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Clip Compression Model Is Useful for Thoracic Spinal Cord Injuries

Histologic and Functional Correlates

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Study Design. Experimental investigation of an acute thoracic spinal cord injury model in rats involving acute clip compression that simulates human injury.

Objective. To assess the dose-response of this model for the relationship between the force of injury on the rat thoracic spinal cord and histological and functional outcome measures.

Summary of Background Data. Acute extradural clip compression injury has been a reliable model for producing acute experimental cervical spinal cord injury; however, this model has not been formally evaluated with dose-response curves for acute injury of the thoracic spinal cord.

Methods. After laminectomy at T2 in Sprague-Dawley rats, a modified aneurysm clip exerting a closing force of 20, 26, or 35 g was applied extradurally around the spinal cord at T2, and then rapidly released with cord compression persisting for 1 minute. These forces were selected to simulate acute compression injuries of mild to moderate, moderate, and moderate to severe degrees, respectively (n = 8/group). Motor activity was assessed weekly for 4 weeks with the Basso, Beattie, and Bresnahan (BBB) open field locomotor test. The injured spinal cord was then examined histologically including quantification of cavitation.

Results. A significant main effect was observed for clip force and BBB score ($F(2,20) = 5.42$, $P = 0.013$). For 4 weeks after injury, the BBB scores for the 20 g and 35 g clip injury groups were significantly different ($P < 0.05$). The cavitation volume at 4 weeks was directly proportional to the severity of injury: the 20 g group had significantly smaller cavities than the 35 g group ($P < 0.05$), and the cavitation volume correlated with the BBB scores.

Conclusion. The rat thoracic cord clip compression model is a reproducible, clinically relevant spinal cord injury model. This is the first time that the force of clip compression injury in the rat thoracic cord has been correlated with both functional and histologic outcome measures.

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The common mechanisms of injury in human spinal cord injury (SCI) are compression, contusion, laceration, transection, and traction of the spinal cord,[1] and no single animal model can simulate all these diverse mechanisms. There have been several reviews of animal models in SCI[2–4]; fortunately, there are several reliable and consistent animal models, and some replicate human injuries reasonably well.[4,5] The combination of acute impact followed by persisting compression is the most common mechanism of SCI in humans[1]; therefore, our laboratory has concentrated on the acute clip compression model in rats, one of the first to simulate this impact-compression injury.[6–8] Most of our studies have involved compression of the lower cervical cord at C7–T1. Other compression-impact models in common use include the New York University weight-drop impactor,[9] the Ohio State University electromagnetic spinal cord injury device,[10] and the Infinite Horizons impactor,[11,12] each of which has advantages and limitations. For example, the Infinite Horizons device is expensive, impacts the spinal cord from the dorsal surface only, has limited dwell times, and requires both stabilization by forceps and horizontal positioning of the spinal column at the time of SCI. Non-impact models include photochemical injury, which involves intravenous administration of the photosensitive rose bengal dye followed by irradiation[13–15] to create graded tissue infarction as a result of ischemia, one of the common secondary mechanisms of injury.[1,16,17] This model is less invasive because irradiation can reach the spinal cord without laminectomy. Laceration and transection are less frequent in human SCI; therefore, impact-compression models are more relevant to human traumatic SCI.

Some compression models involve "placement" of a static weight on the cord and do not involve impact.[18] Impact-compression models use a variety of strategies and devices, such as a predetermined weight and height from which the weight is dropped on to the cord, or a predetermined amount of spinal cord displacement to induce injury to the spinal cord. von Euler *et al* used bulldog clips of varying forces and placed them on the cord vertically.[19] The Infinite Horizons device can deliver varying forces on the cord in rats[12] and mice,[20] although displacement can also be measured.

In general, the impact-compression models are quite reproducible with less interoperator variance than the traditional weight-drop model of Allen.[21] However, the spinal cord in most of the impact-compression models is only briefly compressed (for example, dwell time in the Infinite Horizons model is a maximum of 60 seconds), which does not reproduce the effect of the persisting compression of the cord that is present in the majority of human injuries including dislocations, fracture-dislocations, and burst fractures.[1,17,22,23] In contrast, the extradural clip compression injury model replicates the combination of acute impact and persisting compression, characteristic of most SCI in humans. This model was introduced in 1978[6] and was one of the first non-transection models in the rodent.[5] When the clip closes rapidly, cord contusion is produced by a compression force applied to both the dorsal and ventral aspects of the spinal cord. The force can be varied based on the strength of closure of the blades of the clip, which can be varied depending on the physical characteristics of the spring attached to the clip. Although clip compression has been one of the most frequently used models in experimental SCI, there has not been a study correlating the severity of thoracic cord clip compression in the rat with locomotor function and quantitative histologic changes in the injured spinal cord. In the present paper, we investigated 3 different forces of clip compression injury at T2 in the rat with clips of closing force of 20, 26, or 35 g. We found that histologic changes in the spinal cord and the functional scores in the first 4 weeks after thoracic SCI correlated with the severity of injury.

■ Methods

Spinal Cord Injury. The protocol for this experiment was approved by the Toronto Western Research Institute Animal Care Committees in accordance with the policies established by the Canadian Council on Animal Care. Twenty-four adult female Sprague-Dawley rats (Charles River, Quebec, Canada) weighing 250 to 300 g were anesthetized with 2% halothane and 2:1 mixture of nitrous oxide and oxygen. A 3-mL injection of saline was given subcutaneously before surgery, the animals were placed on a heating pad at 36°C during surgery, and then a laminectomy was performed at T2 to expose the spinal cord. A dissecting hook, with similar curvature and thickness as the clip (Figure 1A), was used to dissect the extradural plane between the dura and the adjacent vertebrae. The clips and applicators are manufactured to specification (Walsh Manufacturing, Oakville, ON., Canada). With the clip held in the applicator in its opened position, the lower blade of the clip was passed extradurally anterior to the cord with avoidance of damage to the adjacent nerve roots. The clip was then rapidly released from the applicator to produce acute impact-compression injury (Figure 1B). The clip was left compressing the spinal cord for 1 minute before removal with the applicator. Three groups of rats were injured in this study with clips of 20, 26, or 35 g closing forces, respectively (n = 8/group). Before use the force of the clips was measured as described previously.[24] After injury, the muscles were sutured using 3–0 vicryl suture (Ethicon, Somerville, NJ) and the skin was closed with Michel clips (Fine Science Tool, BC, Canada). Buprenorphine (0.03 mg/kg, Temgesic, Schering-Plough, UK) was given subcutaneously before the animals awakened, and then every 12 hours for 48 hours.

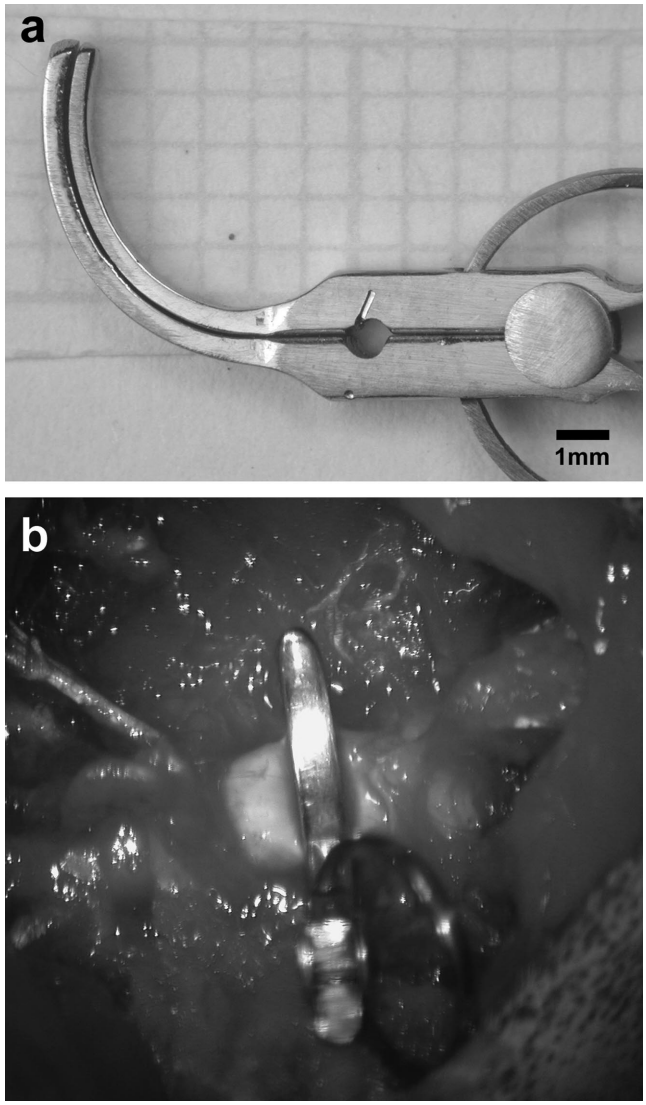

Figure 1. **a**, A modified aneurysm clip is used to create impact-compression injury of the spinal cord. Scale bar = 1 mm. **b**, An intraoperative picture showing a clip compressing the spinal cord at T2 to create the injury.

The rats were housed singly in a temperature-controlled room at 26°C for 28 days with a 12-hour light/dark cycle. Bladders were expressed 3 times daily until spontaneous voiding occurred, and any hematuria or urinary tract infection was treated with ampicillin (100 mg/kg, s.c., Novopharm, Toronto, Canada) twice daily for 5 days. Water was removed during the dark cycle, and food was provided *ad libitum*.

Locomotor Function. Hind limb motor function was assessed weekly for 4 weeks using the open field locomotor test developed by Basso, Beattie, and Bresnahan (BBB).[25] The score of each hind limb was recorded and the averages are presented.

Histology. All animals were sacrificed 28 days after SCI. They were deeply anesthetized by intraperitoneal injection of sodium pentobarbital (Somnotol) and were perfused transcardially with 500 mL of 10% neutral buffered formalin (EMD Chemi-

cals Inc., Gibbstown, NJ) after intraventricular injection of 1 mL heparin (1000 IU/mL, LEO Pharma Inc.). A 1.5-cm segment of the spinal cord centered around the injury site was harvested and postfixed in neutral buffered formalin. All tissues were processed through alcohol and chloroform, and then embedded in paraffin blocks. Three spinal cords from each of the 3 injury groups were randomly selected, and 8-μm serial cross sections were made. The sections were stained with Luxol fast blue (LFB) and counterstained with hematoxylin and eosin at every 40 μm to encompass the entire injury site.

Image Analysis. Image analysis was performed with a Nikon TE300 inverted bright field microscope, and images of LFB/H&E stained sections were captured with an Optronic CCD camera connected to the microscope using a 2× objective lens. The area of cavitation of each section was traced using Adobe Photoshop. Any necrotic tissue within the cavities was counted as part of the lesion. The cavity area ($Area^{cav}$) and the total tissue area ($Area^{total}$) were measured using the BQ Nova Prime 6.50.10 (Bioquant Image Analysis Corp., Nashville, TN) image analysis software package. The spared tissue area was calculated as $Area^{total}$ minus $Area^{cav}$. The total cavity volume (Vol^{cav}) and total tissue volume (Vol^{total}) were calculated using the Cavalieri method.[26] Briefly, this method is a summation of the measured area of each section multiplied by the intersection distance. Then, the percentage cavitation ($\%Vol^{Cav}$) was determined according to the following equation[27]:

$$\%Vol^{Cav} = Vol^{cav}/Vol^{total} \times 100\%. \quad (1)$$

The cavity length ($Length^{Cav}$) was calculated according to equation (2):

$$Length^{Cav} = n \times d \quad (2)$$

where n is the number of sections with a cavity and (d) is the intersection distance.

Statistical Analysis. The BBB locomotor scores for the hind limbs of each rat were averaged to obtain 1 score for each weekly test session. The scores of all animals in the same experimental group in the same week were averaged, and statistical analysis of these scores was performed using 2-way repeated measures analysis of variance (ANOVA) and a pairwise multiple *post hoc* comparison using the Bonferroni *t* test.[28] One-way ANOVAs were used to compare cavity volume, percentage cavitation, cavity length, spared tissue, and total tissue area at the epicenter between experimental groups. Tukey *post hoc* analysis was used. Pearson product moment correlation was used to test correlation. An alpha level of significance at 0.05 was used in all statistical analyses.

■ Results

Locomotor Function

The average BBB score of both hind limbs of each rat was recorded weekly for 4 weeks as shown in Figure 2. There was spontaneous functional improvement with time for all 3 injury severities, with the greatest improvement after the 20 g clip compression and the least improvement after the 35 g injury. The BBB curves appeared to be approaching a plateau at 4 weeks. This spontaneous improvement and tendency to plateau at about 4 weeks has been reported in other injury models.[12,19,25,29] A significant main effect was observed for each clip by BBB score ($F(2,20) = 5.42$, $P = 0.013$), demonstrating a statistical difference between the 20, 26, and 35 g clip injuries and a correlation between severity of injury and locomotor function. Among the 3 groups, the time-averaged 20 g clip injury BBB scores were significantly different from those of the 35 g group ($P < 0.05$). At 1 and 2 weeks, the 20 g clip injury BBB scores were significantly different from those of the 35 g group ($P < 0.05$). Although the 20 g injury group showed consistently better behavior than the 26 g group, the differences were not significant.

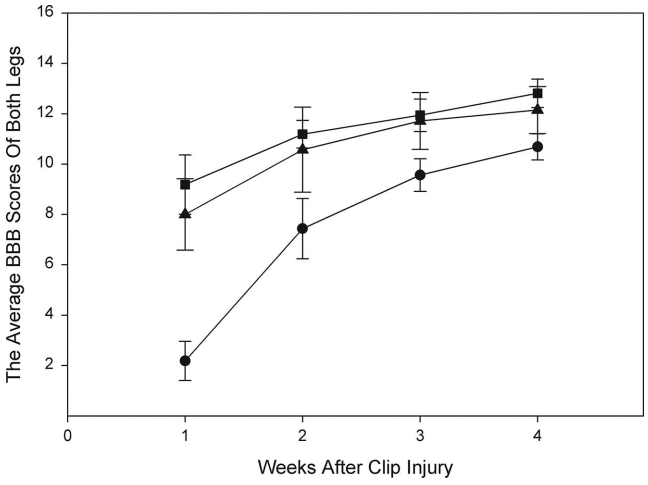

Figure 2. BBB scores, after different forces of compression injury of the thoracic spinal cord, recorded weekly for 4 weeks after clip compression of: (■) 20 g, (▲) 26 g, or (●) 35 g. (n = 8/group, average ± SEM are shown). There was a progressive decline in locomotor function with increasing force of injury.

Histologic Assessment

Figure 3 shows representative sections at the epicenter of the 3 experimental groups. There was progressive loss of tissue and increased cavitation with increasing clip force. The loss was most marked centrally and was well demarcated from the surrounding persisting rim of tissue in all 3 groups. The persisting tissue was mainly white matter with some preserved myelin and was infiltrated with macrophages. The 20 g group (Figure 3A) had the thickest rim of spared white matter, followed by the 26 g group (Figure 3B), and the 35 g group (Figure 3C) had only a thin rim of spared white matter.

Cavitation Analysis

As shown in Table 1, one-way ANOVA showed significant differences between the 20 g and 35 g clip injuries ($P < 0.05$) in cavity volume and percent spared tissue area at the epicenter. The force of the impact-compression correlated significantly with the cavity volume ($r = 0.729$, $P < 0.05$), the percent spared tissue area at the injury epicenter ($r = -0.814$, $P < 0.01$) and the percent cavitation ($r = 0.758$, $P < 0.05$). The cavity volume and percent cavitation increased with clip force, and the percent area of spared tissue at the injury epicenter decreased with clip force. While the length of the cavity increased with clip force, the differences observed

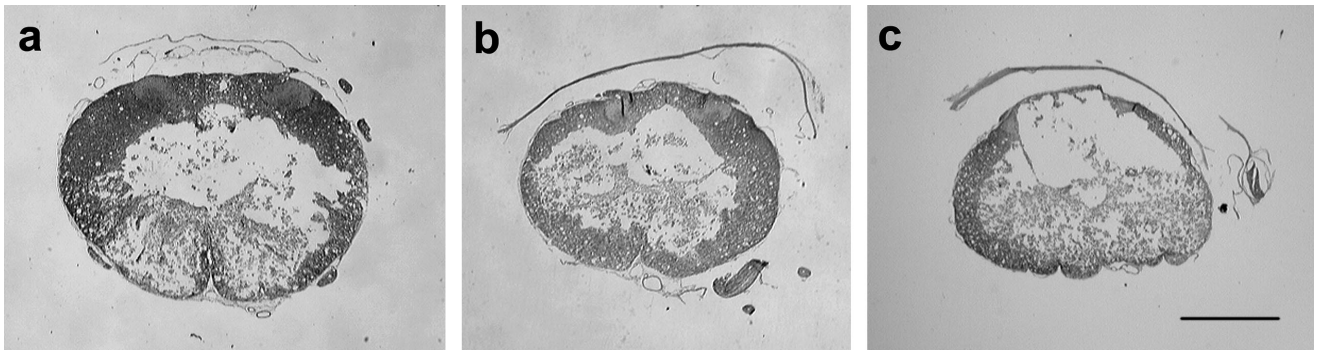

Figure 3. Representative spinal cord sections stained with LFB/hematoxylin and eosin showing the epicenter of the cavities after 3 different forces of compression injury: **a**, 20 g; **b**, 26 g; **c**, 35 g. Scale bar = 1 mm. There was a progressive enlargement of the cavitation with increasing force of injury.

were not significantly different from each other. Interestingly, a significant difference was observed in the total tissue area at the injury epicenter between the 35 g group, which was significantly smaller, than both 20 g and 26 g groups. Moreover, locomotor function correlated with cavity volume: BBB scores at 4 weeks postinjury correlated with cavity volume ($r = -0.728$, $P < 0.05$), demonstrating increasing behavioral deficit as cavity volume increased (Figure 4).

■ Discussion

Our group has used the clip impact-compression injury model to injure the spinal cord at the cervical,[30–32] thoracic,[33] and lumbar[34] levels for the past 25 years, and this model has given reliable and consistent results for studying acute and chronic SCI in rats. This SCI model has also been used by many other investigators.[27,35–38] The clips have been used for examining a variety of injury mechanisms, neuroprotective and regenerative measures including inflammatory cytokines,[39] axonal physiology and morphology,[40] localized drug delivery,[41,42] secondary injury antagonists,[43] and cell transplantation.[38,44,45] The clip impact-compression model has also been useful for experimental SCI in the mouse.[46,47] The clip blades exert force on the spinal cord bidirectionally and simultaneously from the ventral and dorsal surfaces, which simulates the common mechanisms in human SCI such as fracture-dislocation and burst-compression fractures. The acute extradural clip compression model has several major advantages including consistency and reliability, ease of use, ability to model injuries of low to high severity and at all levels of the spinal column, low cost, and most important, simulation of the commonest type of acute spinal cord injury in humans.[1] However, none of the previous studies with the Kerr-Lougheed modified aneurysm clip has correlated the severity of thoracic cord SCI in rats with locomotor function and quantitative histology. Our previous studies of cervical cord SCI showed excellent correlation between clip force and clinical function assessed by the inclined plane technique.[48,49] The present study describes for the first time both functional and histologic outcomes following thoracic SCI induced by the clip impact-compression model in the rat. The results will be useful for planning future studies. The range of clip forces applied 20 g to 35 g was chosen to represent the range of injury severities associated with incomplete injuries in humans graded by the system of the American Spinal Injury Association (ASIA) as ASIA Grades B to D.[50] More severe injuries such as a 50 g injury at T4 in the rat produces the clinical and histologic features of a complete SCI,[51] graded as ASIA A in the human.

In the initial phase of the development of this model of experimental SCI, we found that a 1-minute duration of clip compression was the time required to produce a consistent pathologic and clinical effect in rats with clips of a range of forces varying from very minimal force (*e.g.*, 2.3 g) to maximal forces (up to 178 g). With clips of this range of forces, we varied the duration of compression from 3 seconds to as long as 4 hours, and found a correlation between force and time of compression and outcome measures including histopathologic effects and clinical recovery after clip injuries in rats at C7–T1. The results of most of these studies were published in 2 papers.[48,49] In these previous studies, we found greater

Table 1. Cavitation Analysis 4 Weeks After Injury at 3 Different Forces of Acute Clip Impact-Compression Injury

Clip Force (g)	Cavity Volume (mm^3)	% Cavitation	Cavity Length (μm)	% Spared Tissue Area at the Epicenter	Total Tissue Area at the Epicenter (mm^2)
20	1.50 ± 0.22*	19	1613 ± 218	59.32 ± 4.85*	5.54 ± 0.26*
26	2.85 ± 0.57	36	1920 ± 174	39.18 ± 8.07	5.13 ± 0.35*
35	3.20 ± 0.24	42	2067 ± 218	28.18 ± 2.95	3.57 ± 0.18

Values are the mean ± SEM; n = 3.
*Significant difference *versus* 35-g group ($P < 0.05$).

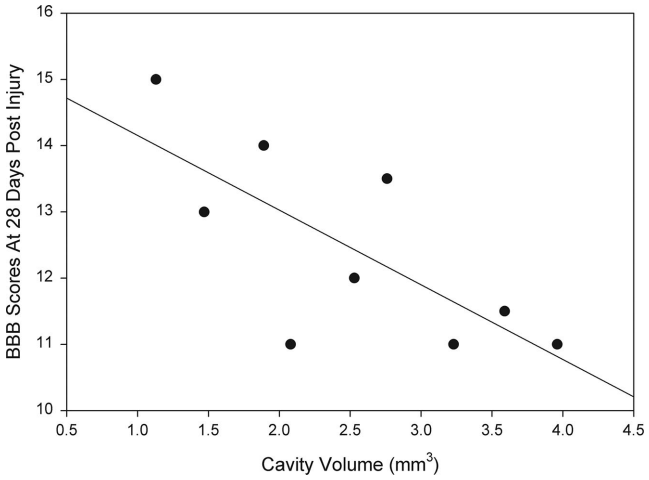

Figure 4. Regression analysis illustrates that BBB locomotor scores at 28 days after injury correlated significantly with cavity volume in the 9 animals (3 randomly selected from each of the 20, 26, and 35 g groups) ($r = 0.728$; $P = 0.026$).

consistency of results when the duration was at least 1 minute. None of these studies involved rats with thoracic cord injuries, and therefore, the present study was undertaken to determine whether the same dose-response relationships between force of compression and histopathologic effects and clinical recovery were present at T2. We wanted to eliminate the clinical deficits in the upper limbs that were present with the C7–T1 injuries. Thus, the purpose of the present study was to examine whether the results would be similar for thoracic injuries. In the former studies at C7–T1, the standard deviations for measures of clinical recovery such as the inclined plane, were greater after durations of compression of less than 1 minute, whereas after longer durations of compression, there was much less clinical recovery. Thus, in the present study, we chose the 1-minute duration of compression.

The clip impact-compression model differs from other compression models used in many other SCI studies because after the initial acute impact of the spinal cord due to rapid closure of the clip blades, there is a period of continuing compression when the clip remains in its closed position for a predetermined length of time exerting continuous compression. This temporal effect of compression injury is not achieved in most other compression models, such as the Infinite Horizons model, which has a limited dwell time. Previously, we examined these temporal effects after cervical cord SCI in the rat.[48,49] The ability to study varying compression times is an advantage of the clip technique as it can be used to examine the duration of cord compression and the value of early decompression which are important issues in human SCI.[52] We are not aware of any comparative studies of the histology and functional outcomes among the various models of experimental SCI, and it would be useful to have some comparative data, especially with respect to how closely these other models simulate human SCI. As noted previously, clip compression SCI in the rat produces a very similar histopathologic appearance to human SCI due to acute compression.

When the clip closes around the spinal cord, an acute injury is sustained. This mechanical injury results from tissue displacement during contusion. As was shown in the BBB scores (Figure 2), the clip compression injury model is reproducible, with increased clip forces correlating with lower BBB scores. Variability of acute spinal cord displacement was greatest in the lower range of closing forces (*i.e.*, 20 g and 26 g) because of tissue dynamics,[12] which translated into greater variability observed in BBB scores. Similar observations have been reported in other contusion models.[12,25,29] To reduce variability, clips with low closing forces should be calibrated more frequently because the springs are more susceptible to weakening by the repetitive opening and closing of the blades during experiments.

The reproducibility of the clip compression model was also assessed in terms of histologic outcome (Figure 3) where changes in cavity volume increased as the clip closing force increased. Cavity volume is commonly used in SCI research as a morphologic outcome measure and a tool for assessing severity of injury because it correlates positively with locomotor function.[12,53–55] In accordance with other injury models, there was a significant correlation between cavity volume and locomotor function in the present study of thoracic SCI (Figure 4). Cavity volume increased and spared tissue area at the epicenter decreased as the injury severity increased. Furthermore, the total tissue area at the epicenter decreased as the severity of injury increased (Table 1).

von Euler *et al*[19] performed a similar study at T8 in rats with bulldog type clips of varying severity compressing the cord for 30 seconds and found similar results even though the clips were applied so that the blades closed in the vertical plane whereas our blades closed in the anteroposterior plane. They also confirmed that the plateau in functional recovery occurred at about 3 weeks after SCI.

It is of interest to consider the relative response of the cervical and thoracic spinal cord to clip compression injury. In our previous work, we used the inclined plane as the clinical functional outcome measure,[48,49] whereas in the present study, we used the BBB open field locomotor scoring method. Thus, it is not possible to make a direct quantitative comparison between the absolute values of these 2 functional outcome measures. However, it is possible to compare the responses on the basis of the percent of full recovery with clips of similar force in the present T2 injuries *versus* the former C7–T1 injuries. For example, the 16 g clip injury of 1 minute duration in the previous study at C7–T1 (the closest clip force in that study for comparison with the present study) produced a 70° result out of a normal 80° (87.5% recovery) based on the inclined plane score at 4 weeks, whereas the 20 g clip for 1 minute at T2 in the present study at 4 weeks produced a score of 12 out of a normal 21 point BBB score (57.1% recovery). Thus, we would predict that

thoracic cord injuries have less recovery potential, which parallels the situation in humans.[22]

In the present study, we showed the association between the closing force of the clip, cavity volume, and BBB score after thoracic cord injury. It is noteworthy that many Phase 1 clinical trials in humans have been performed on thoracic cord injuries; thus, it is useful to prove that the clip compression model can be used to simulate these injuries. The major benefit of the clip compression model is its ability to include sustained compression of the spinal cord, which is clinically relevant, and is not reproduced in contusion models, such as the weight-drop model. Moreover, the clip compression model is easily adaptable for use at the cervical level, which is not true for several of the contusion models where the adjacent and overlying spinal musculature can interfere with lesion making.[56] Since 55% of cases of human SCI occur at the cervical level,[57] the clip compression model serves as an excellent and reproducible model for the development of clinically useful treatments. Other favorable features of the clip compression model are its low expense, consistent behavioral functional and histologic results, ability to vary the force and duration of compression, and exertion of bidirectional force on the spinal cord, simulating the common clinical syndromes in human SCI. We would predict that the clip compression model would also be useful for lumbar injuries which in humans involve essentially the same forces as thoracic injuries, although lumbar injuries have not been studied to date with this technique.

■ Key Points

- The acute extradural spinal cord clip compression model is an inexpensive and consistent model for studying thoracic spinal cord injury.
- There is a dose-response relationship between severity of acute clip compression injury of the thoracic spinal cord and locomotor function.
- There is a dose-response relationship between severity of acute clip compression injury of the thoracic cord and histologic change in the spinal cord.

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