A CRITICAL ANALYSIS OF EXPERIMENTAL SPINAL CORD INJURY MODELS

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ABSTRACT

This critical review examines the several models which have been proposed to study mechanisms of acute spinal cord injury. From a physiologic point of view, each model offers particular advantages and is useful to address specific questions about the pathophysiology. From a biomechanics point of view, however, adequate simulation of clinically occurring spinal cord injuries requires control of impact parameters which are important to injury outcome, such as amount of compression and velocity of loading. A controlled contusion technique developed by the authors provides this control and results in clinically relevant experimental injury. Both transient and maintained compression are important in determining the neurologic outcome of injury. When combined with an improved understanding of vertebral failure kinematics, neurologic injury potential may be estimated for specific vertebral loading (and failure) parameters.

Beyond the biomechanics of injury, physiology must be carefully considered in the experimental protocol. The effects of alternative anesthetics, respiratory parameters, adjunctive agents and laminectomy will be reviewed. Standardized protocol would facilitate communication and comparability between laboratories. Also, the severity and outcome of clinical injury may be affected by factors such as high blood alcohol and hemorrhagic shock. Experimental study of these factors requires particular attention to baseline physiologic parameters in the experimental setting.

INTRODUCTION

The mechanism of serious neck injury is an important area of research in occupant protection. Although the biomechanics of fracture/dislocation of the cervical vertebrae has been the object of considerable research, the principal clinical concern is injuries resulting in spinal cord contusion and permanent loss of function. The Abbreviated Injury Severity scale clearly recognizes the greater significance of spinal cord injuries resulting in permanent paralysis (paraplegia or quadriplegia, depending on injury site) compared with musculoskeletal injury without neurologic deficit.(Table I) To effectively reduce the risk of significant neck injury, research in occupant protection must interpret general kinematic studies of cervical spine articulation and fracture/dislocation in light of physiologic studies of spinal cord contusion and permanent functional changes. This paper summarizes the available models for study of the pathophysiology of graded spinal cord injury and the contusion parameters which define the injury outcome.

The primary objectives for a spinal cord injury model are to have a clinically relevant experimental procedure which also has the ability to generate reproducible gradations of injury severity. These objectives have led to a diversity of experimental models for spinal cord injury, most of which only partially satisfy the two requirements. The most common are drop-

weight contusion and slow compression by balloon inflation or weight application. [1, 12, 22, 4] Slow rates of compression provide the greatest reproducibility of graded injury severity, but are not a realistic model for traumatic cord compression. The drop-weight model results in dynamic compression relevant to clinical traumatic injury, but exhibits high variability at moderate injury severity levels or with slight changes in experimental parameters.[12, 24]

The response of the spinal cord to dynamic compression injury is composed of three distinct phases: 1) the compression event with immediate mechanical damage to blood vessels, neurons and axons; 2) the acute phase spanning several hours following compression during which time the pathology responsible for loss of function develops; and 3) the resulting permanent tissue destruction and functional loss. Since tissue destruction progresses over several hours post-contusion, an opportunity exists to minimize the extent of tissue damage and disability if the underlying mechanisms are understood.[14, 19, 30] Further, determination of the contusion parameters which differentiate between spontaneous recovery and permanent paralysis will enable better interpretation of biomechanical data on the musculoskeletal failure modes to determine the likelihood of neurological deficit.

General Morphologic Observations: The morphology of traumatized spinal cord has been extensively studied by light and electron microscopy, and some consistent observations can be cited. Immediately following contusion only petechial hemorrhages are observed, limited to central gray matter.[14, 19] The extent of hemorrhage progresses with time, dependent on severity of injury, and eventually extends into the white matter of the cord for injuries resulting in paralysis or paraparesis.[14, 33] The progressive development of spinal cord pathology is illustrated in Figure 1, which shows typical cross-sections of the spinal cord at time intervals following contusion. Higher magnification would reveal shrunken axons and damaged myelin in the fiber tracts of the white matter. Similar progression of tissue destruction is observed in clinical spinal cord injury.

Functional Assessment: Any study of spinal cord injury must assess function as well as morphology of the spinal cord since functional changes and morphology do not always correspond. Although behavioral assessment of function is possible, and any technique assessing dysfunction must be validated against behavior, it is neither the most quantitative nor consistent method. Quantitative assessment of function can be made within hours post-contusion using averaged somatosensory evoked potentials (SEP's) to measure spinal cord conduction.[15, 30] The technique has been used both clinically and experimentally to measure function, and SEP recovery at 4-6 hours generally predicts final behavioral recovery, even though strictly speaking the SEP provides information only about sensory pathways.[15] Typical evoked responses after spinal cord contusion injury are shown in Figure 2.

EXPERIMENTAL INJURY TECHNIQUES

Drop-Weight: The drop-weight technique for dynamic spinal cord compression was first introduced by Allen in 1911 and is currently used by many investigators with slight modifications.[1, 24, 17] The principle attractions of the model are its simplicity, the reproducibility of paralysing injuries and the similarity of resultant pathology and dysfunction to clinical injury observations.[14, 9, 30]

Briefly, a hollow, vented guide tube is placed perpendicular to the dorsal surface of the spinal cord following a laminectomy. A lightweight

plastic impounder rests on the exposed spinal cord dura. The weight, usually standardized at 20gm, drops through the guide tube to strike the impounder and compress the spinal cord. Injury severity is quantified as the gm-cm product of drop-weight mass and the drop height. It is essential to note both the weight used and the gm-cm product, since the same gm-cm product often does not result in comparable injuries when different drop-weight masses are used.[12, 28] Multiple impacts also represent a potential source of variability, and in the absence of a 'capture' technique for the drop-weight, the second impact may cause cord compression of up to 60% of the amount of primary compression.[24, 28]

Modifications to the original technique have been aimed at improved reproducibility and control of injury severity. At the very least, it is critical that the spine be stabilized and the drop-weight mass standardized.[12, 24] The size and shape of the impounder interface with the spinal cord will also affect the injury severity, as will the size of the laminectomy relative to the impounder tip.[24] The optimal laminectomy is just large enough to clear the impounder tip, although any laminectomy can cause changes in spinal cord blood flow and metabolism.[2, 5] These metabolic and blood flow changes can make difficult the interpretation of data regarding the role of ischemia and local tissue hypoxia or anoxia in determining the severity of spinal cord injury. Further, the thoracic spinal cord has been the most common site of experimental injury, yet most clinical injuries occur in cervical or lumbar regions. Differences in vascular perfusion of these two spinal cord regions could lead to differing injury outcome.

The major disadvantage of the common drop-weight procedure is that it does not allow independent control of depth of compression and contact velocity. This limitation may be responsible for the observed variability at moderate injury severity.[12, 28] Studies of trauma in other organ systems have shown that force or kinetic energy measures are poor predictors of injury result when compared to parameters of compression and velocity.[26, 32] Selection of compression and velocity could be achieved in the drop-weight technique, but only through trial and error selection of the appropriate combination of weight and height for a standardized impounder tip and laminectomy. Although the necessary drop height for a desired contact velocity can be calculated, the amount of compression in the standard free-fall drop-weight model can only be determined by measurement of impounder travel relative to the spine.

Recent modifications reported by Ford constrain the impounder travel and avoid the problems of spinal movement by incorporating a steel anvil as part of the apparatus.[17] The anvil is placed beneath (anterior to) the spinal cord, and the drop-weight drives the impounder toward the anvil, causing cord compression. Electromagnetic control of the drop-weight is incorporated to prevent multiple impacts. Since travel is constrained, drop-weight mass can be chosen high enough to ensure the desired amount of compression without exceeding it. This modification may enable reproducible graded-severity spinal cord injuries using the drop-weight technique by improving the independence of compression amount and contact velocity, but involves extensive surgical preparation and manipulation of the spinal cord which may affect cord metabolism and injury outcome.[5]

Slow Compression: Slow cord compression by balloon inflation, application of weights, or advancement of a screw against the dura have been used to induce either dorsal or ventral spinal cord injury.[4, 9, 22] Neural conduction through the site of compression is compromised only when compression is sufficient to block local blood flow.[21] This requires

compression in excess of 80%.[29] Slow compression results in reproducible injuries of graded functional and histologic severity, but the relevance to clinical spinal cord traumatic injury is questionable. The duration of compression in dynamic spinal cord contusion is less than 5 seconds, yet compression of 75% or more at a contact velocity of 3m/s resulted in loss of somatosensory evoked potentials at six hours post-contusion.[6] In contrast, slow application of the same amount of compression has no permanent effect unless maintained for more than 7min.[21, 31] Dynamic compression of 50% results in impaired conduction (increased latency, decreased amplitude) through the injured site when response is assessed over the same period.[6]

The difference in outcome between slow and fast compression is not a result of blood flow changes, since local blood flow alterations after dynamic spinal cord compression parallel those seen following slow compression.[21, 22] In both cases, ischemia occurs during cord compression and immediately following, with a delayed period of hyperemia after cord decompression.[29] Rather, the parameters of compression appear to initiate fundamentally different injury pathophysiology in the two models, with dynamic compression resulting in more severe pathologic change and tissue destruction.

In Vitro Studies: Mechanical effects of dynamic compression on spinal cord conduction have not been studied carefully, perhaps because the immediate conduction block after dynamic compression is often transient. It remains to be determined however, whether mechanical axon injury might sensitize or otherwise 'set the stage' for later permanent disruption of axonal conduction.[13, 20]

It has been demonstrated, for instance, that dynamic compression causes axonal membranes to become permeable to large macromolecules such as horseradish peroxidase (HRP), which could contribute to intra-axonal edema.[25] Increased permeability would also disrupt normal ionic gradients across the membrane and prevent propagation of action potentials. Mechanisms of damage to nerve membranes can best be studied using an *in vitro* spinal cord preparation, where tissue oxygenation and metabolite availability can be controlled to avoid secondary injury due to ischemia or its sequelae. Rat spinal cord can be successfully maintained in a tissue bath after longitudinal hemisection, and normal conduction continues for several hours.[27] Conduction in the isolated cord is less sensitive to contusion injury than it is *in vivo*, presumably because the secondary metabolic injury has been averted.

Controlled Contusion: The controlled contusion technique uses a constrained-stroke pneumatic impactor mounted on an adjustable frame to provide independent control over depth of compression and contact velocity.[6] A midline dorsal incision and tissue retraction exposes the intact dura without laminectomy. The device, shown in Figure 3, enables accurate and repeatable selection of these injury parameters. More importantly, neurophysiologically distinct injury severity levels can be reproducibly generated, including a moderate severity injury with impaired neuronal conduction evidenced by increased latency(Table II).[6] Such a moderate injury, which is not reliably produced by the drop-weight technique, represents a threshold between spontaneous recovery and permanent paralysis and is promising for the study of tissue injury mechanisms.

The interaction of compression and contact velocity was studied to enable comparison of direct cord compression injury with parameters of cord compression determined from biomechanical studies of cervical spine failure. Latencies for SEP's at four hours post-contusion are given in Table III for 25 and 50% compression. Contact velocity of 3.0m/s is comparable to the

calculated contact velocity for a weight drop contusion injury from a height of 20cm.[6] Compression of 25% had minimal effects on the SEP latency, but 50% compression resulted in an increase to approximately double control. Compression of 75% was tested in three subjects at each contact velocity, and no recovery of somatosensory evoked response was observed in any instance. It is clear that functional recovery measured by SEP latency at four hours correlates to the amount of cord compression rather than the contact velocity. Morphologic examination found that the extent of hemorrhage and necrosis correlated with contact velocity.(Figure 4) Hemorrhage was more extensive after 25%, 10.0m/s compression than after 50%, 0.6m/s compression, although functional recovery was better after 25% compression.

Control of injury parameters thus alters the subacute manifestations of functional and histologic spinal cord injury. Correlation between extent of hemorrhagic necrosis and subacute loss of conduction as reported in the literature may result from the biomechanics of the injury model used, rather than a causal role of hemorrhage in progressive pathophysiology. It is important to remember that the present set of experiments focused on the first four hours post-contusion. Delayed loss of conduction could occur secondary to extensive central hemorrhage, after the four-hour period. Such initial recovery followed by permanent loss of function has been observed clinically, and may reflect the injury biomechanics.[19, 30]

INJURY PHYSIOLOGY

Since anesthetic and surgical procedures may interact with injury pathophysiology and affect the injury outcome, particular attention should be placed on the details of the experimental protocol, its standardization and the possible effects of drugs or procedures on injury physiology. This section will briefly review some of the major potential interactions and outline recommendations to minimize artifactual results.

Hemodynamics: Hemorrhage is one of the earliest consequences of spinal cord traumatic injury, beginning in the central gray matter and expanding with time to include the white matter as well.[7, 14, 33] The expanding hemorrhage has been implicated in development of necrosis, and may also contribute to immediate and delayed vasospasm and local cord ischemia.[10] Since spinal cord autoregulation of blood flow is impaired after trauma, systemic blood pressure may significantly affect the development of central hemorrhage by altering the flow to the area.[7, 8] Thus, it is important to monitor blood pressure and provide supportive therapy. Similarly, agents which affect the clotting process should be used only in full awareness of their potential interaction with injury physiology and in the presence of appropriate controls.

Systemic blood pressure may also affect the time course of local spinal cord ischemia, since autoregulation is lost. Blood flow is reduced following cord trauma in proportion to the severity of the injury.[7, 8, 14, 34] Mechanisms include vasospasm, platelet aggregation and general hypotension combined with loss of spinal cord autoregulation.[15, 20] Since gray matter has higher metabolic demand and blood flow than white matter, and shows a larger decrease in flow following injury, it is more sensitive to post-contusion ischemia.[4, 18, 21, 22] The effect of ischemia appears to be additive to compressive effects, but lesions are principally central with little or no long-tract conduction abnormalities.[21, 22] Prevention of post-contusion hypotension enhances behavioral recovery in experimental injury, demonstrating the importance of systemic pressure in recovery from spinal cord

injury.[16]

The blood-spinal cord barrier is disrupted following cord contusion, resulting in prompt development of vasogenic edema.[7, 14, 19, 30, 32] We have found that moderate cord contusion results in significant edema as measured by tissue water content by 15min post-contusion.(Figure 5) However, in minor cord injury the edema develops more slowly, and is increasing even as cord conduction improves. These observations cast questions on an hypothesized role for edema as a prime causative factor in spinal cord dysfunction.

Biochemical Factors: Relative tissue ischemia has further local metabolic consequences, including accumulation of lactate and generation of free radicals.[3, 4, 11] Lactate accumulation results in acidosis and activation of catabolic enzymes. Also, production of high-energy phosphate compounds will be reduced, compromising the normal intracellular versus extracellular balance of ions. The result is impaired or blocked conduction in axons, reduced excitability of neurons, and intracellular edema. Since production of lactate depends on conversion of glucose metabolism from aerobic to anerobic, the glucose level may be important to injury outcome. Hence, a consistent procedure should be adopted for fasting animals prior to cord injury, or glucose levels should be monitored.

Ischemia or hypoxia will also liberate free radicals from the electron transport system since adequate oxygen will not be present to allow completion of glucose oxidation. These highly reactive species can initiate auto-catalytic peroxidation of membrane lipids, leading to loss of cellular integrity and function.[11] Since barbiturate anesthetics can act as free radical trapping agents, it is preferable to employ other anesthetic agents to avoid an unintended therapeutic action.

An anesthetic which is minimally depressive of central neuronal activity is desired, since metabolic changes reflect not only supply of high energy compounds but their consumption as well. Reduced metabolic supply may be adequate if neuronal activity is suppressed by inappropriate choice of anesthetic. Evaluation of cord conduction will also be impaired if the anesthetic agent is strongly depressant. A Ketamine/xylazine combination appears to offer an acceptable compromise between adequate anesthesia for surgery and experimental injury and avoidance of interactions with injury physiology or depressant action on the nervous system.

SUMMARY AND RECOMMENDATIONS

1) The conflicting objectives of clinical relevance and reproducible graded injury severity can be resolved by control of compression depth and contact velocity. Independent control of these parameters also permits comparison between direct spinal cord injury models and parameters of spinal cord compression derived from biomechanical studies of vertebral failure. Such comparison will allow projection of the likely neurologic injury given a known biomechanical failure mode.
2) While the controlled contusion technique is the most direct solution to these goals, the drop-weight technique may be modifiable by constraints on impounder travel and careful selection of drop weight mass and height. In either injury technique, however, the spine must be held rigidly to ensure reproducibility of injury severity. Also, laminectomy should be avoided if possible to circumvent post-laminectomy metabolic and blood flow changes which will complicate

assessment of injury physiology.

3) The site of injury should be chosen to represent clinically relevant spinal cord injury. Since most clinical injuries occur in cervical or lumbar cord, experimental injury in these regions would be preferable to the more commonly employed thoracic region. Data obtained in the thoracic region may well be transferable to the cervical and lumbar cord, but anatomic differences (cervical and lumbar enlargements for motoneurons innervating the extremities) and vascular supply patterns suggest the possibility of outcome differences.

4) A standard anesthetic and drug protocol should be adopted. Since free radical degradation of membranes may be involved, barbiturate anesthesia should be avoided as a potential free radical scavenger. Halothane/nitrous oxide or ketamine/xylazine anesthesia appear to be the best choices. Adjunctive agents should be avoided since the blood-spinal cord barrier is disrupted and drugs will have access to the spinal cord tissue, where they may affect injury physiology. Standard supportive therapy should be used to ensure adequate ventilation of the animal and maintenance of both body and spinal cord temperature.

TABLE I
CERVICAL SPINE INJURIES

AIS	INJURY DESCRIPTION	OUTCOME
	SPINAL CORD	
6	Cord crush at C-3 or above	Death
5	Cord crush at C-4 or below	Paralysis
5	Complete cord lesion	Paralysis
4	Incomplete cord lesion	Spasticity
3	Cord contusion	Transient loss
	NERVE DAMAGE	
3	Nerve root damage	Local deficits
3	Brachial plexus damage	Local deficits
	MUSCULO-SKELETAL	
3	Disc rupture; nerve root damage	Local deficits
3	Dislocation; fracture of lamina	Transient loss
2	Fracture, spinous/transverse process	Normal function
1	Acute strain, no fracture/dislocation	Normal function

TABLE II
LATENCY TO INITIAL POSITIVITY OF HINDLIMB SENSORY EVOKED POTENTIAL AT FOUR HOURS POST-CONTUSION

Compression Amount	Latency (ms±S.D.)
Control	9.72±0.82
10-30%	10.43±1.18
40-60%	19.88±0.61*
>75%	No Recovery

*Differs from control latency, $p<0.01$.

TABLE III
MEAN LATENCY OF HINDLIMB EVOKED SOMATOSENSORY POTENTIAL AT FOUR HOURS POST-CONTUSION: CONTACT VELOCITY 3.0m/s

% Cord Compression	Contact Velocity(m/s)	Latency(ms±S.D.)
25	0.6	9.9±0.8
	3.0	10.2±1.2
	10.0	11.9±1.4
50	0.6	19.2±0.9*
	3.0	20.2±1.0*
	10.0	22.4±1.5*

*Differs from control latency of 9.7±0.8ms, $p<0.01$.

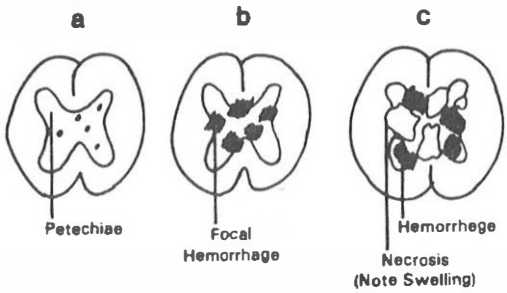

Figure 1: Progressive development of spinal cord pathology following a 50% compression at 3.0m/s. a) Fifteen minutes post-contusion; b) One hour post-contusion; c) Four hours post-contusion.

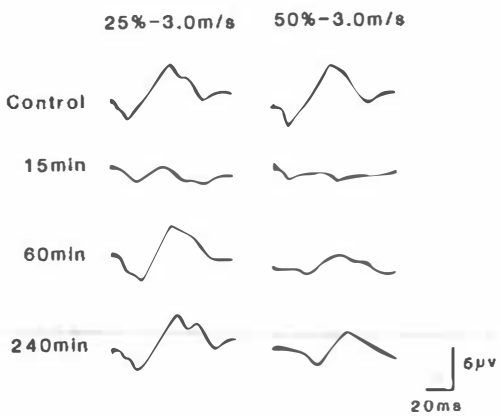

Figure 2: Somatosensory evoked responses recorded at time intervals following 25% and 50% spinal cord compression at 3.0m/s. Reprinted with permission, J. Neurosurg. vol. 62.

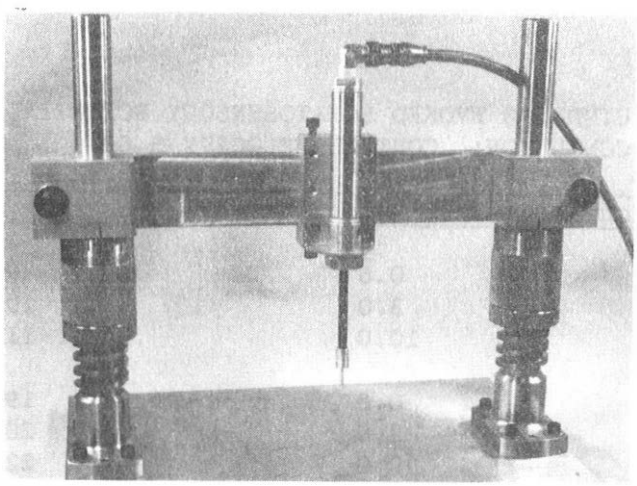

Figure 3: Controlled contusion injury device. Cylinder stroke and retraction are controlled by solenoid-valved air supply; duration of compression is controlled by timing circuitry.

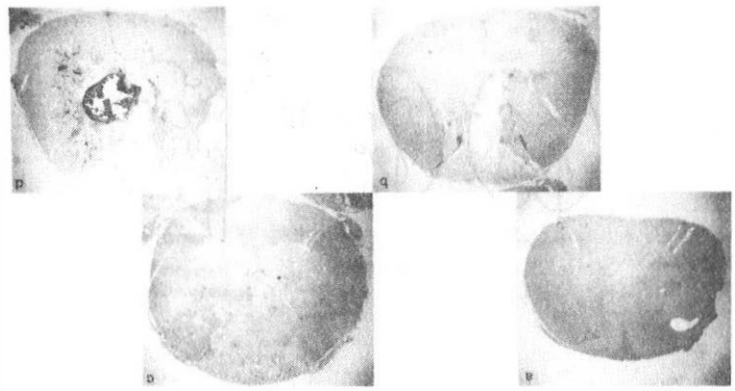

Figure 4: Morphology at four hours for various combinations of compression amount and contact velocity. a) 25%, 0.6m/s; b)25%, 10.0m/s; c)50%, 0.6m/s; d)50%, 10.0m/s. Reprinted with permission, J. Neurosurg. vol. 62.

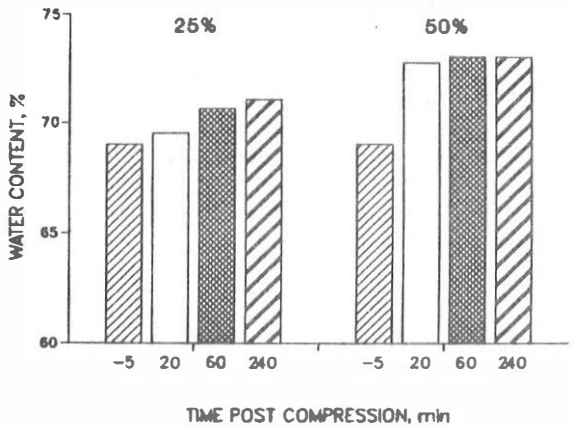

Figure 5: Fluid content of spinal cord tissue at time points after 25% and 50% contusion at 3.0m/s.

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