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Biomechanical Analysis of Brain Injury Models

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ABSTRACT

Traumatic brain injury models were designed to study the characteristics of human brain injury. The properties of experimental injury models were reviewed from the biomechanical point of view in this article. Weight-drop models with or without skull protection were compared in terms of experimental setup, possible error source, and biomechanical prospect. The modified percussion models with or without rigid cortical impact were contrasted with regard to reliability, histo-pathological production, and deformation. The focal contusion model by mechanical suction force was considered as isolated cortical injury without compression brain injury. Each experimental injury model had advantages and limitations, therefore, no single model produces full injury features seen in human head injury.

Key words: Head injury, experimental animal model, diffuse axonal injury, biomechanics, cerebral ischemia

INTRODUCTION

The traumatic brain injury models were designed to replicate the full nature of the human brain injury, and the injury response specified in physiological, behavioral, or anatomical terms must be reproducible and quantifiable over a continuum of injury severity. However, it is apparent that no single model can induce various neuropathological sequel associated with whole brain injury. Even in the same type of animal, it is difficult to characterize the end result of brain injury owing to the diversity of impact mechanisms and anatomical properties of brain.

There are several advantages of using single, controlled mechanical input to produce a brain injury. If the mechanical input is designed to be quantifiable and graded, correlation can be made between the brain deformation parameters (applied force, amount of strain, and duration of contact time), the resultant pathology, and functional changes. Such analysis will ultimately lead to enhanced understanding of the interaction between the physical input, the severity of injury response, and the functional outcome.

Numerous sub-primate animal models have been extensively studied for non-penetrating head injury in the human. The relatively small size and moderate cost of rodents makes them attractive for the experiment, and there has been a substantial increase in the use of rats for traumatic brain injury research during the last decade. There are other advantages: the precise knowledge of the age and genetic background of the animal, the existence of normative data for a wide range of physiological and behavioral variables, compatibility with neuro-

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chemical and molecular techniques, high resistance to infections, and lower dose of drugs owing to low animal body weight. On the other hand, they have important disadvantages. The differences in physical properties (brain anatomy and mass weight) complicate biomechanical studies. They have more potential for developing post-traumatic seizures. It is more difficult to induce prolonged unconsciousness and widespread axonal injury in rat compared with other species. Rats have an extremely steep injury tolerance curve; the change from no injury to fatality occurs over a very narrow range of injury. Finally, testing for more complicated and subtle behavioral deficits cannot be done easily.

Despite the relative disadvantages of mimicking human head injury, the use of laboratory animal models provides a wide range of neurochemical, molecular, and neurophysiological data. The biomechanical point of understanding on the model can support pros and cons of developing experimental brain models in laboratory environment.

BRAIN INJURY MODELS

As a model for closed head injury in rats, Shapira et al. (1988) proposed using a calibrated weight-drop device. In this study, small animal cerebral trauma was reproduced to determine the time course and magnitude of cerebral edema, its resolution, and the evolution of the pathological changes followed over several days after trauma. The weight-drop device enabled gradation of the degree of insult based on the momentum of impact to the skull by altering the height from which the moving plate was dropped. For the experiment, Sabra rats between 250 and 300 g were anesthetized with ether and allowed to breathe spontaneously. By dropping the weight directly onto the exposed skull from a height of 7 cm, they obtained 30% mortality rate. Rats were studied at 1 min, 15 min, 60 min, 18 h, 4 and 10 d after trauma. A brief apnea and transient hypertension are the only significant systemic effects as a result of injury. Hypertension did not reach the level that may impair cerebral perfusion and develop secondary ischemic events. The model produced small epidural, subdural hematomas and a frontal cortical contusion of 0.3～0.5 cm. Ipsilateral brain edema (measured by gravimetric technique) was detected as early as 15 min after the trauma, reaching its maximum at 18 h and returning to the control levels at 10 days post-injury. The brain edema at 18 h post-injury was similar to those observed in clinical circumstances of severe head injury, and edema was significant only at the contused hemisphere. There were only small changes in water content in the cerebellum and brain stem. The neurological dysfunction as a result of the injury correlates significantly with the pathological score. Therefore, the clinical outcome of the injury might be predicted by the neurological dysfunction observed at a very early stage, at 1 h as well as at 18 h.

Meaney et al. (1994) proposed modified cortical impact model for brain injury study. Models employing fluid percussion and weight-drop techniques using the rat have provided plenty of neurophysiological and histopathological changes resulting from traumatic brain injuries (Yamaki et al., 1994) In general, the fluid percussion model may cause prominent brain stem injury associated with a high mortality rate. Accurate reconstruction of varying velocity of the falling weight and subsequent amount of brain damage had been restricted to the weight-drop model. In order to describe mechanical brain injury, independent control of contact velocity and amount of brain deformation were characterized in the controlled cortical impact model. The features of this model included constant injury reproduction with cortical contusion and distal axonal injury, cognitive, memory, and motor deficits mimicking human head injury. The most common form of severe human head injury displays diffuse axonal injury with prolonged coma without intracranial mass lesion and the second highest mortality rate among all types of head injury. Biomechanical studies in the cortical impact model have shown the varying degree of primary axonal injury in the forebrain and brain stem. However, the authors claimed that the extent of axonal damage in the forebrain was limited to the contused area. The authors examined whether opened contralateral dura mater during direct rigid cortical impact injury of hemisphere can produce widespread, bilateral forebrain axonal deformation injury. Deformation patterns were examined using surrogate skull-brain models. The results disclosed that the contralateral dura mater

opening significantly reduced surrogate tissue herniation through the foramen magnum and instead redirected surrogate tissue movement across the sagittal midline to increase shear strain in the contralateral cortex. This experiment suggested that the axonal injury of neurons could be produced selectively by controlling the factors of local strain tensor and trajectory of axonal population.

A new experimental model for focal cerebral contusion was developed by Mathew et al. (1996). Authors used a non-ablative mechanical suction force applied through the intact dura. A 2-ml spring-loaded plunger was connected to a plastic tip (diameter 5 mm) to deliver constant negative force through the intact dura. The left parietal craniectomy was performed and exerted a suction pressure of -700 mmHg for 5 s on four groups of animal (spontaneous breathing, mechanical ventilation, sham, and injured group). No difference was found in the physiological variables such as pulse rate, blood pressure, blood gas, temperature, and intracranial pressure (ICP) between sham-operated and contusion injured animals at any time point. There was no transient alteration in arterial pressure during cortical injury. In addition to previous reports, the authors remarked the following new pathological findings: (1) early swelling of neuronal dendritic processes and later astrocyte response did occur; (2) early disruption of the blood-brain barrier (BBB) did not occur. However, the appearance of perivascular protein leakage at 24 h suggested a later increase in BBB permeability preceding an inflammatory response; (3) observed ipsilateral diffuse astrocyte response without diffuse axonal damage. CBF (cerebral blood flow) measurement using $_{14}$C-iodoantipyrine autoradiography timely after induction of negative-pressure suction injury revealed significant blood flow reduction in the sensorimotor cortex at the site of the injury below the ischemic threshold. However, the magnitude and duration of the reduction in blood flow are not consistent with the threshold of ischemic cell damage.

The traumatic coma data bank study indicates that diffuse brain injury has a high mortality and morbidity rate, with comatose status even with normal computed tomography scan. In approximately 40% of severe head injuries, diffuse brain injuries cause one-third of deaths owing to head injury and persisting neurological disability in survivors. However, it is difficult to replicate this type of injury in experimental models using fluid percussion or cortical impact techniques, which also cause brain stem injury or focal brain concussion. In order to study a higher degree of injury with widespread brain dysfunction, a direct dural impact model with protected skull using a stainless steel helmet was proposed with pathophysiological and biomechanical reasoning. In the first part (Marmarou et al., 1994), the authors analyzed the biomechanical characteristics of the model and studied the cause of death in injured rats. They divided the animals into two groups associated with the mechanical ventilation. In group 1, animals were allowed to breathe spontaneously during the experiment. The authors reported that severe injury (mortality rate $\cong$50%) with prolonged apnea, convulsion, and hypertensive response was achieved by dropping a 450-g weight from a height of 2 m. The moderate injury (no mortality, no skull fracture) with brief apnea and transient hypotension was induced by a 450-g weight from a height of 1 m. In group 2, they studied severely injured rats with tracheal intubation with or without mechanical ventilation and found that early respiratory support reduces mortality significantly (from 50% to less than 10%) in severe head injury. The second paper describes post-traumatic clinical and pathological findings of the two animal groups from the first paper (Marmarou et al., 1994). The gross brain pathological findings of the model did not differ whether the animals were mechanically ventilated or not. In macroscopical findings, no focal lesion was found, and petechial hemorrhages in the dorsal portion of the brain stem were detected only in severe traumatic brain injury. The severity and extent of the microscopical changes was directly related to the degree of the trauma. The model produced different stages of graded widespread injury of the neurons, axons, and microvasculature in supraventricular areas, but there was no supratentorial focal brain lesion in the two groups. Brain edema, vascular congestion and diffuse axonal swelling were also seen in the brain stem.

BIOMECHANICAL COMPARISON

The focal brain injury model by Shapira et al. closely reproduced the cortical contusion. With this model, there is a significant correlation between the edema that peaked in the contused hemisphere at 18 h and the degree of neurological dysfunction. It suggested that cellular swelling and cytotoxic edema play a major role in the sequence of events leading to brain edema after cortical contusion. Therefore, this is a useful experimental model that reproduces the stereotypical fashion of a cortical contusion with subsequent cerebral edema. However, the authors did not describe the incidence of skull fracture in this model. Skull fracture is an important factor to differentiate coup contusion (contusion that appears in the site of impact) and fracture contusion (contusion with penetrating injury from depressed fracture). The fracture contusion is frequently associated with intracranial hematomas that may induce further cerebral damage. The modified weight-drop device was designed to deliver standard impact to the rat skull. Impact was delivered by a silicon-coated metal tip (diameter 5 mm). The measurement of impactor tip velocity was highly reproducible using a piezoelectric accelerometer. The device can change the distance of the moving platform over the fixed surface, but the size (30× 20 cm) and weight (1600 g) of the platform are not variable. Therefore, manipulating the height from which the platform is allowed to fall determined the impact momentum. The device has four bars to hold the platform apart, so friction can be a major factor, because impact may be absorbed by weight-holding pins and diminished by air resistance. The unmovable metal bottom platform did not allow any head acceleration, but contact phenomena. The small size of the impactor tip (5 mm) on the metal bottom plate induced a higher magnitude of the force delivered on the animal, with a high mortality rate (43%). This model induced 0.5 J over the skull (1600 g fall from height 7 cm), which is relatively less than the kinetic energy induced by the other article (450 g fall from 2 m). The control of the duration of an impact force and distance of skull compression was ignored in this experiment.

The level of trauma severity of the rigid cortical impact model by Meaney et al. is dependent on both the impactor contact velocity and the amount of cortical deformation. The low velocity (2 m/s), low deformation (2～3 mm) impact injuries from other studies (impactor diameter 1.25 cm) did not produce any superficial damage and cerebral vascular tissue alteration. More deformation (3.5～5.0 mm) produced immediate subdural hematoma and fatality within minutes. The medium velocity (3 m/s) and more deformation (3～4.5 mm) induced delayed cardiac responses, increased hypotensive period after trauma and immediate fatality with 4.5 mm. All impact in high velocity (4 m/s) produced acute subdural hematoma, contusion of the brain stem and cervical spinal cord. The brain stem herniation and partial transaction of the spinal cord were observed in severe cases. The authors used the surrogate skull-brain model and the animal model to compare, therefore limiting the pattern of impact deformation owing to different mechanical properties of the model. The models were also evaluated with different indentation tip on different scaling (physical model: 12.5 mm, animal model: 3 mm diameter); the generated energy by impacts to each model is not comparable to each other. As the authors stated, pathobiological aspects of forebrain axonal injury can be selectively studied from the brain stem injury using this model. However, the injury response does not resemble the severe human closed injury because the direction of the impact force and brain displacement after impact are altered owing to contralateral opened dura and craniotomy.

The model by Mathew et al. analyzed the characteristic of isolated cortical injury that was produced by pulling rather than compressing the brain cortex. Suction pressure over the intact dura mater induced focal cortical contusion without hemorrhage or hematoma that perplex brain for further injury by neurochemical cascade. The focal impact injury model fabricated graded trauma severity by using different levels of cerebral indentation and contact velocity. Inspection of the brain and impact parameters in the impact injury model can reveal the pattern of pathological changes that correlates with brain injury and impact force. However, the suction injury model in this study was limited by the duration of the vacuum period, because negative pressure less than -700 mmHg was not enough to

reproduce lesions, and pressure greater than 700 mmHg ruptured dura mater based on the report. The dissipation energy of the negative suction pressure might have additional traumatic effect to the cortex. From the pressure transducer record, the mechanical suction device made a reactive rippling pressure wave during the first 15 ms after the three-way tap opened to release negative pressure. It may enlarge cortex damage further because pressure is overshooting from -300 mmHg to positive pressure in that short duration. The pressure suction pulse did not induce a brief ICP increase, which otherwise is a hallmark in every common traumatic brain injury. Pressure pulse is applied for 5 sec, which is a relatively longer period than for head trauma. Therefore, the model does not resemble the short-duration impact experiences in human traumatic brain injury and did not easily produce cortical hemorrhage consistent with cerebral contusions, but rather a very localized disruption of the BBB. Although this model did not represent the common traumatic cortical contusion in human, it could be used to identify the primary and secondary pathological, physiological, and functional sequel associated with brain cortical contusions, without considering the effects of other primary pathologies.

Axonal damage is caused only by angular and rotational acceleration and not by contact phenomena. Since the amount of axonal damage was probably determined by the severity of rotational acceleration, the magnitude, duration and beginning rate of angular acceleration and the direction of head movement are the critical factors to assess the axonal damage in the weight drop model (Marmarou et al., 1994). The foam (stiffness 2500 N/m) underneath the rat head can produce a resistance over the repeated usage to the head acceleration, movement of head, and dampening of impact energy even though the authors claimed that the foam has negligible resistance to acceleration. If inertial effect is minimized owing to the stiffness of the foam, it will stop the head from acceleration. The large and blunt impactor prevented contact phenomena; however, the metal helmet that protects the skull from fracture may promote the existence of transient shock waves that generate localized hemorrhage in the brain tissue and skull. Friction phenomena between Plexiglas and metal weights can cause a variable decrease in velocity to the impact force. Piper et al. showed that the velocity of a 450-g weight dropped from 2 m above can vary by as much as 40%, depending on the degree of initial friction (Piper et al., 1996). The severity of post-traumatic clinical and pathological changes in both respiratory groups (spontaneous breathing and ventilated) was similar. However, the progressively increased PCO2 and transient alteration of brain stem auditory evoked potentials in the spontaneous breathing group suggest post-traumatic central respiratory dysfunction. The high mortality rate in spontaneous breathing animals is related to the respiratory dysfunction, and it can be reversed by early respiratory support. Mildly injured rats showed pathological features consistent with Adams grade-I diffuse axonal injury and severely injured rats with grade-III diffuse axonal injury. The model simulated the clinical and pathological features of the mild head trauma and suggested that diffuse axonal injury might be associated with subtle neurological dysfunction owing to minor head injury.

CONCLUSION

The ideal model for human brain injury should produce clinically classified head injuries from very specific forms of mechanical input. Observation of characteristics of the mechanical input such as amplitude, velocity, contact duration, direction, and application rate of injury force can furnish the head injury type, range, and severity. This applies to animal models of traumatic brain injury commonly associated with biomechanical analysis and clinical studies. Thus, animal models were developed to replicate the full extent of human traumatic brain injury based on the hypotheses that implied that non-human traumatic brain injury reproduces human injury. Associated with these hypotheses, the study of head injury has developed assumptions to generalize animal models, implicating that the mechanism to produce injury and species difference are not important, even from the ancient effort. However, the central problem still remains, because of the nature of human injury. In reality, it is clear that biomechanical forces and characteristics associated

with each injury are not necessarily the same at all. This diversity of human nature enables no single animal model to faithfully duplicate the potential pathophysiological, anatomical, and behavioral changes in brain tissue. Several investigators have developed experimental models of mechanical brain injury to trace various aspects of the biomechanical and medical responses. Such models were designed differently in order to fulfill the investigator's scientific objectives and goals, mainly owing to the complex pathophysiological phenomena encountered in the human injury. The direct dural impact model with protected skull successfully produced diffuse axonal injury in the rodent so that the measured engineering parameters contributed to establish a relationship between impact force, velocity, and magnitude of tissue deformation. The model made different stages of graded widespread injury in the neural structures. However, the foam stiffness, metal helmet, and friction phenomena in the impact device can cause variable injury output owing to various impact forces. These controlled mechanical variables needed to be accurately determined and monitored during usage of the device, because stiffness of the foam bed and friction between metal weight and vertical tube changed in time and made accuracy and repeatability of head injury degree difficult to compare. Another model for closed head injury in rat used a calibrated weight-drop device, which consisted of a silicone-covered metal tip and heavy metal platform. The model reproduced closely the focal brain injury with cortical contusion and showed negative correlation between the brain edema and the degree of neurological dysfunction. High late mortality rate (over 60%), possible skull fracture (occurrence is not listed), and structure of device are the drawbacks of the system. Based on their data, the velocity of the moving plate during the fall showed a biphasic pattern. The device has four bars to hold platform apart and large surface of platform that creates significant air resistance at a certain level; thus, friction caused major velocity alteration in the device. Based on the data from the experiment, the fall velocity of the impact device under 3-cm height was 3 times faster than the one over 3-cm height fall. Therefore, the degree of head injury induced by over 3-cm fall is not linearly proportional to the height of the fall. Unfortunately, the duration of an impact force and the distance of skull compression are not controllable either. Fluid percussion models (central and lateral type) in a review of the literature are commonly characterized by brief loss of behavioral reaction and alteration in metabolism, CBF and BBB permeability with motor and memory deficit. Meaney et al. examined whether intracranial geometry can change the pattern of brain axonal injury by using modified cortical impact model, opening the contralateral dura mater, which could direct mechanical deformation and strain formation across the brain tissue. The surrogated skull-brain model unveiled contralateral opening that allowed significant reduction of tissue herniation through the foramen magnum. The injury pattern revealed numerous axonal retraction balls in the sub- and deep cortical layers beneath the contralateral craniotomy area. However, the injury pattern with opened dura mater over the contralateral hemisphere needs to be related with size of contralateral craniotomy and magnitude of damage. The direction of impact force and location of the alternative opening in the skull are important factors to study injury mechanism. In the model, the direction of impact force is always perpendicular to the foramen magnum and aligned with the opening of contralateral dura mater; the impact force may exit directly to the contralateral opening instead of the foramen magnum without deforming the brain stem area. For a similar reason, with or without contralateral craniotomy, shear strain measurement near the foramen magnum may provide the various direction of impact force. Cortical impact models utilize a pneumatic piston to deform exposed cortex and provide controlled impact and quantifiable biomechanical parameters. Despite the measurable and controllable impact parameters, it invoked localized contusion combined with wide spread of contusion at the site of impact and promoted axonal injury, transient cardiopulmonary changes, and subsequent brain stem tensions. From the previous experiments, we have learned that injury compressing the cortex develops strain field in regions of axonal injury, which is too complicated to analyze. Mathew et al. [3] devised a simple reproducible rat model of focal cortical injury that uses a mechanical suction force instead of compressing

brain cortex. Clinically, cerebral cortical contusions are the most frequent finding of traumatic brain injury and regularly associated with perivascular hemorrhage of the cortical vessel. The leakage of blood component can cascade progressively to neuronal degeneration and necrosis. Numerous models have already reproduced the clinical picture of traumatic brain injury as a combination of focal and diffuse injuries. Cortical contusion was featured in these models. However, research for the mechanism of contusion is limited by the lack of reliable animal model of focal cortical injury. The long duration vacuum pulse to the intact dura of the rat developed nonhemorrhagic focal cortical lesion. The investigation of physiological variables [PO2, PCO2, pH, mean arterial blood pressure (MABP) and ICP] revealed that there were not significant differences between sham and cortically contused animals during the experiment. General histopathological observation showed that contusion generated by cortical suction is sharply defined focal lesion. This distinguishes focal cortical suction from other models, usually combined with focal and diffuse injury. As a shortfall of the model, the duration of pressure pulses (5 sec) applied to cortex is not controllable and relatively longer than previous short-duration studies (25 ms). Interestingly, the suction impact model included intact high stiff dura mater that may account for less cortical hemorrhage and very localized BBB disruption. The cortical evacuation technique used by Shreiber et al. (1996) induced graded local hemorrhagic lesions through open dura mater without damage to other areas. They found vacuum force about 410 mmHg for 25 ms induced focal hemorrhagic neuronal loss and axonal damage in the white matter beneath the injury site.

Each experimental injury model had advantages and limitations, so no single method produces full injury features seen in human head injury. Adequate descriptions of the relative three-dimensional distribution of primary lesions and reactive changes throughout the traumatic brain injury are not yet available because experimental models still differ from human models. The attention to biomechanical parameters with physiological factors should be directed towards improved analysis of results between the different centers.

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