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A model of acute compressive spinal cord injury with a minimally invasive balloon in goats

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ABSTRACT

Research into spinal cord injury depends upon animal models of trauma. While investigations using small animals have yielded critical insights into the cellular mechanisms of neurotrauma, no effective therapies have been translated to human clinical treatments. There are considerable differences in pathophysiology, scale, and anatomical organization between rodents and primates. Here, the established method of inflating balloons to compress the cord within the spinal canal was adapted for use in goats. By using surgical techniques to insert a kyphoplasty balloon, spinal cord injury was accomplished with minimal trauma to the surrounding tissues, as is common in other traumatic models. Dye volumes of 0, 1.26 ± 0.18, and 2.82 ± 0.20 mL were injected into the balloon to produce spinal occupancies of 0%, 33 ± 2%, and 89 ± 4%, as evaluated by X-ray and computerized tomography imaging. A significant dose response was observed for the different levels of trauma, with reduced conduction of somatosensory evoked potentials and impaired mobility 7 days after injury. From the strong correlations between injection volume, balloon pressure, spinal occupancy, nerve function, and animal behavior, we conclude that hydraulic compression in goats is a useful model of spinal cord injury.

1. Introduction

Spinal cord injury (SCI) is a severely debilitating condition that affects more than a quarter million people in the United States [1]. Despite tremendous efforts attempting to develop new pharmacological therapies, surgical interventions, and rehabilitation strategies, virtually no effective treatments have been established and the prognosis following SCI remains poor. This situation forces researchers to rethink the traditional therapeutic methods and to develop novel strategies that can lead to effective treatments.

The efforts to improve understanding of the mechanisms of spinal pathology and the efficacy of various treatment strategies depend upon the use of animal models. Relatively few investigations into traumatic SCI use large animals [2], and significant differences have been observed between small animal species in their response to spinal compression [3], indicating that choice of animal model is crucial in ensuring validity of any findings. Existing models have generated some insights regarding the mechanisms of injury as well as potential treatments of spinal cord injury. However, translating this knowledge to human clinical injuries has proven difficult. In fact, although many treatments have been shown to work in small animals, these therapies are seldom effective in larger animals [2,4] and even less in treating human SCI. Therefore, it is obvious that one of the fundamental problems in spinal research is that the existing animal models do not adequately mimic the physical pathology associated with most human spinal injuries.

Another problem in SCI research is that the vast majority of current methods used to induce injury are quite invasive and not clinically relevant. As noted by Fukuda et al., besides choosing proper animals of sufficient size to represent humans and producing injury reliably, an effective model of SCI should create damage without unduly traumatizing the surrounding tissues [5]. Therefore, we suggest that the ability to induce known and various levels of focal injury without invasive procedures is another critical factor in studying SCI disorders.

In order to overcome these obstacles, we have established a SCI model that can reliably produce focal injuries with high reproducibility in a large animal. Specifically, known volumes of contrast liquid were used to inflate a kyphoplasty balloon, exerting a controlled compression on goat spinal cord with minimal injury to the vertebrae or surrounding soft tissues. The magnitude of pressure within the balloon correlated highly with degree of spinal compression, as observed with X-ray imaging and computed tomography (CT). Extent of compression was related to electrophysiological function and behavioral outcomes. By using goats as a

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large animal model, we expect to facilitate the translation of research findings from rodent or other small animal models to generate clinically relevant knowledge in both the mechanism and treatment of human SCI.

2. Materials and methods

2.1. Animal selection

Twenty adult male goats weighing 35–45 kg were used for this study. These animals were provided by and housed at the College of Agriculture, Shanghai Jiao-tong University. Procedures for animal handling were approved by the School of Medicine Animal Care & Welfare Committee, Shanghai Jiao-tong University. Animals were randomly separated into four groups of 5 animals each. Animals in group A received spinal surgery without insertion of balloon. Balloons were surgically positioned within the T_{10}–T_{11} spinal canal of animals in the B group, but were not inflated. For group C, the spinal cord was partially compressed by inflating the balloon to about 30% of the anterior/posterior diameter of the vertebral canal. In group D, the balloon was inflated to occupy approximately 90% of the canal, based on lateral view.

2.2. Surgical procedure

Techniques for inducing SCI, by using a balloon, were similar to those of Purdy et al., except in that a percutaneous approach was used by Purdy and his colleagues versus a surgical method that was adopted in the current investigation [6,7]. Briefly, the dorsal spinal region was shaved (Fig. 1A), and anesthesia was induced through IV injection with 1% sodium pentobarbital, 40 mg/kg. Surgery was initiated by exposing the L_1 vertebral lamina with an incision through the skin, soft tissues, and paraspinal muscles. Small sections of the vertebral spinous process and the supraspinal and interspinal ligaments were partially excised to allow for instrument manipulation at the surgical site. A rongeur was used to perforate the ligamenta flava and adjacent vertebral lamina. For animals in groups B–D, a kyphoplasty balloon catheter with a marker visible to X-ray (Shanghai Kinetic Medical Co., LTD, Shanghai, China) was inserted into the epidural space within the vertebral canal (Fig. 1B) and moved rostrally to the central dorsal midline of the T_{10}–T_{11} spinal cord segments (Fig. 1), as determined by X-ray.

For the imaging process, an intramuscular injection of ketamine (100 mg) was administered to reduce animal movement. X-ray (Shimadzu, RADspeed, Kyoto, Japan) images (Fig. 2A, B) were used to determine balloon location, as were sagittal and coronal plane thin-section CT high-speed scans (Somatom emotion 6, Siemens, Erlangen, Germany) (Fig. 2E, F, G). A manual syringe was used to inflate the balloon with a solution of iohexol contrast (Ominipaque, GE Healthcare Inc., Shanghai, China) which served as a dye for imaging balloon size and location (Fig. 2). Injection volumes were read from the syringe, and a manometer inside the balloon reported the internal pressure (Fig. 1C arrow). The balloon was inflated gradually over a period of 2 min, and compression was sustained at constant pressure and volume for 10 min before CT imaging. Transverse CT scan images (Fig. 2C, D) were also used to calculate the magnitude of balloon inflation and the degree of spinal cord compression within the vertebral canal. Specifically, balloon inflation was quantified as the distance between the anterior/posterior edges in a lateral view (Fig. 2E, F, G). The degree of cord compression was defined as the proportion of the anterior–posterior diameter of the vertebral canal occupied by the balloon. The CT imaging process lasted approximately 10 min. Therefore, the total spinal cord compression time was approximately 20 min. Only one balloon inflation was performed in each animal. The balloon was deflated for removal, and multiple-layer sutures were used to close the incision. Intramuscular injections of 80,000 units of gentamicin were applied daily after the surgery up to 5 days to prevent post-operational infection. At the conclusion of the experiment and following extraction of the spinal cord under anesthesia, all the animals were euthanized through IV injection of 1% sodium pentobarbital (100 mg/kg) at the conclusion of the experiment.

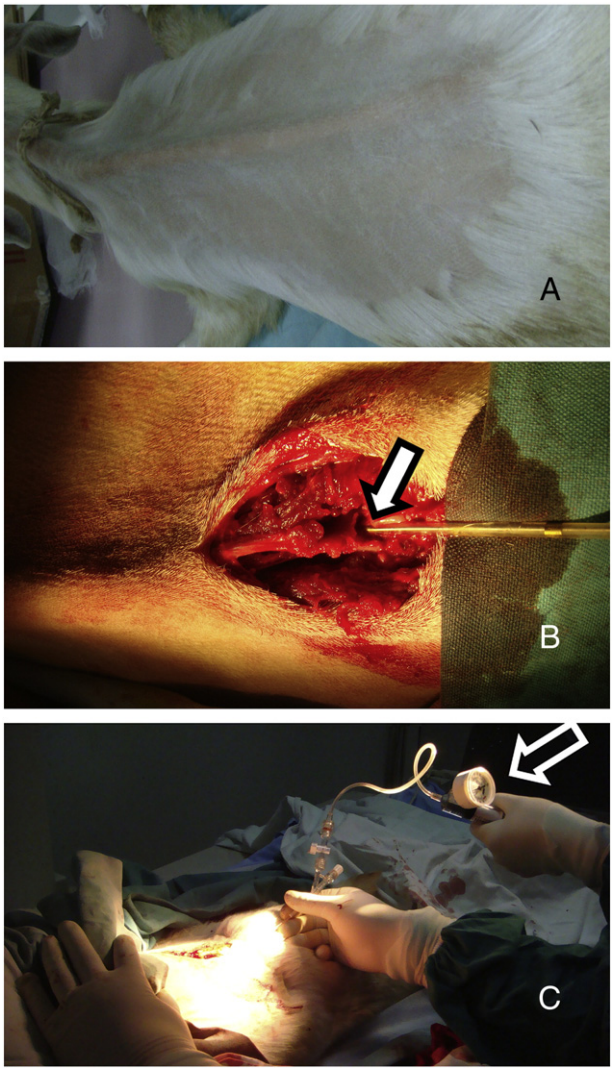

Fig. 1. Surgical procedures. A) The goats' dorsal spinal region was shaved in preparation for surgery, and the spinal processes were clearly visible. B) Following the incision of skin and muscle, an opening was created in the ligamentum flavum at the L_1 vertebral level, as indicated by an arrow. C) A kyphoplasty balloon catheter was inserted and moved rostrally. A manometer inside the balloon measured pressure as observed on an external dial (open arrow).

2.3. Recording of somatosensory evoked potentials

Somatosensory evoked potentials (SSEP) were measured for each animal. SSEP values were recorded 24 h before and 7 days after surgery. Briefly, an electrode pair was used to stimulate the tibial nerve of a hind limb. Evoked electrical impulses conducted through the spinal cord were recorded from the contra-lateral sensory cortex of the brain by a pair of subdermal electrodes inserted above the level of the contralateral cortex. Reference electrodes were placed in the ipsilateral pinna of the ear. Stimulation, recording, and signal averaging of the data were carried out using a Neuropack 4 stimulator/recorder (Nihon Kohden, Tokyo, Japan) and personal computer.

2.4. Behavioral analysis

Animal neurobehavioral assessments were conducted using an improved Tarlov motor function grade test [8]. Hind leg motor function

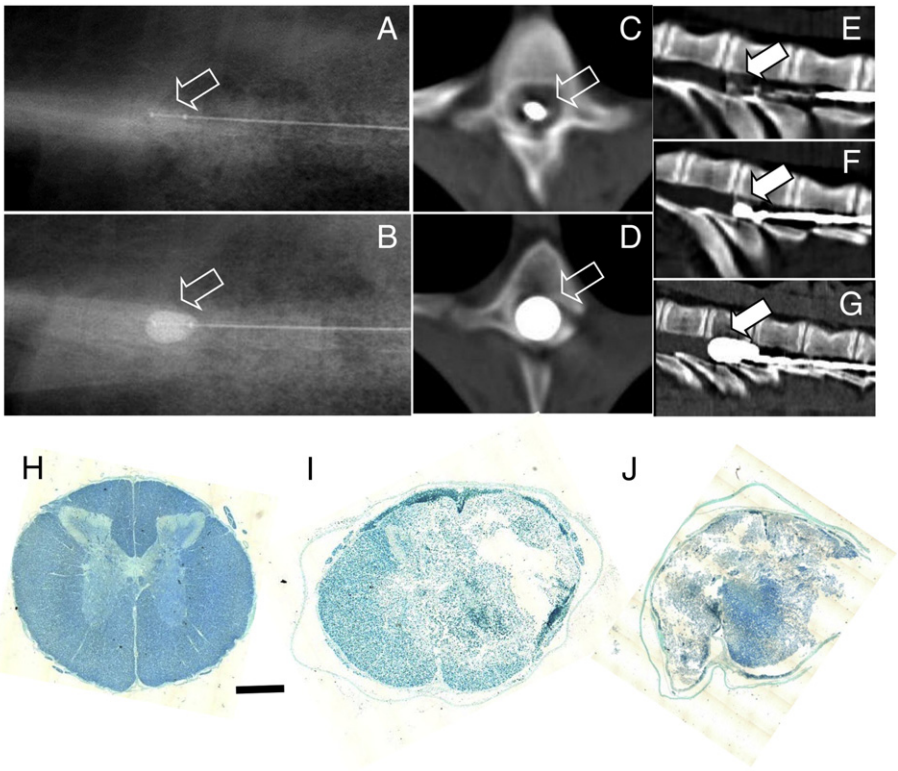

Fig. 2. Balloon imaging and histological analysis of spinal cord. An anterior–posterior X-ray image of marker and balloon catheter (arrows) prior to pressurization (A) and when inflated (B). Transverse CT images reveal the balloon (arrows) size and position inside the vertebral column, when the balloon was partially inflated (C) and fully inflated (D). Reconstructions of CT scans show the lateral view of balloon (arrows) inside the vertebral column when the balloon was not inflated (E, group B), partially (F, group C), and fully inflated (G, group D). Luxol fast blue staining of cross section of the uninjured control (H, group B), moderately injured (I, group C), and severely injured spinal cord (J, group D). Note the graded spinal cord deformation and tissue loss in moderately and severely injured cord. Scale bar = 1 mm (H, I, and J).

was evaluated 24 h before and 7 days after surgery. Behavior was scored by students blinded to the animal treatment groups. The test criteria were the following. 5: Normal gait pattern and ability to jump; 4: Capable of running but unable to jump; 3: Can walk but incapable of running; 2: Stands on hind legs but unable to walk; 1: Able to move hind legs but unable to stand; 0: Paralysis of hind legs.

2.5. Histology of goat spinal cord injury

Animals were deeply anesthetized and then perfused initially with lactated ringers to flush out the blood and then with 10% formalin. The spinal cord was removed and post fixed for 24 h in 10% formalin, and embedded in paraffin. Cross sections at a thickness of 10 μm were cut and stained with luxol fast blue and cresyl violet. Images of sections midway through the lesion were captured. Images at a similar location in control group were also captured for comparison.

2.6. Statistical analysis

All data are given as mean ± standard deviation. Comparisons between groups were conducted using ANOVA followed by Tukey post-hoc test. Significance was ascribed for $p < 0.05$.

3. Results

Results are summarized in Table 1. Animal surgeries for all groups were uneventful. In groups B, C, and D, an expandable balloon system was carefully inserted into the opening at L_1 (Fig. 1B) and slowly moved rostrally to the target (T_{10}–T_{11}) cord segment as guided by X-ray (Fig. 2A & B). In group B, the balloon was inserted and moved to the T_{10}–T_{11} cord segment, but not inflated (Fig. 2A & C). In group C, after insertion and placement at T_{10}, a balloon was partially inflated to occupy 33 ± 2% of that of vertebral canal (Fig. 2C & F) as visualized in a lateral view by an X-ray and CT scan. The average pressure of the inflated balloon for this group was observed to be 220.64 ± 39.31 kPa when injected with 1.26 ± 0.18 mL liquid. In group D, the inserted balloon was inflated to 89 ± 4% of the diameter of the vertebral canal using 2.82 ± 0.20 mL liquid and reaching a pressure of 544.71 ± 28.84 kPa (Fig. 2B, D, & G). It appears that the increased occupancy of the cord by the balloon with elevated pressures produced graded magnitude of spinal cord tissue damage (Fig. 2).

We also estimated the dimensions of the balloon outside of the animal when the balloon was inflated at two pressures. Specifically, the longitudinal diameter was 1.7 cm and the transverse diameter was 0.7 cm when the balloon was inflated to a pressure of 220 kPa. The

Table 1
Summary of experimental results.

Group	Volume (mL)	Spinal occupancy	Pressure (kPa)	SSEP before (μV)	SSEP after (μV)	Normalized SSEP (% pre)	Behavioral score (post)
A	N/A	N/A	N/A	0.528 ± 0.07	0.486 ± 0.05	93.2 ± 14.3%	5
B	N/A	0%	0	0.564 ± 0.06	0.472 ± 0.16	83.3 ± 22.3%	4.6
C	1.26 ± 0.18	33 ± 2%	220.64 + 39.31	0.528 ± 0.12	0.202 ± 0.03	39.8 ± 10.1%	2.6
D	2.82 ± 0.20	89 ± 4%	544.71 ± 28.84	0.6 ± 0.08	0.048 ± 0.03	8.2 ± 5.6%	0.4

longitudinal diameter was 1.7 cm and the transverse diameter was 1.0 cm when the balloon was inflated to a higher pressure of 544 kPa. This indicated that the longitudinal length remained the same while the balloon expanded transversally when pressure increased from 220 to 544 kPa.

Somatosensory evoked potentials (SSEP) were used to estimate the effect of these controlled compressions on the ability of the spinal cord to conduct electrical impulses. Fig. 3A shows the changes in SSEP for one animal before (no injury) and after injury (90% compression). The average SSEP in group A were 0.528 ± 0.07 μV initially, and 0.486 ± 0.05 μV following sham surgery ($n = 5$, $p > 0.05$). In group B, the mean SSEP were 0.564 ± 0.06 μV and 0.472 ± 0.16 μV prior and post balloon placement, respectively ($n = 5$, $p > 0.05$). For group C with moderate compression, the average SSEP were 0.528 ± 0.12 μV (pre-injury) and 0.202 ± 0.03 μV (post-injury) ($n = 5$, $p < 0.001$). Finally, in group D, severe compression reduced the mean SSEP from 0.6 ± 0.08 μV to 0.048 ± 0.03 μV ($n = 5$, $p < 0.001$) (Fig. 3B).

For all animals, behavior prior to surgery was observed to be normal and scored as 5 on the modified Tarlov scale [8]. In group A, behavioral scores were unchanged after surgery ($n = 5$, $p > 0.05$). For group B, the average score following balloon placement was 4.6 ($n = 5$, $p > 0.05$).

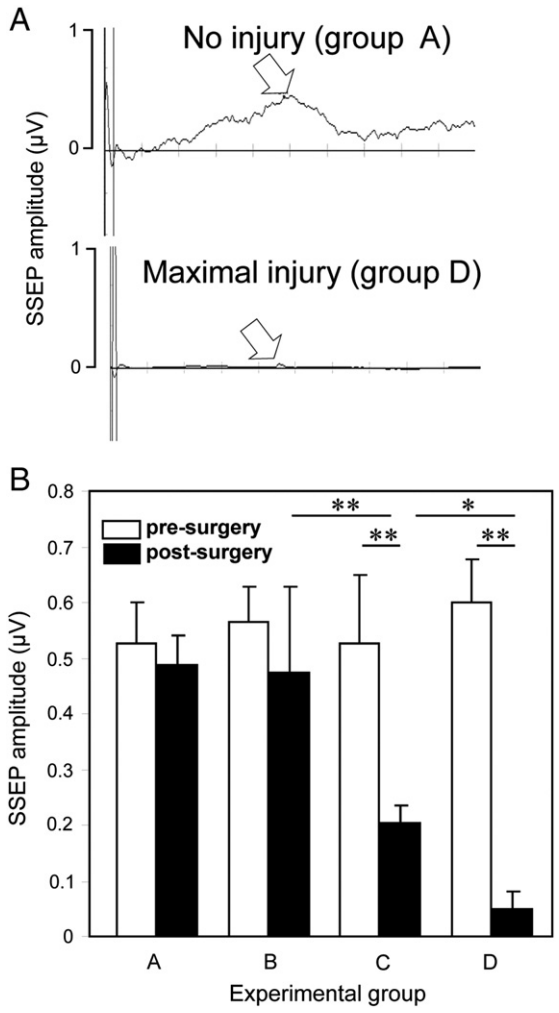

Fig. 3. Electrophysiological conduction. Representative somatosensory evoked potentials (SSEP) for animals in the non-injured and maximal injury groups, with a notable decrease in the peak amplitude after compression (arrows). B) Comparisons of SSEP amplitudes pre- and post-surgery/injury and among various groups reveal significant impairment of conduction following compression injury. In addition, injury also produced significant decreases of amplitudes between groups B and C as well as between C and D. All data are expressed as mean ± SD. **$p < 0.001$; *$p < 0.01$. E vs F: $P < 0.001$; G vs H: $P < 0.001$; D vs F: $p < 0.001$; F vs H: $p < 0.01$, $n = 5$ for all groups.

The mean behavioral score was 2.6 following partial inflation of the balloon in group C ($n = 5$, $p < 0.0001$). For group D, severe compression reduced the mean behavioral score to 0.4 ($n = 5$, $p < 0.0001$) (Fig. 4).

4. Discussion

Appropriate animal models are essential for laboratory biological research. Investigations into spinal neurotrauma generally use rodents exposed to controlled transection, contusion, or compression of the cord. The most studied injury modality is transection, in which the dura and spinal cord are lacerated with a sharp instrument. This allows for precise delineation of the anatomic extent of injury and regeneration. However, human injuries frequently involve acute blows to the spine followed by closed trauma to the cord from vertebral dislocation or fracture [9]. Experimental contusion injuries to the spine produce widespread damage, typically through the impact of a weight dropped a known height [10] or by electromagnetically driven probes resulting in either controlled mechanical displacement [11] or force [12]. These models mimic the acute trauma characteristic of the onset of spinal injury, but are typically of limited duration: clinical trauma frequently results in vertebral displacement or other injury producing sustained mechanical injury to the cord.

Sustained injury of the cord has been accomplished through flat forceps [13] and aneurysm clips [14], calibrated to deliver compression of constant distance or force, respectively. However, all the models described above share a fundamental weakness in that they require an extensive invasive surgery including laminectomy to expose the cord. Such surgical procedures can involve the removal of large portions of the vertebral column and associated ligaments and musculature. While clinical SCI frequently involves compound trauma, laminectomies can cause complications not common in SCI and create conditions that do not favor healing [5].

Tarlov et al. [15] pioneered the use of balloons to produce spinal cord injury, attempting to create a closed injury similar to human clinical pathologies. However, early studies with hydraulic compression experienced difficulty in reliably controlling the size and severity of injury [16]. Vanicky et al. were the first to use angioplasty balloon catheters for spinal compression in rats without extensive tissue trauma [17]. This technique has been used extensively in rats and has been adapted for use in dogs [5–7].

Spinal compression through balloon inflation as used in the current study has several distinct advantages over other injury modalities. Foremost, the current method produces minimal bone and soft tissue trauma compared to conventional surgeries which expose the spinal canal.

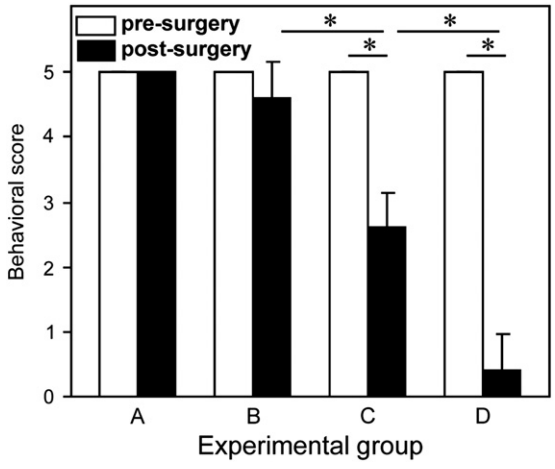

Fig. 4. Behavioral scores. Comparison of behavioral scores 24 h before and 7 days post surgery/injury. All data are expressed as mean ± SD. *$p < 0.001$. E vs F: $p < 0.001$; G vs H: $p < 0.001$; D vs F: $p < 0.001$; F vs H: $p < 0.001$, $n = 5$ for all groups.

Furthermore, what damage it does incur is located several vertebrae distal to the site of compression. The use of modern imaging modalities allows for rapid balloon placement and inflation (Fig. 2). The magnitude and extent of injury can be reliably controlled by varying the volume and pressure used to inflate the balloon (Fig. 5A, B). Furthermore, the tools and techniques used are common throughout veterinary clinics and academic medical centers worldwide. As most cord injuries in humans are closed trauma, the current balloon-induced goat SCI is more clinically relevant than the most established animal models. Notably, however, spinal cord contusion caused by weight drop technique produces a sudden initial physical deformation of the spinal cord that more closely mimics human clinical acute SCI. In this regard, the current balloon-induced spinal cord compression model produces tissue deformation with limited speed, an area that warrants future technical improvement.

Another advantageous feature of the balloon system is that the pressure can be maintained for variable durations. This will allow for a prolonged or even chronic spinal cord compression injury. For example, an investigation on duration of inflation of the balloon can study the effects of timing for decompression surgery on functional recovery. This is a very practical issue surgeons face routinely in the clinic, and one subject to much contention [18]. Although a detailed investigation has been done using small rodents, studies using large animals have not yet been reported [18].

Theoretically, non-human primates are the ideal animal models due to their similarities to humans. However, primate usage is limited by expense and ethical considerations. Small rodents are the most common animal models due to their low costs and ease of housing and handling. Such rodent studies have been invaluable in developing an understanding of SCI physiology and pathology. However, knowledge gained from research in rodents and dogs may not always be applicable in the clinical setting, due to differences in spinal cord size and structure [6]. Although many treatments have been shown to work in small animals, these therapies are not effective in larger animals [2,4]. We propose that research using a large animal, with a size between human and small animals, could produce valuable knowledge to better guide the clinical research in human patients.

For this reason, we chose goats as our laboratory animals. Besides their similarity to humans in overall size, the goat vertebral canal is larger and much closer to human compared to small animals. Specifically, the anterior/posterior distance of the goat thoracic vertebral canal observed in this study is 8.2 ± 0.2 mm and the left/right distance is 9.5 ± 0.6 mm. This is much larger than the spinal canals of small rodents (approximately 2.3 mm by 4.5 mm), and significantly closer to that of the human vertebral column (16.2 mm and 14.7 mm respectively) [19]. Another advantage for neurological research is the shape of the goat vertebral column, which is uniform and regular, simplifying related surgeries and manipulation. Furthermore, goats are tame and easy to handle.

However, there are nevertheless a few noticeable differences between vertebral columns of humans and goats. In human there are five lumbar vertebrates and the conus medullaris usually ends at L1. However, goat and sheep usually have 6–7 lumbar vertebrae and the conus medullaris usually ends at the point between the lumbar and sacral vertebrae [20,21]. We chose to enter the vertebral column at L1 because it is located in the middle of the abdominal region, which offers an easy location for the surgery. Operation below this level will make the surgery location closer to perineum region which increases the risk of surgery-related infection. Despite the fact that the spinal cord extends caudal beyond L1, the procedure of gaining access to vertebrate through L1 likely causes minimal damage to the spinal cord which is evident by the lack of damage in control group (group B).

Although a similar balloon system has been used to produce spinal cord injury in small animals and dogs, this is the first time such method has been used in animals as large as goats. Here are a few differences between the study by Purdy et al. in dogs and ours using goats. In the study carried out by Purdy et al. [6,7], a balloon study was carried out in dog and only the diameter of the balloon was varied while the inflation

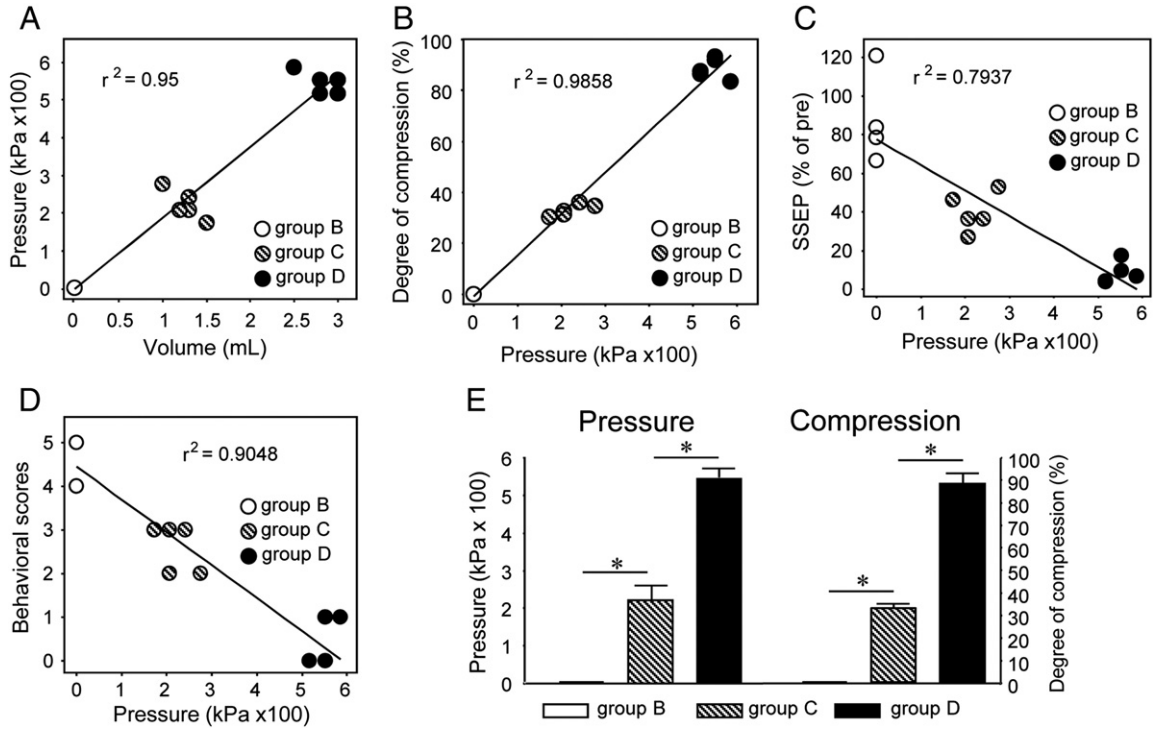

Fig. 5. Correlations of various injury parameters. A) The volume of liquid injected into the balloon was clearly related to the produced pressure. Changes in pressure were proportional to the degree of spinal cord compression (B) and the resulting loss of SSEP conduction ability (C) and motor behavior (D). E) Bar graph comparing the pressure and compression at three injury levels. *$p < 0.001$, $n = 5$ for all groups.

pressure remained the same. It was concluded that the increased diameter of the balloon can produce graded cord damage while pressure remained the same. In the current study, the increased pressure and consequent expansion of the balloon transversely produced various levels of spinal cord damage. Therefore, the variables in the current study are both pressure and size of the balloon transversely.

Due to the increased diameter of the vertebral canal in goats compared to rodents, we feel that balloon insertion should be much less likely to cause trauma. This may contribute in part to the low variability in compression (Fig. 5E) and functional loss (Figs. 3, 4). The fact that graded increases in balloon volume produced closely correlated changes in balloon pressure ($r^2 = 0.95$, Fig. 5A) and degree of spinal compression ($r^2 = 0.9858$, Fig. 5B) demonstrated the practicality and reliability of using such a system in causing reproducible, graded SCI in large animals (Fig. 5E).

Using a combination of imaging, electrophysiology, and behavioral analysis, we have found that the injury severity based on balloon inflation is closely related to functional loss, behavioral deficits, and morphological abnormalities. For example, three distinct injury levels, sham (group B), moderate compression (group C), and severe compression (group D) produced graded reductions in function (SSEP) (Fig. 3), motor behavior (Fig. 4), and structural integrities (Fig. 2). Furthermore, the significant correlation between the dose (inflation pressure) and response (functional and behavior deficits) strongly indicates that the functional loss seen in this model is the result of physical trauma of the cord (Fig. 5C, D). This supports the established theory that the functional loss seen in spinal cord injury is indeed a function of physical compression of the spinal cord [5]. Furthermore, the close correlation ($r^2 = 0.9884$) between the deficits in spinal cord conduction as estimated by SSEP and the motor deficits assessed by the Tarlov test (Fig. 6) further verified the value of SSEP in predicting behavioral loss.

Through this study, we also showed that X-ray and CT imaging are reliable methods of monitoring balloon volume during spinal surgery. CT scans provided rapid and high quality images of the spinal canal during surgery (Fig. 2C, D). This would be impractical with magnetic resonance imaging due to the nature of the scanning technology and increased time necessary. Other studies using MRI to quantify hydraulic spinal compression required moving animals during surgery, which could induce additional trauma to the cord [6]. The CT imaging technique used here has several other advantages over the MRI imaging systems used in modeling SCI, notably the lower cost of CT imaging and the greater availability of CT scanners. As injection volume was highly correlated with pressure and compression (Fig. 5A, B), extensive CT imaging may be unnecessary for administering controlled spinal trauma.

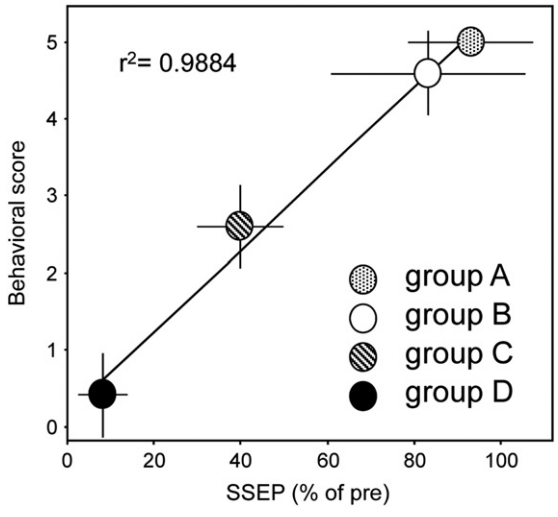

Fig. 6. Mean behavioral scores strongly correlated with changes in the magnitude of somatosensory evoked potentials.

To the best of our knowledge, no one has used controlled hydraulic techniques to study compressive SCI in species larger than dogs. In this model, the magnitude of pressure within the balloon correlated with the degree of spinal compression, which was directly related to the resulting functional and behavioral deficits. From these studies, it is evident that this method of inducing acute spinal cord injury in large animals is feasible and could potentially be used in various types of spinal trauma research. Although the injuries sustained by balloon inflation were assessed in the acute stage of this pilot study, it is likely that long term deficits will also result from this trauma which could be investigated in the follow-up study. It is envisioned that future investigation will look into the detailed time course of injury development at acute and even sub-acute stages of weeks to months post-trauma. Taken together, the advantages of animal size, minimally invasive surgery, and variable degree of compression make this a model that could potentially be used as a segue between basic or small animal research and human clinical studies.

Conflict of interest statement

The authors have no conflict of interest to declare.

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