MEDICAL SCIENCE MONITOR

ANIMAL STUDY

e-ISSN 1643-3750
© Med Sci Monit, 2019; 25: 9192-9199
DOI: 10.12659/MSM.919313

Received: 2019.08.10
Accepted: 2019.11.06
Published: 2019.12.02

# Effect of Spinal Shortening for Protection of Spinal Cord Function in Canines with Spinal Cord Angulation

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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**Source of support:** This work was supported by grants from the National Natural Science Foundation of China (No. 81460347 and 81560373) and grants from the "Special and Joint Program" of Yunnan Provincial Science and Technology Department & Kunming Medical University (No. 2018FE001-226)

**Background:** Posterior vertebral column resection (PVCR) has been widely used as a treatment for severe spinal deformity. By using the canine model of vertebral column resection, this study explored the effect of spinal shortening on blood flow and function of the spinal cord during spinal cord angulation.

**Material/Methods:** The canine model of L1 vertebral column resection was constructed with the PVCR technique. The canines were divided into 5 groups according to the degree of shortening: the 0/4 group, the 1/4 group, the 2/4 group, the 3/4 group, and the control group. Spinal cord blood flow, neuroelectrophysiology, HE staining, nitric oxide, and endothelin-1 were measured during the procedure of vertebral column resection and spinal cord angulation.

**Results:** The results showed that, in the 1/4 group and the 2/4 group, the blood flow of the spinal cord decreased by 16.5% and 10.6%, respectively, with no obvious damage in the spinal cord; in the 0/4 group and the 3/4 group, the blood flow decreased by 23.5% and 23.1%, respectively, with significant damage in the spinal cord.

**Conclusions:** When the spinal cord is shortened by 1/4 to 2/4, the tolerance of the spinal cord can increase and spinal cord injury resulting from angulation can be avoided. However, when the shortening reaches 3/4, it is harmful to the spinal cord. Proper shortening of the spinal cord by 1/4 to 2/4 may increase the tolerance of the spinal cord to the damage caused by angulation during PVCR.

**MeSH Keywords:** Regional Blood Flow • Spinal Cord • Spinal Cord Ischemia

**Full-text PDF:** https://www.medscimonit.com/abstract/index/idArt/919313

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## Background

The high incidence of neurological deficits associated with spinal orthopedic surgery in humans has been a concern to clinicians. In the past 20 years, with the application of pedicle fixation for various spinal deformities, the control and correction effects for mild and moderate malformations have been significantly improved. However, the incidence of surgery-related neurological deficits has not improved significantly compared with 20 years ago [1]. Surgical treatment of severe and stiff spinal deformities is more challenging than the treatment of mild-to-moderate idiopathic malformations, which are different in terms of preoperative preparation, operation time, and cardiopulmonary function. More importantly, the treatment of severe stiffness and deformity is accompanied by significant blood loss and higher risk of neurological complications. A series of surgical techniques for the treatment of severe spinal deformity have been applied in clinical practice, such as anterior relaxation combined with posterior correction, pedicle subtraction osteotomy (PSO), anterior and posterior combined vertebral column resection, and posterior vertebral column resection (PVCR), with PVCR being considered the most effective [2]. The spinal cord is completely exposed in the surgical field when using PVCR for correction. If the spinal cord is displaced, the surgeon can immediately restore its position. Unfortunately, there was still a high risk of neurological complications. Recent studies from several PVCR treatment centers worldwide reported a high risk of neurological damage: Suk et al. [3] reported the incidence of neurological complications is 17.1% (12/70), Lenke et al. [4] reported an incidence rate of 27.2% (40/147), and Zhang et al. [5] reported an incidence of 16.1% (10/62). Our previous studies found that irreversible nerve damage could be avoided with the use of PVCR for correction of severe spinal deformities and for proper shortening of the spinal cord [6]. Our inference was that the spinal cord was completely decompressed after total spinal resection. More importantly, reasonable spinal shortening could increase the tolerance of the spinal cord to displacement. However, it was unclear how and to what extent the spinal shortening could prevent damage caused by spinal cord angulation.

Therefore, in the present study, a beagle dog model of L1 vertebral column resection was constructed, with the spinal shortening and angulation performed using the mature PVCR technique, to explore the potential biological mechanism and to lay the foundation for optimizing future orthopedic surgery.

## Material and Methods

The Institutional Ethics Committee of our hospital approved the use of dogs in this study. The study was conducted in compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23).

### Grouping

Twenty-five (25) beagle dogs (weight 10.4±0.1kg) were purchased from the Animal Center of Kunming Medical University (Kunming, China). According to the height of the L1 vertebral body and the thickness of the upper and lower discs, the dogs were randomly classified into 5 groups: the 0/4 group (n=5), the 1/4 group (n=5), the 2/4 group (n=5), the 3/4 group (n=5), and the control group (n=5). All groups underwent PVCR. In the control group, only the L1 segment spinal cord specimens were collected.

### Preoperative preparation

The weights and body temperatures of the experimental dogs were measured immediately when they were sent to the operation room. Anesthesia was quickly induced by using 1.2% isoflurane, then the anesthesia apparatus was connected, and anesthesia was continued by inhalation of 1.2% isoflurane. The depth of anesthesia was maintained at 1 MAC. The neurophysiological monitor was connected to corresponding electrodes after anesthesia was stabilized. The voltage pulse mode stimulation was given to the somatosensory evoked potential (abbreviated as SEP) at the wave width of 0.2 ms, frequency of 2 Hz, and intensity of 0.5–1 mA. The intensity was based on the obvious twitching of the limbs, and the analysis time was 20 ms for an average of 100 to 200 times. Neurophysiological monitoring started before the surgery, and the latency and amplitude baseline were set as the reference values for neurophysiological changes in the experimental animals. The SEP latency would be reduced by 10% or the volatility would be reduced by 50% as a warning value.

### Surgery

Based on PVCR technique [3], surgery was performed by the same group of surgeons, and the surgery included the following stages: exposure, implantation of pedicle screws, laminectomy, vertebral column resection, shortening, and angulation, as explained in detail below.

Exposure: the L1 vertebral body was located and a T11–L4 posterior incision was made. The entry point of pedicle screws on T11–L4 was then exposed.

Implantation of pedicle screws: a total of 4 pairs of pedicle screws were implanted in T12, T13, L2, and L3, respectively. The L1 vertebral body was not implanted with a pedicle screw as it was to be resected.





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Laminectomy: the rongeur was used to bite off the L1 spinous process and the scalpel was used to cut the upper and lower interspinous ligaments of the L1 spinous process. The laminar rongeur was used to bite off the T13–L1 lamina to expose the fat behind the spinal cord, and then the fat was removed to expose the spinal cord.

Vertebral column resection: the bilateral transverse processes of L1 were exposed and removed. The lateral wall of the pedicle and vertebral body on each side were exposed after subperiosteal dissection, and segmental blood vessels of the L1 were ligatured at the same time. Bilateral superior and inferior articular processes were removed to fully expose the spinal canal and the nerve root. Intraspinal blood vessels were cauterized with electrodes to reduce bleeding. The pedicle, most of the vertebral body, and the adjacent intervertebral discs on one side were resected carefully to avoid damage to the spinal cord, and the pedicle screws were then connected on the side. The same procedure was performed on the opposite side to resect the pedicle, the vertebral body, and the adjacent intervertebral discs, then the residual bone in front of the dural sac was removed completely. The pedicle screws on the side were also connected to maintain the stability of the spinal column.

Spinal shortening and angulation: the vernier caliper was used to measure the L1 vertebral body resection gap. The actual height of this gap should be the height of the L1 vertebral body plus the thickness of the upper and lower intervertebral discs. According to the group assignment, the spine was shortened with compression forceps by 0/4, 1/4, 2/4, or 3/4 of the height of L1 vertebral body. After the shortening, the spinal cord was angled 40° to the left.

### Real-time monitoring of the blood flow of the spinal cord

The blood flow unit parameter of the Laser Doppler flowmeter (PERIMED PeriFlux 5000 mainframe) PF 5010 was set to 0.2τ. The laser probe was placed on the surface of the spinal cord without pressing it, at the left side of the dorsal spinal artery. When detecting spinal cord blood flow at different times, the laser probe was placed at the same position to reduce error. Spinal cord blood flow was obtained by laser Doppler flowmetry after L1 vertebral column resection and spinal cord angulation. Since the measurement of each blood flow value was non-repeatable, the spinal cord blood flow was measured at 0 min, 5 min, and 30 min, respectively, and the mean value was taken as the actual obtained spinal cord blood flow.

### Pathology and detection of microcirculation metabolism

At 1 h after the spinal cord was angled, a spinal L1 spinal cord specimen 1.5–2.5 cm in length was cut and collected. The collected spinal cord specimens were stained with HE and photographed. The content of ET-1 in the spinal cord samples of experimental animals was determined by radioimmunoassay according to the protocol of the ET1 test kit (Biyuntian, China). The level of ET-1 in the spinal cord samples of experimental animals was determined by radioimmunoassay according to the instructions of the total NO detection kit (Biyuntian, China).

### Statistical analysis

Data are expressed as mean±standard error. Statistical analysis was performed using SPSS 18.0 software (SPSS, Inc., Chicago, IL, USA). The spinal cord bleeding, total NO, and ET-1 were analyzed with the paired *t* test, and the significant level was set to $P<0.05$.

## Results

The L1 vertebral column resection model of each group was successfully established (Figure 1).

At the completion of vertebral column resection (VCR), the spinal cord blood flow was 304.19±11.82PU in the 0/4 group, 299.73±15.72 PU in the 1/4 group, 308.68±11.41 PU in the 2/4 group, and 306.58 ± 9.35 PU in the 3/4 group, with no statistically significant differences among groups. When the spinal cord was shortened and angled, the spinal cord blood flow became 234.34±9.59 PU in the 0/4 group, 254.60±8.90 PU in the 1/4 group, 275.88±8.01 PU in the 2/4 group, and 235.65±10.71 PU in the 3/4 group, with a statistically significant difference compared with the levels at the completion of VCR ($p<0.05$) (Figure 2). The rate of blood flow decline after spinal cord angulation in each group was 23.50% in the 0/4 group, 16.50% in the 1/4 group, 10.60% in the 2/4 group, and 23.10% in the 3/4 group (Figure 2).

During the neurophysiological monitoring, the 1/4 group and 2/4 group did not reach the warning value, while the 0/4 group and 3/4 group did.

The total NO in the spinal cord tissues of each group was 41.6±4.07 mmol/L in the 0/4 group, 34.±2.93 mmol/L in the 1/4 group, 32.6±2.20 mmol/L in the 2/4 group, 45.3±4.21 mmol/L in the 3/4 group, and 29.3±3.29 mmol/L in the control group. There was a statistically significant difference between the experimental groups and the control group ($p<0.05$) (Figure 3).

The ET-1 measurement was 3.9±0.22 ug/g in the 0/4 group, 2.6±0.15 ug/g in the 1/4 group, 2.3±0.24 ug/g in the 2/4 group, 4.8±0.31 ug/g in the 3/4 group, and 2.4±0.28 ug/g in the control group. Compared with the control group, the 1/4 group and





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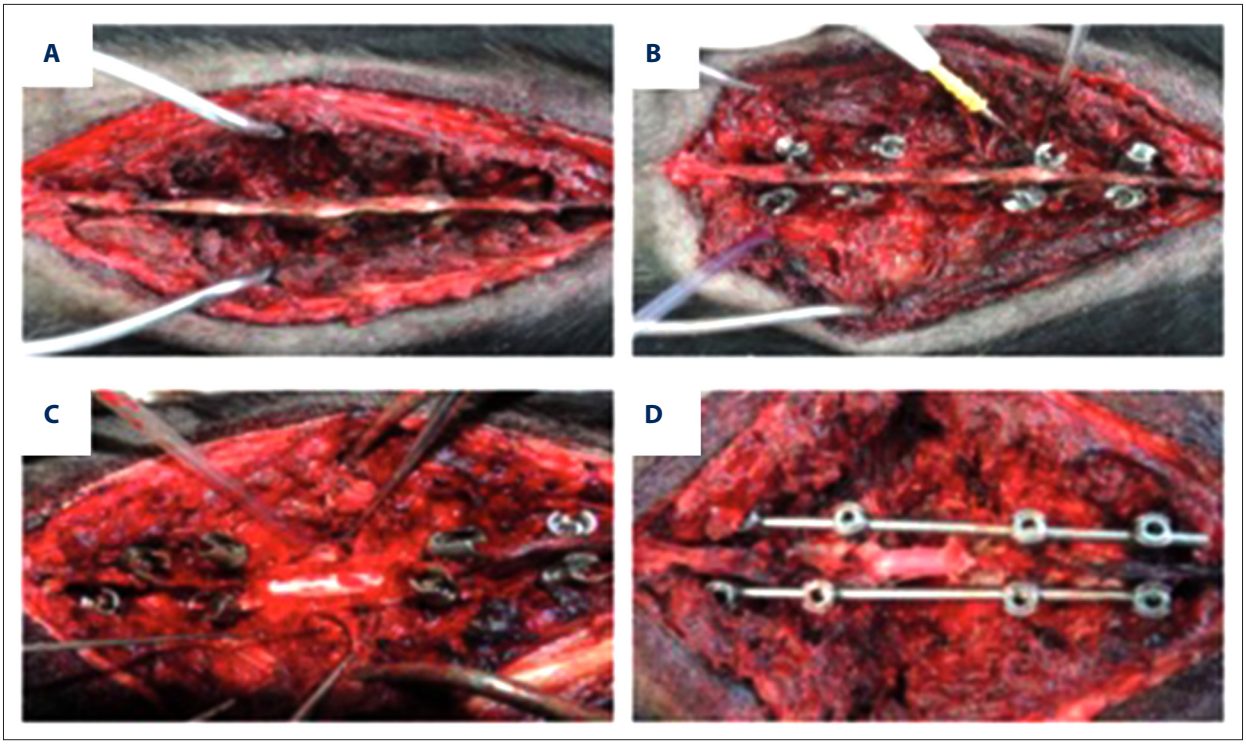


**Figure 1.** The canine L1 vertebral column resection model. (**A**) Exposure. (**B**) Implantation of pedicle screws. (**C**) Laminectomy. (**D**) Vertebral column resection.

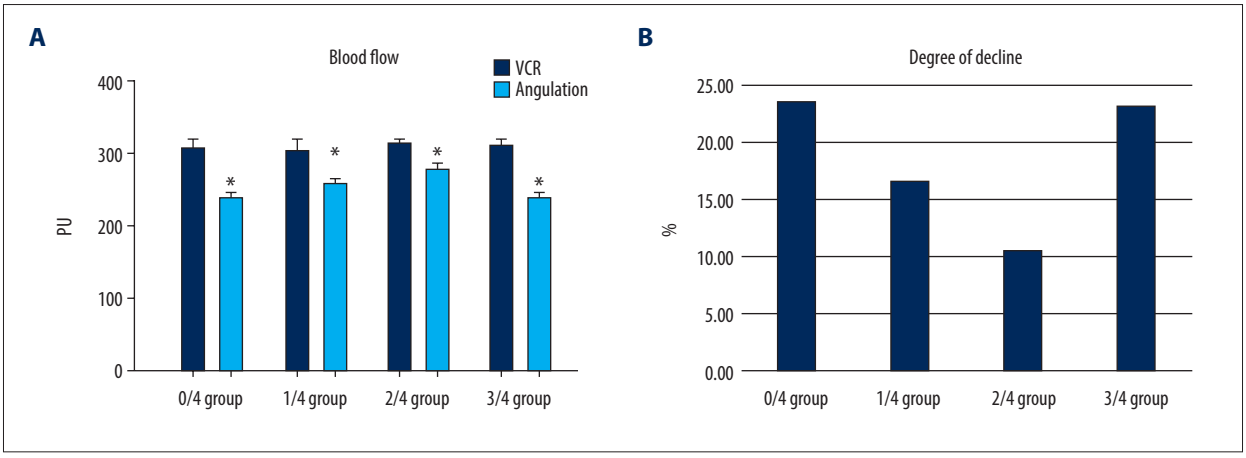


**Figure 2.** Changes in blood flow at the completion of VCR and during angulation. (**A**) The amount of blood flow in each group during VCR and angulation. (**B**) Blood flow reduction rate after spinal cord angulation in different groups. * P<0.05.

2/4 group were no significantly different, while 0/4 group and the 3/4 group were significantly difference (p<0.05) (Figure 4).

In the 1/4 group, 2/4 group, and control group, there were no obvious abnormalities in the neuronal tissues of the white matter or gray matter in the spinal cord. In the 0/4 group and 3/4 group, neuronal cell edema was observed in the white matter region of the spinal cord, and the nuclei were dissolved and ruptured (Figure 5).

## Discussion

One of the features of spinal deformities is the abnormal spinal cord in the deformed spinal canal, especially in severe cases. In the process of corrective surgery, it is inevitable for the spinal cord and nerves to be displaced and pulled. Unlike traumatic acute spinal cord injury, which is characterized by mechanical injury factors, spinal cord injury during corrective surgery is more often due to spinal cord displacement and tension, secondary neuronal edema, and ischemic changes. As spinal





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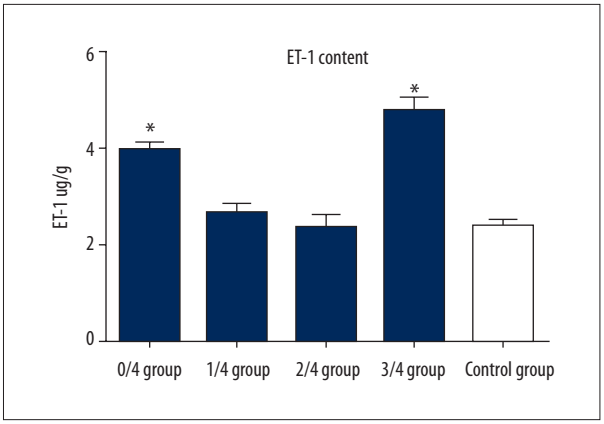


**Figure 3.** ET-1 content in spinal cord tissue of each group. * P<0.05.

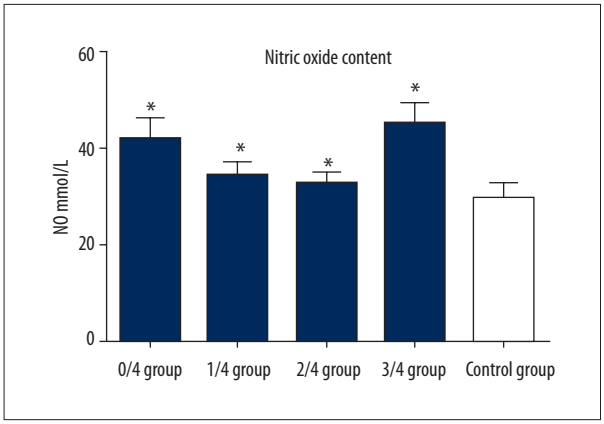


**Figure 4.** Total NO content in the spinal cord tissue of each group. * P<0.05.

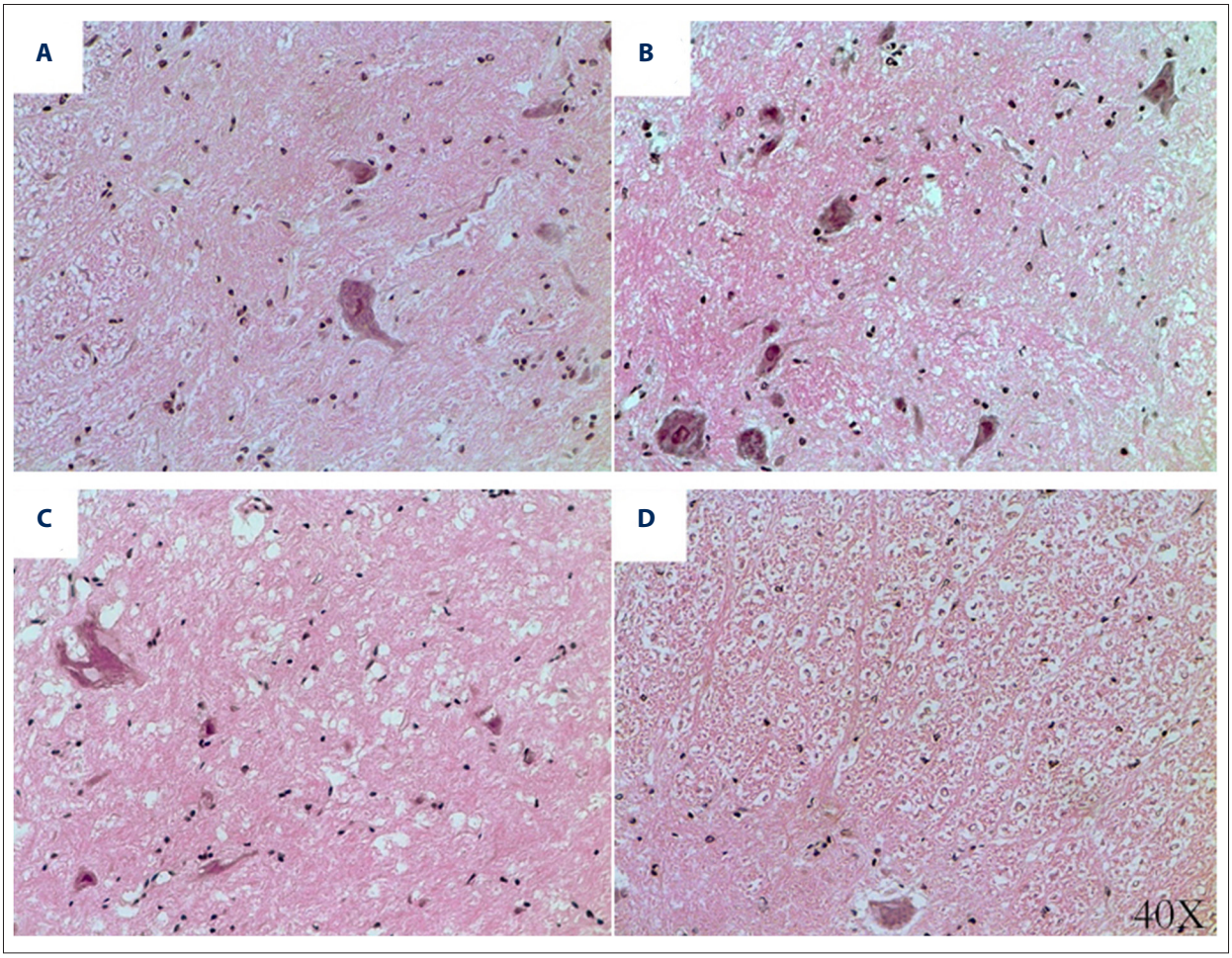


**Figure 5.** HE staining of spinal cord in each group. (**A**) There were no obvious abnormalities in the nerve tissue of the control group. (**B**) No obvious abnormalities were found in the 2/4 group of nerve tissues. (**C**) In the group 0/4, neuronal cell edema was observed in the white matter region of the spinal cord, and the nucleus was dissolved and ruptured. (**D**) In the 3/4 group, obvious edema, neuronal cell edema, and nuclear lysis and rupture were observed in the white matter region of the spinal cord.





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cord tissue has dense blood vessels and is extremely sensitive to hypoxia caused by spinal cord injury, spinal cord blood flow after spinal cord injury plays a crucial role in the recovery of spinal cord function [7–9]. Spinal cord blood flow should be restored as soon as possible in the case of acute spinal cord injury to prevent secondary spinal cord injury [10]. In this study, we used a laser Doppler flow monitor (LDF) to monitor spinal cord blood flow. As a mature technology for monitoring blood flow, LDF has the advantages of noninvasiveness, convenience, reliability, and real-time monitoring, and is thus widely used in animal experiments and in humans. In previous studies, it was found that spinal cord injury had various degrees of abnormalities in spinal cord blood flow. More importantly, the abnormal blood flow of the spinal cord can reflect its function [11–13]. The canine spinal cord terminates at the level of the lumbar 6-7 vertebral body, and its epidural and spinal surface is similar to the abundant collateral vascular network in humans [14]. Therefore, in this experiment, we established the beagle dog L1 total spine resection model based on the clinical practice of PVCR surgery for severe stiff spinal deformity.

In previous experiments of spine shortening, Kawahara et al. [15] used dogs as experimental animals, fixing T11 and T12, and L1 and L2, and removing T13. They reported the following results: (1) when the range of shortening was less than 1/3 of the height of the vertebral body, it would be safe, as the morphology of the dura and spinal cord did not change significantly; (2) when the range of shortening was between 1/3 to 2/3 of the vertebral height, it would be a warning, as the dura mater was wrinkled but the spinal cord was not deformed; and (3) when the range of shortening was greater than 2/3 of the vertebral heights, it would be risky, as the dural folds simultaneously compressed the spinal cord, causing functional and morphological changes. In the experiment, their evaluation of the spinal cord function was applied to the evoked potential, and the proximal end of the spinal cord of the T13 segment was directly stimulated to receive the recorded data at the distal end. Although this method is somewhat close to the real situation, it is not suitable for clinical use. Modi et al. [16] used pigs as experimental animals, modeled by posterior spinal resection and pedicle screw fixation for T10 and T13, and T11 and T12 vertebral bodies. Studies show that spinal cord injury occurs when the distance of shortening is 104.2%, but no spinal cord injury occurs when it is less than 73.8%. Alemdaroğlu et al. [17] used sheep as the model of spinal shortening. The anterior approach was used to fix the T10-L1 vertebral body with a single rod. The T12 vertebral body was removed posteriorly, and the lower part of the T11 lamina and the T13 vertebral plate were exposed. They believed that there was a greater correlation between the morphological changes of the spinal cord during the shortening and the number of laminae removed. During spinal shortening, spinal cord tolerance was better with the resecting of 1 lamina than in the excising of 1 to 1.5 lamina(s), but there was no significant difference in the spinal cord tolerance compared to the situation when laminectomy was greater than 2 laminas.

Although the changes during the shortening of the spinal cord were studied, the tolerance of the spinal cord to its angular displacement after different degrees of shortening received little research attention. Previously, we observed in patients with normal preoperative neurological function, the spinal cord could tolerate a certain degree of displacement during orthopedic surgery. Visible shortening displacement of the dural sac within 3 cm, angled within 20° and twisted 10°, was reported to have no effect on normal function of the spinal cord [18]. Based on previous studies, we first performed experiments in the 0/4 group. When the angle of the spinal cord reached 40°, the latency of SEP in this group of dogs decreased by more than 10%, and the amplitude decreased by more than 50%. In previous studies, neuroelectrophysiologists found that the latency of SEP decreased by more than 10%, and the decrease of amplitude by more than 50% represented damage to the spinal cord [19–21]. This indicated that the spinal cord angle of more than 40° without shortening would be extremely dangerous to the spinal cord. Orthopedic surgeons should avoid this during surgery. In the 1/4 and 2/4 groups, although the blood flow decreased, the degree was smaller. Especially in the 2/4 group, the degree only decreased by 10.50%. Moreover, although the neurophysiological monitoring of the 2 groups showed different degrees of change, they did not exceed the warning value. Pathological sections showed no significant difference between the nerve tissues of the 1/4 and 2/4 group and that of the control group. We speculated that because of the tension in the spinal cord itself, it was extremely easy to reach the critical point the spinal cord tissue and blood vessels could tolerate when the spinal cord was displaced. When the spinal cord was shortened by 1/4 and 2/4, the tension of the spinal cord would be reduced in advance, and when the displacement occurred, the spinal cord tissue and the blood supply artery would have more buffer space. However, further trials are needed to verify the relationship between changes in the tension of the spinal cord and its blood flow and function. To study the risk of excessive acute shortening of the spinal cord, the spinal shortening in the 3/4 group was set in the study. This group of blood flow decreased by 23.30%, and the report from the neurological monitoring also exceeded the warning value, which was consistent with previous studies. Therefore, the above results might indicate some buffer space in the spinal cord when the spinal cord was properly shortened by 1/4 to 2/4. The tolerance of the spinal cord to angular displacement increased, but excessive shortening would be unacceptable.





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To study the microcirculation metabolism of the spinal cord, we also measured nitric oxide (NO) and endothelin-1 (ET-1) in this study. In 1988, Yanagisawa [22] isolated ET from porcine aortic epithelial cell culture for the first time, showing that ET-1 had a strong vasoconstrictor effect *in vivo*. ET-1 levels can significantly increase in cases of brain trauma, cerebral hemorrhage, and ischemic brain disease [23]. Under normal physiological conditions, plasma and spinal cord tissue have lower levels of ET-1. Since ET-1 is a large protein that does not penetrate the blood-cerebrospinal fluid barrier, the increase in ET-1 content in the injured area is not from the blood system. ET-1 can also promote NO synthesis, and NO inhibits the synthesis of ET-1 through a negative feedback pathway [24]. The dynamic balance between them becomes an important factor affecting the microcirculatory state after spinal cord injury. The NO in neural tissue is synthesized by nitric oxide synthase (NOS) and is divided into 3 types: endothelial NOS (eNOS), neuronal NOS (iNOS), and induced NOS (iNOS). Of these, NO synthesized by endothelial NOS (eNOS) from vascular endothelial cells has a stable blood vessel wall structure and maintains physiological functions such as vascular tone. Nevertheless, NO produced by nNOS and iNOS after neuronal ischemic injury has neurotoxic effects [25–27]. In the present study, we examined the total NO content in the spinal cord. The ET-1 and NO in the 0/4 group and the 3/4 group were significantly higher. This result is similar to the change of the injury-related factors in some previous studies of spinal cord injury [28,29]. In the corresponding 0/4 group and 3/4 group, blood flow, neurophysiological monitoring, and pathological sections also showed abnormalities, indicating that self-regulation of spinal microcirculation had decompensated. There was no significant change in ET-1 in the 1/4 and 2/4 groups, and the total NO slightly increased, which might result from a slight decrease in the blood flow causing an increase in total NO. This decrease might be caused by self-regulation of eNO secretion by vascular endothelial cells. Due to the small degree of decrease in blood flow, no obvious spinal cord injury occurred after the self-regulation of spinal cord blood vessels, resulting in no significant change in ET-1. The report of the corresponding neurophysiological monitoring did not exceed the warning value, and no obvious edema or necrosis was observed in the pathological sections. This suggests that the proper spinal shortening has a protective effect on the microcirculation when the spinal cord is angled.

## Conclusions

The above results show that spinal shortening by 1/4-2/4 can increase tolerance of the spinal cord and avoid spinal cord injury caused by angulation of the spinal cord. However, when the degree of shortening reaches 3/4, it can be harmful to the spinal cord. Proper spinal shortening by 1/4-2/4 during PVCR in clinical practice may increase the tolerance of the spinal cord to angulation damage.

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