Changes of Blood Flow, Oxygen tension, Action Potential and Vascular Permeability Induced by Arterial Ischemia or Venous Congestion on the Spinal Cord in Canine Model

Shigeru Kobayashi,[1,2] Hidezo Yoshizawa,[†] Seiichiro Shimada,[1] Alexander Rodríguez Guerrero,[1] Masaya Miyachi[3]

[1]Faculty of Medical Sciences, Department of Orthopaedics and Rehabilitation Medicine, The University of Fukui, Shimoaizuki 23, Matsuoka, Fukui 910-1193, Japan, [2]Research and Education Program for Life Science, The University of Fukui, Fukui, Japan, [3]Miyachi Hospital, Toyokawa, Aichi, Japan

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ABSTRACT: It is generally considered that the genesis of myelopathy associated with the degenerative conditions of the spine may result from both mechanical compression and circulatory disturbance. Many references about spinal cord tissue ischemic damage can be found in the literature, but not detailed studies about spinal cord microvasculature damage related to congestion or blood permeability. This study investigates the effect of ischemia and congestion on the spinal cord using an in vivo model. The aorta was clamped as an ischemia model of the spinal cord and the inferior vena cava was clamped as a congestion model at the 6th costal level for 30 min using forceps transpleurally. Measurements of blood flow, partial oxygen pressure, and conduction velocity in the spinal cord were repeated over a period of 1 h after release of clamping. Finally, we examined the status of blood-spinal cord barrier under fluorescence and transmission electron microscope. Immediately after clamping of the inferior vena cava, the central venous pressure increased by about four times. Blood flow, oxygen tension and action potential were more severely affected by the aorta clamping; but this ischemic model did not show any changes of blood permeability in the spinal cord. The intramedullar edema was more easily produced by venous congestion than by arterial ischemia. In conclusions, venous congestion may be a preceding and essential factor of circulatory disturbance in the compressed spinal cord inducing myelopathy. © 2012 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. J Orthop Res 31:139–146, 2013

Keywords: animal model; spinal cord; blood flow, blood-spinal cord barrier, edema

The spinal cord is often involved in disease processes and injuries, such as spinal canal stenosis, disc herniation, ossification of posterior longitudinal ligament, tumor, and vertebral fracture. It is generally considered that the genesis of myelopathy associated with the pathological conditions of the spine, may result from mechanical compression of the spinal cord. This factor may change the blood flow and produce spinal cord dysfunction.[1,2] Ischemia can be produced by permanent exclusion of the essential intercostals arterial blood supply or temporary blood flow interruption to the spinal cord. However, the basic pathophysiology of circulatory disturbance induced by venous congestion is not fully understood. Since Kadyi's first description of the venous system of the spinal cord, there have been few other studies on the subject.[3] Regarding the intramedullary vascular system, the central part of the spinal cord is supplied unilaterally by branches from the central artery entering the anterior part of the cord while the veins run out in anterior and posterior directions having a bilateral distribution. The intramedullary venous anastomoses that connect the superficial anterior and posterior medullary veins are unique, as reported by Herren and Alexander[4] and by Crock and Yoshizawa[5] Based on the anatomy of these intramedullary veins, impaired drainage of the spinal cord is assumed to be caused only by their compression circumferentially, whereas obstruction of the venous outflow from the intradural veins into the extradural venous plexuses may be of equal importance.[6–8] However, there has been very little experimental work on blood permeability in the spinal cord vessels and physiological effects induced by venous congestion. The aim of the present experimental investigation was to examine the effect of ischemia and congestion on the spinal cord.

METHODS

Animals and Preparation

The experiment was carried out under the control of the local animal ethics committee in accordance with the guidelines on animal experiments in our university, Japanese government animal protection and management law, and Japanese government notification on feeding and safekeeping of animals. The 58 mongrel adult dogs, weighing 7–15 kg, were anesthetized with intramuscular injection of 3 ml of Ketalar (Ketamine 50 mg/ml; Warner-Lambert, Morris Plains, NJ) and ventilated on a respirator under general anesthesia (O_2, 3 ml/min; N_2O, 3 ml/min; halothane, 1.5 ml/min). The femoral artery and vein were canulated, arterial blood pressure and central venous pressure (CVP) were monitored in all animals throughout the experiment. The arterial blood pressure was measured with a catheter placed into the iliac artery via the femoral artery. The CVP was measured by means of a catheter positioned in the femoral vein and advanced into the abdominal vena cava.

Each animal was placed in the prone position on a frame. At first, the third lumbar laminae were removed, the dural tube was exposed widely, and the dura mater was incised centrally exposing the spinal cord. Next, the sixth rib was removed and a transpleural approach was used to access the

[†]Retired.

Correspondence to: Shigeru Kobayashi (T: +81-776-61-8383; F: +81-776-61-8125; E-mail: kshigeru@u-fukui.ac.jp)

aorta and inferior vena cava. The aorta was clamped to reproduce an ischemia model of the lumbar cord (Fig. 1A) and the inferior vena cava was clamped to reproduce a congestion model (Fig. 1B); both at the 6th costal level for 30 min using forceps transpleurally. Body temperature was continuously measured with a subcutaneous thermometer around the laminectomy during the operation and was kept relatively stable between 36 and 37°C with the aid of a heating lamp. Immediately before and after aortic or vena cava clamping, sodium bicarbonate was infused to compensate for the expected acidosis. Blood gas analysis was monitored intermittently and the electrocardiogram was registered continuously, keeping the animals at constant physiologic levels during the experiment. Measurements of blood flow, partial oxygen pressure (PO_2) and action potential in the lumbar cord were repeated over a period of 30 min after release of clamping.

Measurement of Spinal Cord Blood Flow

Regional blood flow was measured in the lumbar cord using the electrochemically generated hydrogen clearance technique.[9] To measure the spinal cord blood flow in 28 animals, a tissue blood flow meter (DHM-3001; M.T. Giken Co., Tokyo, Japan) was employed. A small platinum electrode with a diameter of 200 μm (MHD-60; M.T. Giken Co.) was inserted 1–3 mm deep into the spinal cord. In our model, a 600 mV potential was applied between the platinum electrode and a silver/silver chloride reference electrode (MH-10; M.T. Giken Co.) inserted in the subcutaneous tissue adjacent to the laminectomy, and the change in current resulting from the oxidation of hydrogen at the electrode tip was continuously recorded. We used a direct current of 20 A for 25 s to electrochemically generate hydrogen in the spinal cord. We measured the blood flow twice before clamping the aorta ($n = 14$) or vena cava ($n = 14$), in order to establish the average intraparenchymal blood flow in animals. The hydrogen washout curve was recorded until the current reached baseline. Blood flow was calculated from monoexponential tissue desaturation curves according to the Fick principle. The natural logarithm of the current recorded during the first 10 min of each clearance curve was calculated for every 30 s interval from the onset of hydrogen washout. Blood flow was calculated from the slope of the line fitted to these data by the method of least squares.[10] If the clearance curve had an initial fast component, the slope of the slow component only was used as the measure of blood flow.[11] Finally the animals were killed by the intravenous administration of potassium chloride, and the diffusion value of the hydrogen in the spinal cord was measured 40 min later. Regional blood flow (RBF) was calculated from the equation: $RBF = 69.3\lambda \times (1/T_a - 1/T_d)$ where T_a is the half-time of hydrogen clearance in alive state, T_d is the half-time of hydrogen clearance in cardiac arrest, and λ is the partition coefficient for hydrogen between blood and tissue (=1). RBF expressed in ml/min/100g.[12]

After these experiments were finished, a small quantity of India ink inserted along the needle confirmed whether the needle's tip was inside the gray matter or the white matter. The spinal cord extracted and the specimens were cleared by the Spalteholz technique.[13] The needle position in the spinal cord was observed with a stereoscopic microscope (Fig. 1C).

Measurement of Intraparenchymal PO_2

PO_2 in the spinal cord was measured by the polarographical method (Model POG-5000S PO_2 Meter; M.T. Giken Co.).[14] To prevent individual electrode interference, a PO_2 needle type platinum electrode with a diameter of 10 μm (POE-10N; M.T. Giken Co.) was polarized −800 mV for local tissue O_2 recordings, referenced to a disk silver–silver chloride

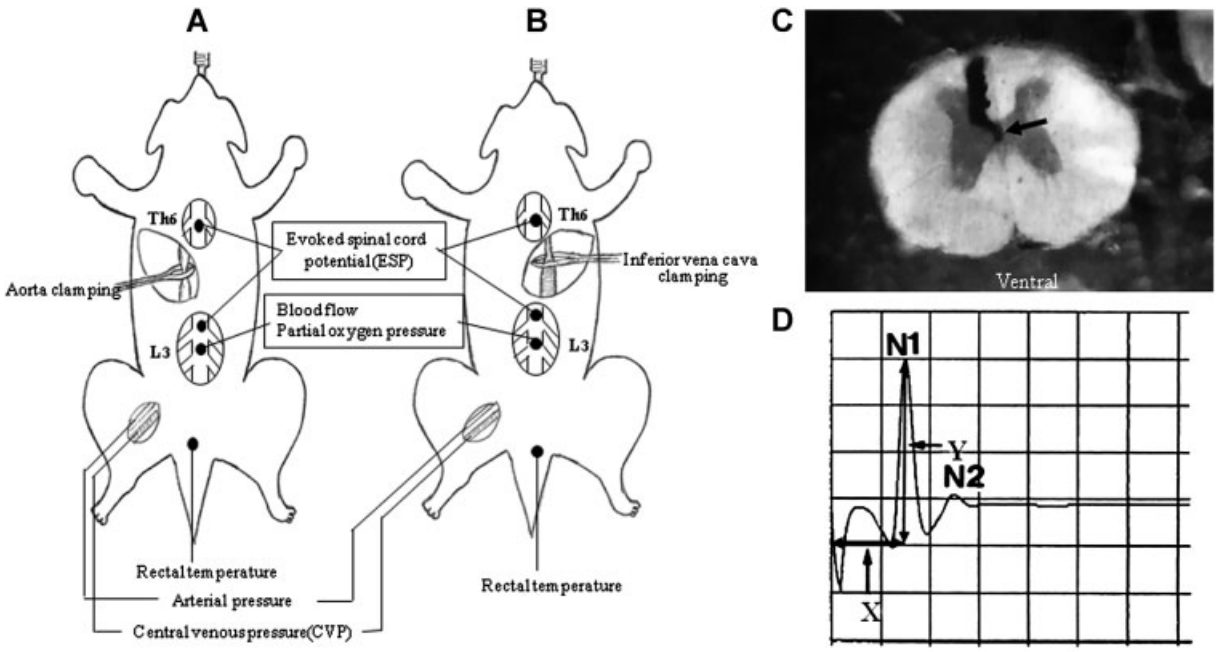

Figure 1. (A) For the ischemic model of the spinal cord, the aorta [Ao] was clamped ($n = 28$). (B) For the congestion model of the spinal cord, the inferior vena cava [V] was clamped ($n = 28$). In both groups, the third lumbar laminae were removed, and the dura mater was exposed widely. Measurements of blood flow, partial oxygen pressure (PO_2) and evoked potential in the spinal cord were repeated over a period of 30 min after release of clamping. (C) Confirmation of the needle position after blood flow and PO_2 measurement were finished. This needle tip was situated in the gray matter (arrow). (D) Measurement of latency and amplitude in spinal evoked potential (SEP). *X*, latency; *Y*, amplitude; *N*1, first wave; *N*2, second wave.

(Ag–AgCl) electrode (MH 10; M.T. Giken Co.) fixed to the subcutaneous tissue of the low back. Before and immediately after each experiment, the surface PO_2 electrodes were calibrated in 0.9% sodium chloride solutions at 37.0 ± 0.5°C equilibrated with gas mixtures of known oxygen content (2% and 5% oxygen in nitrogen and purified nitrogen). After calibration, the electrode was inserted 1–3 mm deep into the spinal cord. After intraganglionic PO_2 stabilized, we recorded it twice and calculated the average value of the normal state before clamping the aorta ($n = 10$) or vena cava ($n = 10$). After clamping, the PO_2 value was registered continuously. After these experiments were finished, the needle position in the spinal cord was confirmed to make the cleared section as above-mentioned.

Electrophysiological Study

Electrophysiological studies were carried out using an electromyographic meter (Neuromatic-2000C; Dantec Medical A/S, Copenhagen, Denmark) using all animals measured blood flow and PO_2. The amplitude and the latency of ascending and descending spinal evoked potentials (SEP) were monitored during the process of clamping the aorta or vena cava. Two electrodes were placed in the epidural space at the level of T_6 and L_2 vertebrae. The spinal cord was stimulated with 0.2-ms duration square wave voltage pulses at a rate of 5 Hz, using a bipolar electrode. The stimulus intensity was adjusted to 1.5–2 times of the motor threshold and 50 responses were summated. The evoked potential was recorded directly on the dura mater after clamping the aorta or vena cava, and then the amplitude was measured before and after clamping. The basic wave of SEP consists of a first wave ($N1$) and a second wave ($N2$; Fig. 1D). It is generally said that the first and second wave are conducted in the postero-lateral column and the posterior column, respectively. In this study, we measured amplitude and latency using a first wave. All changes were relative to baseline values.

Fluorescence Microscopic Study

Finally, we examined the status of the blood-spinal cord barrier under fluorescence microscope after injection of Evans blue albumin (EBA) into the cephalic vein to find out what sort of circulatory disturbance occurred in the spinal cord.[15] After clamping of the aorta ($n = 5$) or the vena cava ($n = 5$) for 30 min, EBA (10 ml/kg, molecular weight approximately 59,000) and HRP (type-II, molecular weight approximately 43,000 Sigma Co., St. Louis, MO) were injected intravenously and allowed to circulate for 30 min. EBA was prepared by mixing 5% bovine albumin (Wako Chemical Co., Osaka, Japan) with 1% Evans blue (Sigma Chemical Co.). The animals were fixed by intra-aortal perfusion with 4% paraformaldehyde in 0.15 M cacodylate buffer, pH 7.2 at 20°C. The lumbar cord sections were resected with the dural sac. After the lumbar cord sections fixed with 4% paraformaldehyde for 24 h, 20-μm thick sections were mounted with 50% aqueous glycerin to be examined under the fluorescence microscope at 380 mμW (BX-51; Olympus, Tokyo, Japan).

Statistical Analysis

From the record of each animal in both groups, arterial blood flow, CVP, spinal cord blood flow, PO_2, latency, and amplitude during the experiment were determined. Unless otherwise stated, data are presented as the mean ± the standard error of the mean (SEM) of at least five separate experiments. And also, the averaged data were expressed as percentage of the average value before clamping of aorta or inferior vena cava. Comparison values were performed using a repeated-measures analysis of variance and post hoc (Scheffé) compared before and after clamping of the aorta or inferior vena cava. Data were entered into a database and analyzed by using SPSS statistical soft-ware, version 14.0.J (SPSS Inc., Chicago, IL). A probability of 5% was considered statistically significant.

RESULTS

Immediately after aorta clamping ($n = 24$), blood pressure in the femoral artery dropped to 20–34 mmHg in the meantime ($p < 0.05$; Fig. 2A), central venous pressure was slightly elevated (Fig. 2B). When the vena cava was clamped ($n = 24$), central venous pressure increased about three to four times compared to the pressure before clamping ($p < 0.05$; Fig. 2B) and blood pressure in the femoral artery dropped to 69.3 ± 6.8 mmHg (average ± SEM; $p < 0.05$; Fig. 2A). After release of clamping, both arterial and venous pressures quickly returned to the basal pressure. In this study, the absolute blood flow volume in the gray matter and white matter was 38.8 ± 5.6 ($n = 14$) and 15.3 ± 2.5 ml/min/100 g ($n = 14$), respectively. The blood flow in the gray matter due to aorta and vena cava clamping fell to 76.2 ± 10.5% of the blood flow before clamping in the ischemic model ($p < 0.05$) and to 37.9 ± 19.7% in the congestion model ($p < 0.05$; Fig. 3A). The blood flow in the white matter fell to 73.7 ± 10.8% of the blood flow before clamping in the

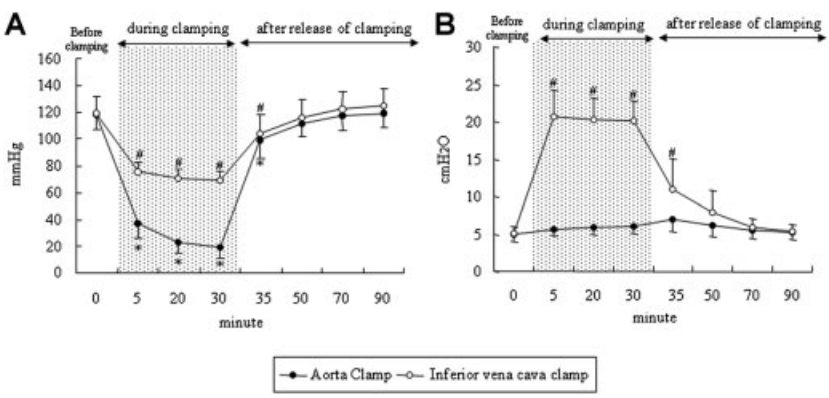

Figure 2. Changes in blood pressure after aorta or inferior vena cava clamping. (A) Changes in blood pressure in the femoral artery. Arterial blood pressure significantly decreased during clamping than pre-clamp data ($^{+,*}p < 0.05$, Scheffé test). (B) Changes in central venous pressure. Central venous pressure increased about three to four times when compared to the pressure before clamping ($^{*}p < 0.05$, Scheffé test). The averaged data were expressed as percentage of the average value before clamping.

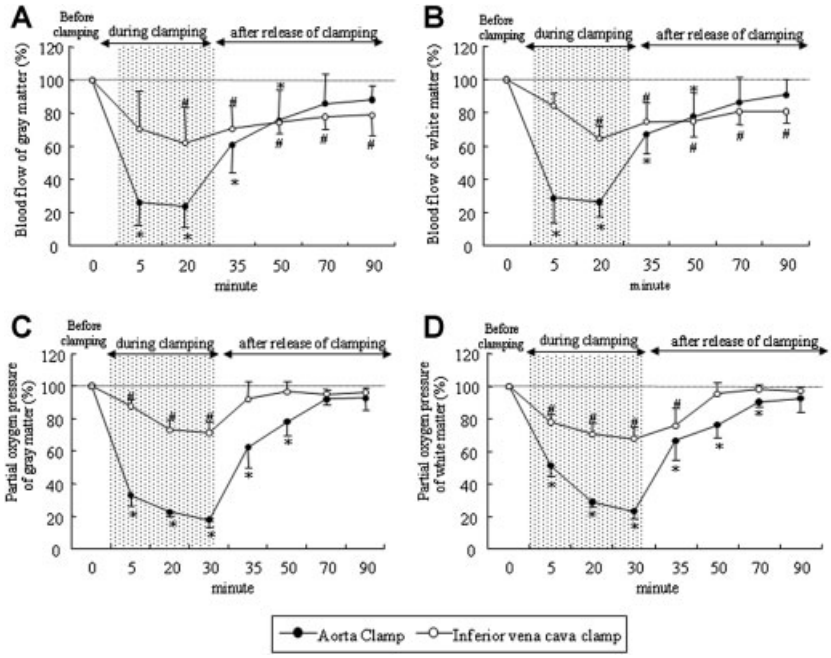

Figure 3. Changes in spinal cord blood flow (A and B) and intraparenchymal PO_2 (C and D) after aorta or inferior vena cava clamping. (A and C) Gray matter, (B and D) White matter. After clamping, the rate was significantly decreased compared to pre-clamping data ($^{*,\#}p < 0.05$, Scheffé test). The averaged data were expressed as percentage of the average value before clamping.

ischemic model ($p < 0.05$) and to 35.5 ± 8.8% in the congestion model ($p < 0.05$; Fig. 3B). When the clamp was released, the blood flow in the ischemic model was restored within 1 h. The blood flow in the congestion model, however, did not recover and remained reduced level in the gray ($p < 0.05$) and white matter ($p < 0.05$). The PO_2 in the gray matter and white matter was 26.0 ± 2.1 ($n = 10$) and 12.4 ± 2.3 ml/min/100 g ($n = 10$), respectively. The changes of PO_2 in the lumbar cord indicated a similar tendency to blood flow, 82.2 ± 4.6% and 77.2 ± 3.9% drop in the gray ($p < 0.05$; Fig. 3C) and white matter ($p < 0.05$; Fig. 3D) of the ischemic model ($p < 0.05$), respectively. In the congestion model, 28.9 ± 7.1% and 32.6 ± 4.0% drop in the gray ($p < 0.05$; Fig. 3C) and white matter ($p < 0.05$; Fig. 3D), respectively. After release of clamping, PO_2 in the gray and white matter recovered completely in both models. In the electrophysiological study, the latency of the ascending ($n = 24$) and descending SEP ($n = 24$) prolonged by 122.4% ($p < 0.05$) and 118.8% ($p < 0.05$) in the ischemia model, respectively, and 111.3% ($p < 0.05$) and 113.1% ($p < 0.05$) in the congestion model, respectively (Fig. 4A). When the clamp was released, the latency in the ischemic model was restored within 1 h. The latency of the ascending and descending SEP in the congestion model, however, did not recover and stayed at the prolonged level ($p < 0.05$). The amplitude of the ascending and descending SEP diminished by 8.4% ($p < 0.05$) and 11.9% ($p < 0.05$) in the ischemia model, respectively (Fig. 4B). In the congestion model, however, the amplitude of the ascending and descending SEP only fell to 16.6% ($p < 0.05$) and 17.8% ($p < 0.05$), respectively. These dropped amplitudes returned almost completely to base line within 1 h after release of clamping.

After intravenous injection of EBA, marked extravasation of EBA in the 3th lumbar level of the spinal cord was evidenced after a 30 min clamping of the vena cava; but not by aorta clamping in all the animals, where there was no extravasation of EBA and the blood-spinal cord barrier was preserved in the gray matter (Fig. 5A) and the white matter (Fig. 5B). After clamping of the vena cava, however, the red fluorescence of EBA was seen outside the intraparenchymal microvessels in the gray matter (Fig. 5C) and the white matter (Fig. 5D). EBA diffused throughout the intraparenchymal space and stained in the motor neuron in the gray matter.

DISCUSSION

Changes of Spinal Cord Blood Flow after Ischemic and Congestive Damage

The blood supply of the spinal cord is dependent upon anterior and posterior radicular arteries, each of which joins respectively the anterior longitudinal arterial channel and the postero-lateral arterial channels of the spinal cord, contributing in turn to the pial plexus.[5] The direction of blood flow in these vessels may vary and the local blood supply of the cord will be compensated through the anastomoses of the pial plexus even if radicular blood flow along a nerve root is disturbed. A large number of motor neurons are present in the gray matter and the gray matter is reported to have an abundant vascular network when compared to white matter.[5] Many researchers measured the blood flow in the spinal cord by the

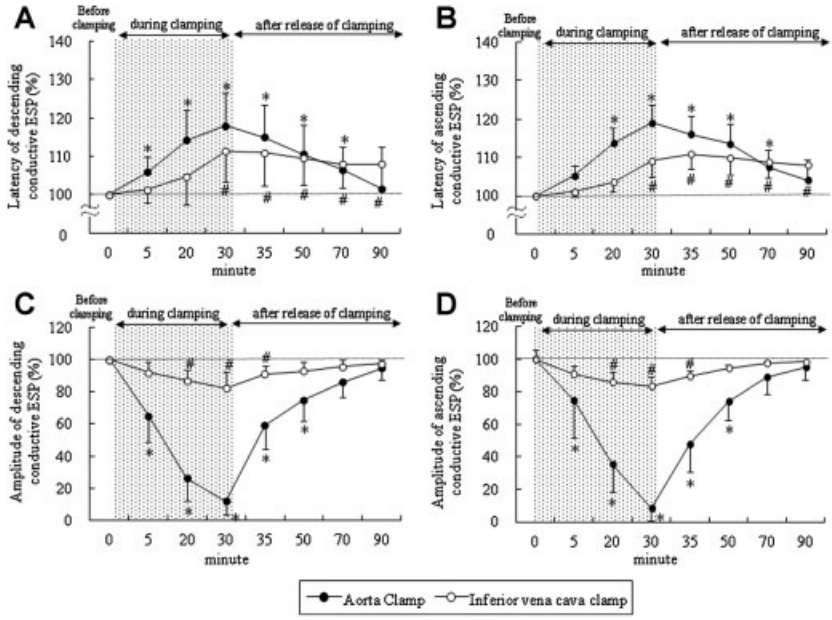

Figure 4. Changes in spinal evoked potential (SEP) after aorta or inferior vena cava clamping. (A and B) Latency, (A) descending conductive SEP, (B) ascending conductive SEP. After clamping, the rate was significantly prolonged when compared to pre-clamping data ($^{*,\#}p < 0.05$, Scheffé test). (C and D) Amplitude, (C) descending conductive SEP. (D) Ascending conductive SEP. After clamping, the rate significantly dropped, compared to pre-clamping data ($^{*,\#}p < 0.05$, Scheffé test). The averaged data were expressed as percentage of the average value before clamping.

electrochemically generated hydrogen washout method and other methods[16–20] and reported that the values of blood flow[16–20] and the partial pressure of oxygen[16] in the gray matter are about twice of those found in the white matter.

So far, there are many references about ischemic damages of the spinal cord tissue reported in the literature,[4,16,21–23] but detailed studies of congestion damages in the spinal cord have not been done. Fried et al.[22] showed experimentally that, in monkeys, paraplegia did not occur even if the so-called artery of Adamkiewicz was ligated. Paralysis followed if the anterior spinal artery was ligated distal to the entry point of the artery of Adamkiewicz into the anterior longitudinal arterial channel of the spinal cord. Woodard and Freeman[23] showed experimentally in adult dogs that the section of one to four sets of adjacent nerve roots along with blood vessels at the lower thoracic level produced no paraplegia. In dogs with five sets of adjacent nerve roots sectioned, transient neurological deficits were frequently observed. Temporary paraplegia occurred when the roots from six adjacent spinal cord segments were sectioned. These results indicate that the smaller radicular arteries and the pial plexus around the spinal cord can maintain an adequate intramedullary blood flow in the spinal cord

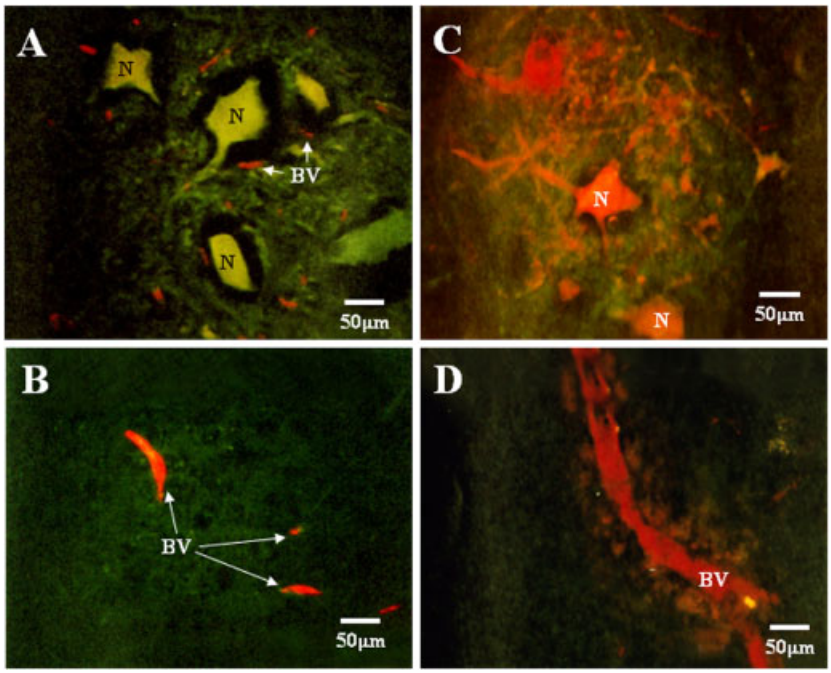

Figure 5. Transverse sections of the lumbar cord seen under a fluorescence microscope. (A and B) Ischemia model. EBA emits a bright red fluorescence in clear contrast to the green fluorescence of the motor neuron in the gray matter (A) and nerve tissue in the white matter (B). After intravenous injection of EBA: EBA was limited inside the blood vessels, and the blood-spinal cord barrier was maintained (C and D). Congestion model: In the gray matter, a motor neuron and intramedullar space emits a bright red fluorescence (C). EBA emits a bright red fluorescence, which leaked outside the blood vessels in the white matter, and intramedullary edema was seen under a fluorescent microscope (D). BV, blood vessel; N, motor neuron.

even after damage to several of the large radicular arteries of Adamkiewicz as no loss of spinal cord function occurs. However, these results are limited to the acute post-operative phase and disturbances of venous circulation were left out of consideration even through both arterial and venous radicular vessels were ligated together with the nerve roots. They also observed that cavitation developed in the spinal cord in the region just dorsal to the central canal 1–4 weeks after section of the spinal nerve roots along with their blood vessels from six adjacent spinal cord segments. They presumed that venous insufficiency was the cause of the cavitations.

The experimental work done by Olmarker et al.[6] showed that the average minimum pressure in an inflated balloon compressing the pial vessels of the pig cauda equina required to stop the flow in the capillaries was 40 mmHg and in the venules was 30 mmHg. The pial venous flow stops by compression with much lower pressure than the arterial flow. Usubiaga et al.[7] demonstrated that clamping of the vena cava could be used experimentally to increase the systemic venous pressure. The same maneuver also produces congestion of the epidural veins and increases the epidural pressure but they did not describe the changes of spinal cord circulation.[8] The present study assessed the influence of arterial ischemia and venous congestion, resulting from obstruction of blood flow without spinal cord compression, on intraparenchymal blood flow and function of neurons. Due to the technical difficulty of making models of partial and/or chronic spinal cord blood flow blockage, we used models of arterial or venous complete blood flow blockage; performed at the 6th costal level, without spinal cord compression. A technical limitation to consider was the impossibility of blocking all the spinal cord blood flow due to the collateral vasculature. As a result, it was confirmed that ischemia in the spinal cord had a more serious influence on blood flow, PO_2, and action potential than congestion. After 30 min of spinal cord ischemia, recovery occurred with reperfusion, but longer ischemic periods will cause a permanent effect on the function of neurons due to oxygen deficiency. When changes in the femoral arterial and central venous pressures were monitored after obstruction of blood flow, both the arterial and venous pressures decreased after aortic blockade and the arterial pressure increased slightly after obstruction of the inferior vena cava (Fig. 2B). However, the central venous pressure showed an approximately fourfold increase immediately after obstruction of the inferior vena cava, and this sudden increase in venous pressure could have a marked influence on the capillary pressure and blood permeability in the spinal cord.

Effect of Ischemic and Congestive Damage on Blood-Spinal Cord Barrier

The arachnoid membrane acts as a diffusion barrier for the spinal cord and the vascular endothelial cells of the intraparenchymal microvessels also create the blood-spinal cord barrier. These barriers protect and maintain the neurons and nerve fibers in a constant environment. The capillary vessels of the spinal cord are lined by endothelial cells that contain only a few pinocytic vesicles and are bound by tight junctions to form the blood-spinal cord barrier.[24] Normally, EBA as the protein tracers that are injected intravenously, do not leak out of the vessels due to this barrier.[25] When arterial ischemia was induced, EBA remained in the blood vessels, indicating maintenance of the integrity of the blood-spinal cord barrier (Fig. 5A and B). On the other hand, venous congestion disrupted the blood-spinal cord barrier and there was extravasation and edema in the spinal cord (Fig. 5C and D). Vasogenic edema is a term introduced by Klatzo et al.[26] to describe the leakage of fluid, which is usually rich in protein, from damaged vessels. It seems probable that EBA also leaks through ruptures in the vessel wall.[27,28] Thus, the blood-spinal cord barrier that regulates vascular permeability in the spinal cord seems to be susceptible to congestion which raises the intra vascular pressure rather than to ischemia which decreases the pressure. Then, edema that increases intraparenchymal pressure can develop easily when venous congestion is applied to the spinal cord, which is closely related to the onset of nerve cell dysfunction. Intraparenchymal edema formation may be the earlier phenomenon inducing the dysfunction of the spinal cord rather than the arterial ischemia in the clinical point of view.

Clinical Importance of the Venous Congestion in the Spinal Cord

It is known that sites of spinal cord compression by spinal canal stenosis frequently show T2-weighted and gadolinium enhancement on MR images, suggesting breakdown of the blood-spinal cord barrier and edema of the spinal cord.[29,30] In patients with severe compression myelopathy, total circumferential compression of the spinal cord associated with closure of the subarachnoid space is assumed to block all routes for the supply of nourishment and removal of waste via the cerebrospinal fluid (CSF), triggering various disorders in combination with chemical factors released by inflammatory cells, such as macrophages.[31–33] Elevation of the capillary pressure induced by venous stasis is thought to cause intraparenchymal edema and the inflammatory response produced by compression, as well as mechanical damage to the blood-spinal cord barrier, because venous blood flow is stopped by compression at a very low pressure.[33] It is therefore important to be aware of venous congestion as well as arterial ischemia during spinal cord compression.

During extensive spine surgical procedures like the management of degenerative disease, spinal deformities or spinal tumors; circulatory disturbances may often lead to spinal cord damage. Spinal cord ischemia is a devastating event that continues to haunt the

vascular surgeon with paraplegia after operation on the thoracic and abdominal aorta as an unpredictable and disastrous complication with reported incidences ranges from 4% to 40%.[34–36] Acute spinal cord dysfunction is believed to be caused by ischemic damage during cross-clamping.[37,38] following permanent exclusion of the essential intercostals arterial blood supply or temporary interruption of blood flow to the spinal cord. This study showed the venous congestion may be a preceding and essential factor of circulatory disturbance inducing myelopathy. It is therefore important to be aware of venous congestion as well as arterial ischemia during vascular surgery.

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