression, recovery was slow and incomplete. Double compression can induce nerve ischemia, which is an important topic in the study of nerve compression-induced diseases. Double nerve compression-induced diseases are commonly found in thoracic outlet syndrome, sciatica, and back-leg pain[27-28]. Compression commonly occurs in at least two regions during peripheral nerve growth, and these diseases are chronic, lead to long periods of hypoperfusion, and affect normal nerve function[29-30]. Surgery or physical therapy cannot completely solve all

the disease symptoms.

Spinal nerve root

Spinal nerve root compression is commonly induced by intervertebral disc protrusion, tumor, and external trauma, which can cause varying degrees of motor and sensory functional disturbances. The cauda-equina nerve root in the dural sac has epidural space and a subarachnoid cavity. In contrast, intraspinal nerve roots have only a single space, and can thus be easily oppressed. Damaged nerve roots are connected to corresponding dorsal root ganglion, resulting in ganglion dysfunction. Blood supply at the spinal nerve root arrives from the proximal end of the spinal artery, and from the distal end of the radicular arteries of intervertebral foramina. The two blood-supply systems anastomose a third of the way from the distal end of the nerve root. The vascular density at the anastomotic site is low. Compared with the peripheral nerve, the arterial and venous networks of the spinal nerve root are not abundant, explaining why the spinal nerve root does not tolerate pressure well[31].

Kobayashi *et al* [32] measured blood flow in the nerve root of 12 patients before and after straight-leg-raising and after discectomy, and confirmed that blood flow decreased by 40–98% (mean 70.6 ± 20.5%), and recovered to normal within 1 minute of lowering the leg. Nerve roots of all patients were smooth during the straight-leg-raising test, and blood flow in nerve roots did not obviously decrease. Jespersen *et al* [33] established rat L_4 and L_6 nerve root compression models, measured local blood flow and spinal-evoked potential under different pressures, and revealed that local blood flow increased in rats from the 0%-, 25%-, and 50%-pressure groups. Moreover, no significant difference in increased volume was detectable among groups. Nerve blood flow was lower in the 75%-pressure group compared with the lower pressure groups. Evoked-potential amplitudes changed in half the animals from the 50% pressure group and spinal-evoked potentials changed in the majority of animals from the 75% pressure group. Nerve conduction was damaged when the nerve was oppressed, but blood flow in nerve root was maintained between the two compression sites. These results were not consistent with the study results of the Takahashi *et al* [26] described above. Whether these differences are correlated with the anatomic structure of different peripheral nerves requires further study.

Median nerve

Median nerve paralysis is mainly induced by compression in the carpal canal. The carpal canal is located in the palm root, with the basal part and both sides composed of carpal bone. The transverse carpal ligament stretches across the carpal canal forming a bone-fiber channel. Chronic injury is often caused by long periods of excessive use of the hand and wrist that lead to luminal stenosis, and finally oppression of the median nerve. A previous study[34] demonstrated that the permeability of the blood-nerve barrier of the median nerve increases when the nerve is oppressed with 60 and 90 g of pressure for 1 hour, as measured by MRI and protein tracing. Under the electron microscope, capillaries were tightly connected, and vesicular transport had increased[34]. Using laser Doppler flowmetry, Barone *et al* [35] revealed that normal nerve blood flow ranged from 47–63 mL/100 g per minute, averaged 56 mL/100 g per minute. Nerve blood flow tended to increase gradually from the injury site to distal end. This conclusion presumed that nerve blood flow was bidirectional. Nerve blood-supply provided blood from the distal end to the proximal end after the proximal end was oppressed, showing a tendency to gradually decrease.

Peroneal and tibial nerves

Rydevik *et al* [36] discovered that the pressure of 20–30 mmHg affected venular blood flow. The pressure of 40–50 mmHg prevented intraneural arteriolar and intrafascicular capillary blood flow. The pressure of 60–80 mmHg completely blocked nerve blood flow. Nerve blood flow was slow 3 and 7 days following 400 mmHg of pressure for 2 hours. These data suggested that acute compression induced neurovascular mechanical injury and blood-nerve barrier destruction, resulting in damage to intraneural microcirculation. De la Motte and Allt[37] reported that a large number of horseradish peroxidase exudated from blood capillaries at 0.5 hours and 2 days following peroneal nerve compression. Injured blood vessels and isolated endothelial cells were visible, but there were no abnormal blood vessels or exudation at the proximal or distal ends of the injured site. Twenty-one days following injury, horseradish peroxidase exudation was found in the endoneurium and surrounding intraneural blood vessels at the injured site and distal end. No remarkable changes were detected at the proximal end of the nerve.

CONCLUSION

In summary, peripheral nerve microcirculation is characterized by: (1) Bidirectional blood supply. The blood supply to the distal segment is significantly larger

than that to the proximal segment. (2) The density of intraneural anastomotic branches varies depending on the location. Anastomotic branches in the middle region are fewer than at the proximal and distal ends. (3) The changes in blood flow are not directly correlated with the changes in vascular density and number during neural regeneration. (4) Peripheral nerve compression at varied pressures and time durations induces varying degrees of neural injury.

Although the symptoms of peripheral nerve compression-induced diseases vary in different regions, pathogenesis following nerve compression is always a mechanical injury accompanied with changes in microcirculation, which in turn induce axonal injury and myelin sheath injury, and finally form scars and fibrosis.

Taken together, improving nerve microcirculation is a critical key for treatment of these diseases. Currently, the method of improving nerve microcirculation contains surgery, vasoactive agents and physical therapy. Studying the effects that blood regulatory and hemodynamic mechanisms, neurotrophic factors, and neural genes have on nerve microcirculation is certainly important for better treatment of nerve compression-induced diseases[38-42].

Acknowledgments: We thank Wei Suo, Tianyu Jiang and Lining Zhang from the Rehabilitation Medicine Center, General Hospital of Chinese PLA for guidance and help in manuscript writing and literature checking.

Funding: This project was funded by the Rehabilitation Management Program following the Battle during the Tenth “Five-Year Plan” Period, No. 200626Z000058.

Author contributions: Xinglin Wang participated in study design and manuscript authorization, and obtained funding. Yueming Gao and Changshui Weng was in charge of reference checking and manuscript writing. All authors approved the final version of the paper.

Conflicts of interest: None declared.

Author statements: The manuscript is original, has not been submitted to or is not under consideration by another publication, has not been previously published in any language or any form, including electronic, and contains no disclosure of confidential information or authorship/patent application/funding source disputations.

REFERENCES

[1] Huang H, Gu J, Chen HQ. Hyperbaric oxygen therapy for peripheral nerve injury. Chongqing Yixue. 2010,39(7):881-883.

[2] Chen DS, Cao GF. Peripheral Nerve Entrapment Disorders. Shanghai: Shanghai Medical College Press. 1999.

[3] Wang JL, Tang JR, Su JH, et al. The influences on expression of VEGF and nervous conduction by improving microcirculation following crushing lesion of sciatic nerve in rats. Nanjing Yike Daxue Xuebao: Ziran Kexue Ban. 2007;27(6):598-601.

[4] Ding J, Gong SS. The expression and significance of VIP and SP in the cochlea of rats. Linchuang Er Bi Yanhou Ke Zazhi. 2004;18(11):681-684.

[5] Zhu ML, Liu HC. Mechanism of substance P and calcitonin gene-related peptide regulate dental pulp microcirculation. Yati Yasui Yazhou Bing Xue Zazhi. 2001;11(4):274-275.

[6] Gupta R, Gray M, Chao T, et al. Schwann cells upregulate vascular endothelial growth factor secondary to chronic nerve compression injury. Muscle Nerve. 2005;31(4): 452-460.

[7] Li JD, Li XP. The effect of surgical trauma on blood flow of the facial nerve in rabbits. Wei Xunhuan Xue Zazhi. 2003; 13(4):13-15.

[8] Sillman JS, Levine RA, Kobler JB. Laser Doppler measurements of intratemporal facial nerve blood flow. Am J Otol. 1994;15(3):327-334.

[9] Yanagida M. MRI enhancement of the facial nerve with Gd-DTPA--first report--experimental study on the enhancement mechanism used in viewing vascular permeability of the facial nerve. Nihon Jibiinkoka Gakkai Kaiho. 1993;96(8):1320-1328.

[10] Gao YM, Wang Xl. Effect of sciatic nerve compression with different pressures and sites on neural blood flow in rats. Zhongguo Jiankang Lilun yu Shijian. 2008;14(12): 1139-1140.

[11] Xu JG, Gu YD. Micro-anatomy of the sciatic nerve of the adult rat and its significance. Shanghai Yixue. 1999(3): 154-156.

[12] Weerasuriya A. Patterns of change in endoneurial capillary permeability and vascular space during nerve regeneration. Brain Res. 1990;510(1):135-139.

[13] Sparrow JR, Kiernan JA. Endoneurial vascular permeability in degenerating and regenerating peripheral nerves. Acta Neuropathol. 1981;53(3):181-188.

[14] Zhang YB, Wu YM, Liu L, et al. Dose-response relationship between nerve growth and angiogenesis of regenerative sciatic nerve. Zhongguo Zuzhi GongchengYanjiu yu Linchuang Kangfu. 2007;11(19): 3854-3857.

[15] Podhajsky RJ, Myers RR. The vascular response to nerve crush: relationship to Wallerian degeneration and regeneration. Brain Res. 1993;623(1):117-123.

[16] Nukada H. Post-traumatic endoneurial neovascularization and nerve regeneration: a morphometric study. Brain Res. 1988;449(1-2):89-96.

[17] Jacobs JM, Ro LS. A morphological study of experimental mononeuropathy in the rat: early ischemic changes. J Neurol Sci. 1994;127(2):143-152.

[18] Ju MS, Lin CC, Fan JL, et al. Transverse elasticity and blood perfusion of sciatic nerves under in situ circular compression. J Biomech. 2006;39(1):97-102.
[19] Xu Q, Midha R, Zochodne DW. The microvascular impact of focal nerve trunk injury. J Neurotrauma. 2010;27(3): 639-646.
[20] Rydevik B, Lundborg G. Permeability of intraneural microvessels and perineurium following acute, graded experimental nerve compression. Scand J Plast Reconstr Surg. 1977;11(3):179-187.
[21] Matsumoto N. Experimental study on compression neuropathy--determination of blood flow by a hydrogen washout technic. Nihon Seikeigeka Gakkai Zasshi. 1983;57(8):805-816.
[22] Wang YJ, Hong Y. Research progress of cauda equina syndrome. Zhongguo Gu yu Guanjie Waike. 2011;4(6): 501-506.
[23] Olmarker K, Rydevik B, Hansson T, et al. Compression-induced changes of the nutritional supply to the porcine cauda equina. J Spinal Disord. 1990;3(1):25-29.
[24] Olmarker K, Rydevik B, Holm S, et al. Effects of experimental graded compression on blood flow in spinal nerve roots. A vital microscopic study on the porcine cauda equina. J Orthop Res. 1989;7(6):817-823.
[25] Delamarter RB, Bohlman HH, Dodge LD, et al. Experimental lumbar spinal stenosis. Analysis of the cortical evoked potentials, microvasculature, and histopathology. J Bone Joint Surg Am. 1990;72(1): 110-120.
[26] Takahashi K, Olmarker K, Holm S, et al. Double-level cauda equina compression: an experimental study with continuous monitoring of intraneural blood flow in the porcine cauda equina. J Orthop Res. 1993;11(1):104-109.
[27] Lo SF, Chou LW, Meng NH, et al. Clinical characteristics and electrodiagnostic features in patients with carpal tunnel syndrome, double crush syndrome, and cervical radiculopathy. Rheumatol Int. 2012;32(5):1257-1263.
[28] Hooper TL, Denton J, McGalliard MK, et al. Thoracic outlet syndrome: a controversial clinical condition. Part 1: anatomy, and clinical examination/diagnosis. J Man Manip Ther. 2010;18(2):74-83.
[29] Gong YP, Hiroaki T, Keisuke A, et al. An experimental study of animal model of double crush syndrome in the peripheral nerve. Zhonghua Shou Waike Zazhi. 2003; 19(2):127-128.
[30] Cui M, Gu ZY, Guo W, et al. Double or multiple nerve crushing syndrome of the upper extremity. Linchuang Guke Zazhi. 2000;3(2):112-113.
[31] Wang Y, Fan YE, Wang RG. Morphology observation of the blood supply to the lumbar nerve roots. Zhongguo Linchuang Jiepou Xue Zazhi. 2001;19(4):311-313.
[32] Kobayashi S, Shizu N, Suzuki Y, et al. Changes in nerve root motion and intraradicular blood flow during an intraoperative straight-leg-raising test. Spine (Phila Pa 1976). 2003;28(13):1427-1434.
[33] Jespersen SM, Christensen K, Svenstrup L, et al. Spinal cord and nerve root blood flow in acute double level spinal stenosis. Spine (Phila Pa 1976). 1997;22(24):2900-2910.
[34] Kobayashi S, Meir A, Baba H, et al. Imaging of intraneural edema by using gadolinium-enhanced MR imaging: experimental compression injury. AJNR Am J Neuroradiol. 2005;26(4):973-980.
[35] Barone CM, Jimenez DF, Frempog-Bodeau A. Blood-flow measurements of injured peripheral nerves by laser Doppler flowmetry. J Reconstr Microsurg. 1992;8(4): 319-323.
[36] Rydevik B, Lundborg G, Bagge U. Effects of graded compression on intraneural blood blow. An in vivo study on rabbit tibial nerve. J Hand Surg Am. 1981;6(1):3-12.
[37] De la Motte DJ, Allt G. Crush injury to peripheral nerve. An electron microscope study employing horseradish peroxidase. Acta Neuropathol. 1976;36(1):9-19.
[38] Mason MR, Tannemaat MR, Malessy MJ, et al. Gene therapy for the peripheral nervous system: a strategy to repair the injured nerve? Curr Gene Ther. 2011;11(2): 75-89.
[39] Rose K, Ooi L, Dalle C, et al. Transcriptional repression of the M channel subunit Kv7.2 in chronic nerve injury. Pain. 2011;152(4):742-754.
[40] Oroglu B, Turker T, Aktas S, et al. Effect of hyperbaric oxygen therapy on tense repair of the peripheral nerves. Undersea Hyperb Med. 2011;38(5):367-373.
[41] Sharma N, Moeller CW, Marzo SJ, et al. Combinatorial treatments enhance recovery following facial nerve crush. Laryngoscope. 2010;120(8):1523-1530.
[42] Zhang H, Xu YM, Bai YH. Physical therapy and progress after peripheral nerve injury. Zhongguo Kangfu. 2011; 26(5):376-379.

(Reviewed by Phillips A, Raye W, Gao JL, Jiang GH)
(Edited by Yu J, Qiu Y, Li CH, Song LP)