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Modeling spinal cord contusion, dislocation, and distraction: Characterization of vertebral clamps, injury severities, and node of Ranvier deformations

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ABSTRACT

Spinal cord contusion and transection models are widely used for studying spinal cord injury (SCI). Clinically, however, other biomechanical injury mechanisms such as vertebral dislocation and distraction frequently occur, but these injuries are difficult to produce in animals. We mechanically characterize a vertebral clamping strategy that enables the modeling of vertebral dislocation and distraction injuries – in addition to the standard contusion paradigm – in the rat cervical spine. These vertebral clamps have a stiffness of 83.6 ± 18.9 N/mm and clamping strength 64.7 ± 10.2 N which allows injuries to be modeled at high-speed (~100 cm/s). Logistic regression indicated that a moderate-to-severe injury, with an acute mortality rate of 10%, occurs at 2.6 mm of C4/5 dorso-ventral dislocation and 4.1 mm of rostro-caudal distraction between C4 and C5. Injuries produced by dislocation and distraction exhibited features of axonal damage that were absent in contusion injuries. We conducted morphometric analysis at the nodes of Ranvier using immunohistochemistry for potassium channels (Kv1.2) in the juxtaparanodal region. Following distraction injuries, elongated nodes of Ranvier were observed up to 4 mm rostral to the lesion. In contrast, contusion injuries produced distortions in nodal geometry which were restricted to the vicinity of the lesion. The greatest deformations in node of Ranvier geometry occurred at the dislocation epicenter. Given the importance of white matter damage in SCI pathology, the distinctiveness of these injury patterns demonstrate that the dislocation and distraction injury models complement existing contusion models. Together, these three animal models span a broader clinical spectrum for more reliably gauging the potential human efficacy of therapeutic strategies.

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1. Introduction

Transections and contusions of the rodent spinal cord remain the most widely used methods for experimentally modeling spinal cord injury (SCI) (Kwon et al., 2002; Young, 2002). While transection provides an idealized setting for unambiguously examining regeneration across a complete lesion, contusions mimic the more clinically relevant milieu typically characterized by hemorrhagic necrosis, ischemia, and inflammation, evolving into a chronic lesion with central cavitation encapsulated by a glial scar and spared peripheral white matter (Bresnahan et al., 1991). Allen reported the first contusion model nearly a century ago where a mass was dropped from a prescribed height onto the dorsal surface of the canine dura (Allen, 1914, 1911). This weight-drop method, characterized by the product of the mass and drop-height, has since evolved and gained widespread use (Gruner, 1992; Noble and Wrathall, 1985; Young, 2002). Alternate methods have appeared

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including injuries parameterized by the contusion displacement (Bresnahan et al., 1987; Jakeman et al., 2000; Noyes, 1987a,b; Somerson and Stokes, 1987; Stokes et al., 1992) and the impact force (Scheff et al., 2003). In addition, compression models have also arisen to simulate the persistent spinal canal occlusion that is common in human injuries (Joshi and Fehlings, 2002; Rivlin and Tator, 1978).

The ongoing development of SCI animal models reflects the persistent need to better mimic the human injury in order to reliably gauge the potential human efficacy of therapeutic strategies. The majority of these animal models, however, produce injury in a similar fashion—by compressing the spinal cord in a dorso-ventral direction. Spinal cord compression injuries certainly occur in humans (Sekhon and Fehlings, 2001), but trauma can also occur when the spinal cord is stretched (Breig, 1970; Silberstein and McLean, 1994), or most frequently, when the spinal cord is sheared at the dislocation between two vertebrae (Sekhon and Fehlings, 2001). This disparity between current injury paradigms and human injuries may partially account for the poor translation of pharmacotherapies which showed positive effects in animal models but were unsuccessful or controversial in treating human SCIs (Hawryluk et al., 2008).

We have recently developed a new injury apparatus that is capable of modeling different biomechanical mechanisms of SCI in addition to the contusion and compression injuries which have become the standard in the field (Bresnahan et al., 1987; Gruner, 1992; Jakeman et al., 2000; Joshi and Fehlings, 2002; Rivlin and Tator, 1978; Scheff et al., 2003; Stokes et al., 1992). In this communication, we describe the methodology in greater detail for modeling three mechanisms of SCI and show novel aspects of white matter damage. In particular, we illustrate the geometry and characterize the mechanical performance of our vertebral clamping strategy, we assess the acute mortality rate in the dislocation and distraction models, and we contrast the acute deformation of the nodes of Ranvier caused by contusion, dislocation, and distraction injury mechanisms.

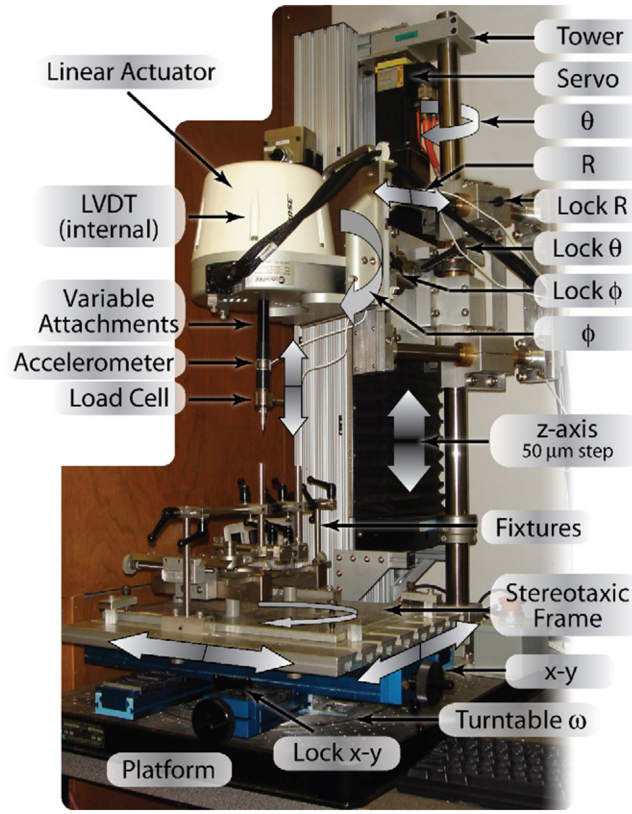

Fig. 1. Multi-mechanism injury system. Seven degrees of freedom enabled positioning of linear actuator and animal at any orientation relative each other. LVDT = linear variable differential transformer for measuring displacement.

2. Materials and methods

2.1. Multi-mechanism injury system

Our SCI device (Fig. 1) was developed around an electromagnetic linear actuator (TestBench ELF LM-1, Bose, Eden Prairie, MN). The apparatus had seven degrees of freedom for positioning the actuator and animal at any orientation relative to each other. The actuator was mounted to a rotary axis (φ), on a translating radial arm (R, θ), which in turn was mounted to a motorized z-axis (Linear Stage 2DB160UBW-SL, Thomson Industries, Ronkonkoma, NY; Servo Motor, BSM63N-375AA, Baldor, Fort Smith, AR; Controller FlexDriveII, Baldor). The z-axis allowed for continuous and incremental (50 μm, 0.002 in.) positioning. A stereotaxic frame (Model 900, David Kopf Instruments, Tujunga, CA), mounted to an x–y table (2.54 mm, 0.1 in. lead, pre-loaded antibacklash nut, Thomson), mounted to a turntable (ω), served as the specimen platform. A customized damped-vibration table (78-111-02DR-SPECIAL, TMC, Peabody, MA) acted as the system's base.

The actuator had a nominal stroke of ±6 mm with a positional repeatability of 6 μm root-mean-square compared to an analog dial-gauge (1 μm resolution, Kafer, Germany). The actuator was controlled by WinTest software (Bose, Eden Prairie, MN). All injuries were conducted under displacement feedback proportional–integral–derivative control though force feedback was also available. The system was tuned to produce injuries at an intended peak velocity of 100 cm/s which is similar in scale to that believed to occur in some human injuries (Nightingale et al., 1996; Panjabi et al., 1995). Transducers were initially sampled at 4 kHz and this was increased to 8 kHz following software upgrade. Displacement was measured using a linear variable differential transformer (Model MHR250, Schaevitz Sensors, Hampshire, UK) integrated within the actuator chassis. Interchangeable load cells were used to measure forces (reported here in Newtons, where 1 N = 100 kdyne) in contusion (22N Model 31, Honeywell-Sensotec, Columbus, OH), fracture-dislocation (225N Model 31, Honeywell-Sensotec) and distraction (225N Model 31, Honeywell-Sensotec; 444N Model 208C02 PCB Piezotronics, Depew, NY). Sensor capacities were chosen to accommodate for potentially high inertial forces (i.e. forces required to accelerate the instrumentation's mass irrespective of the forces applied to the specimen) and were calibrated to specific ranges to optimize measurement accuracy. For contusion injuries, the root-mean-square accuracy – a type of average error (Choo and Oxland, 2003) – over a ±15 N range was 0.03 N with a maximum error of 0.04 N. For dislocation and distraction injuries, the root-mean-square accuracy over a ±100 N range was 0.1 N with a maximum error of 0.2 N. Accelerometers (50G Model 355B03, 500G Model 355B02, PCB Piezotronics) were used for inertial compensation of dynamic force measurements (Stokes et al., 1992). Data were digitally filtered (Lyons, 1997) with a 1 kHz zero-phase Butterworth low-pass filter (4 kHz data with 4-pole, 8 kHz data with 6-pole).

2.2. Vertebral clamping strategy

Our vertebral clamps were designed to wedge beneath the cervical transverse processes against the lateral masses of the vertebrae (Fig. 2A and B). For dislocation (Fig. 2C and F) and dis-

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