A new model of diffuse brain injury in rats

Part I: Pathophysiology and biomechanics

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This report describes the development of an experimental head injury model capable of producing diffuse brain injury in the rodent. A total of 161 anesthetized adult rats were injured utilizing a simple weight-drop device consisting of a segmented brass weight free-falling through a Plexiglas guide tube. Skull fracture was prevented by cementing a small stainless-steel disc on the calvaria. Two groups of rats were tested: Group 1, consisting of 54 rats, to establish fracture threshold; and Group 2, consisting of 107 animals, to determine the primary cause of death at severe injury levels. Data from Group 1 animals showed that a 450-gm weight falling from a 2-m height (0.9 kg-m) resulted in a mortality rate of 44% with a low incidence (12.5%) of skull fracture. Impact was followed by apnea, convulsions, and moderate hypertension. The surviving rats developed decortication flexion deformity of the forelimbs, with behavioral depression and loss of muscle tone. Data from Group 2 animals suggested that the cause of death was due to central respiratory depression; the mortality rate decreased markedly in animals mechanically ventilated during the impact. Analysis of mathematical models showed that this mass-height combination resulted in a brain acceleration of 900 G and a brain compression gradient of 0.28 mm. It is concluded that this simple model is capable of producing a graded brain injury in the rodent without a massive hypertensive surge or excessive brain-stem damage.

**Key Words** • head injury • pathophysiology • biomechanics • experimental model • rat

Diffuse brain injury is associated with high mortality and morbidity rates, and recent studies by the Traumatic Coma Data Bank study group²¹ show that 55% of patients comatose on admission suffer from diffuse brain injury, with 12.6% presenting with a normal computerized tomography scan. This type of injury has been difficult to study in the laboratory as present models, such as fluid-percussion or cortical impact, produce a focal brain contusion and are associated with relatively minimal supratentorial axonal injury. At higher trauma levels, the fluid-percussion model produces a significant brain-stem injury and mechanical studies have shown that the region of maximum tissue strain is focused in the brain stem.²⁷²² This occurs as a result of the mechanical force imposed upon the exposed dura and the resulting fluid volume introduced into the cranial vault.¹ We reasoned that a higher degree of injury could be produced if direct dural impact could be avoided and the mechanical insult delivered to the intact cranium.

This report describes the development of a new rodent closed head injury model in which the skull is protected to prevent fracture. This allows higher impact-acceleration levels to be achieved, which our companion paper has shown to result in a pronounced diffuse brain injury.⁵ The first objective of this study was to identify the trauma levels that would induce mild head injury (with no mortality) and severe head injury (about 50% mortality rate) with a low incidence of skull fracture. The second objective was to begin isolating the cause of death in nonsurvivors in the group of severely head-injured rats. The third objective was to develop a mathematical model to determine the level of acceleration achieved by the two degrees of impact producing the mild and severe head injuries.

**Materials and Methods**

Based on the analysis of our mathematical models, it was determined that one approach to obtaining high
acceleration upon impact would be to lightly support the head in order to permit displacement immediately following impact. Thus, the first series of rats was injured with a simple weight-drop device, and studied to determine the weight-height combination that resulted in a mortality rate of approximately 50% in nonventilated animals (Group 1). Having established this level, it was noted that nonsurvivors experienced prolonged apnea. Thus, a second series of rats (Group 2) was studied to establish whether this respiratory failure was related to a peripheral or central process.

**Trauma Device**

The trauma device consists of a column of brass weights falling freely by gravity onto a metallic helmet fixed to the skull vertex of the rat by dental acrylic. The brass weights, each 50 gm, were threaded so that they could be connected to produce a falling weight ranging from 50 to 500 gm. From a designated height, the weight falls through a 2-m vertical section of a transparent Plexiglas tube held in place with a ring stand. The helmet is a stainless-steel disc 10 mm in diameter and 3 mm thick. The contact side of the disc is grooved concentrically to accept acrylic and firm the contact.

**Induction of Head Trauma**

The scalp of the anesthetized animal was shaved, a midline incision was performed, and the periosteum covering the vertex was reflected. A stream of air was used to keep the area dry. The metallic disc was fixed to the central portion of the skull vault of the rat between the coronal and the lambdoid sutures (Fig. 1). The animal was placed in a prone position on a foam bed of known spring constant* contained within a Plexiglas frame (Fig. 2) and secured in place with two belts. The lower end of the Plexiglas tube was then positioned directly above the helmet. The injury was delivered by dropping the weight from a predetermined height. Rebound impact was prevented simply by sliding the Plexiglas box (foam bed) containing the animal away from the tube immediately following the initial impact. All animal protocols were reviewed and approved by an internal animal review board and were in compliance with guidelines set forth by the National Institutes of Health.

**Group 1 Study**

In Group 1, 54 adult Sprague-Dawley rats were anesthetized using methoxyflurane followed by intraperitoneal injections of alpha-chloralose (initial dose 90 mg/kg, maintenance dose 45 mg/kg). The animals were allowed to breathe spontaneously without tracheal intubation. The area of the inner thigh was shaved and the femoral artery was cannulated for blood pressure monitoring. Rectal body temperature was maintained at 37° ± 0.5°C using a heat lamp. Respiration and heart rate were also monitored and recorded on a strip chart. Following the procedure described before, two differ-

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* Type E bed manufactured by Foam to Size, Inc., Ashland, Virginia.
Diffuse brain injury model

![Diagram showing the basic configuration of the lumped parameter model.](image)

Fig. 3. Diagram showing the basic configuration of the lumped parameter model. The model incorporates two Kelvin solids (with mass components) in a series, representing the material properties of the foam and the rat's head with the helmet. There are six parameters in the model: the mass of the impactor, helmet, and skull (M_i) and of the foam (M_f); the stiffness of the rat's head (K_h: 696.200 N/m) and of the foam (K_f: 2500 N/m); and the mechanical impedance (viscous component) of the head (B_h: 20.40 kg/sec) and of the foam (B_f: 1.0 kg/sec).

ent impacts (450 gm and 500 gm from a height of 2 m) were used to determine the upper limit that would produce a mortality rate of approximately 50% with a low incidence of skull fracture. Having established this severe injury level, the height was reduced to 1 m, decreasing the energy delivery by 50% in order to induce a moderate head injury.

**Group 2 Study**

The 107 animals in Group 2 were anesthetized using isoflurane (1% to 2%) in a 33% oxygen-66% nitrous oxide mixture. The rats were surgically prepared for trauma as previously described for the Group 1 animals. Severe head injury was induced using the 450 gm-2 m weight-height impact. The animals in this group were subdivided into three subgroups: Group 2A, anesthetized via a mask without tracheal intubation and allowed to breathe spontaneously; Group 2B, intubated and allowed to breathe spontaneously; and Group 2C, intubated and mechanically ventilated during and after trauma. In addition, another two groups of animals were anesthetized using a mixture of halothane (1% to 2%) in a 2:1 mixture of nitrous oxide and oxygen in order to study the changes in blood gas levels after this type of head injury. In the first group (Group 2D), 25 animals were anesthetized via a mask; six were control rats, five underwent a 450 gm-1 m weight-height impact, and 14 suffered a 450 gm-2 m impact. The 13 rats in the second group (Group 2E) were intubated and mechanically ventilated during the entire procedure; six were control animals and seven underwent a 450 gm-2 m impact. The levels of pH, pO_2_, pCO_2_, and HCO_3_- in the blood were determined before impact and over a 2-hour period after trauma.

**Biomechanical Analysis**

A mathematical analysis of this simple weight-drop model was performed in order to estimate the acceleration, displacement, and compression gradient of the skull for various weight-height combinations. For this purpose, we elected to first model the impact-acceleration dynamics using a lumped parameter (spring-mass-dash pot) method. The basic configuration of the initial lumped parameter model (Fig. 3) incorporated two Kelvin solids (with mass components) in a series, representing the material properties of the foam and the rat's skull with the helmet. Although a more thorough mathematical analysis will be presented in a separate report, a brief description of the methods and results are presented here in the interest of completeness. For simplification, six physical parameters were considered: mass of head and foam, stiffness of head and foam, and the mechanical impedance (viscous component) of the head and foam. The final equations relating displacement, velocity, and acceleration were derived and a computer provided graphic solutions for the weight-height combinations used in the studies described above.

**Results**

**Group 1 Study**

**Mortality, Skull Fractures, and Trauma Level.** In pilot experiments, fracture was observed in the unprotected skull supported on foam at a mass of 100 gm and a drop height of 50 cm. With the steel helmet in place, a weight-height trauma level of 450 gm-2 m produced a mortality rate of 44% (seven of 16 rats). Of the 16 animals impacted at this injury level, skull fracture was observed in two nonsurvivors (12.5%). At the 500 gm-2 m impact level, 11 (69%) of the 16 rats died and five (31%) survived; skull fracture was observed in five (31%) of the nonsurvivors. Due to the high mortality and skull fracture rates associated with the 500 gm-2 m impact, the 450 gm-2 m impact was considered the upper limit for producing severe head trauma, and this weight-height combination was selected for subsequent studies. The 450 gm-1 m impact (50% of the upper limit for producing severe head trauma) caused no mortality and no skull fracture in the 22 animals tested. Table 1 summarizes the mortality rates and incidence of skull fractures related to the severity of impact.

**Respiratory Distress.** The nine animals surviving the 450 gm-2 m impact experienced apnea immediately after injury, with a reduction in respiratory rate of 20% for up to 30 minutes postinjury. Following this period, respiration in these animals gradually recovered and was not significantly different from that in the control rats by 2 hours postinjury. The seven animals impacted at the 450 gm-2 m level that did not survive experienced
vere hypotension; was allowed to occur until recovery. Respiration is irregular in nonsurvivors, death occurred in five rats a mean (± standard deviation) time of 4.2 ± 2.2 minutes postinjury; the other two rats died at 2 and 3 hours postinjury. The animals impacted at the 450 gm-1 m level also experienced a brief (5- to 10-second) apneic period but rapidly recovered to control respiratory rates.

Response of Blood Pressure. In survivors of the severe head injury (450 gm-2 m impact), the blood pressure increased from a mean preinjury level of 102 ± 16 mm Hg to a peak of 123 ± 37 mm Hg measured at 15 seconds after impact. This was immediately followed by a period of hypotension and gradual return toward normal by 30 minutes postimpact (Figs. 4 and 5). In nonsurvivors, the initial blood pressure profile was identical to that of survivors; however, more severe hypotension ensued without recovery.

The mild surge of blood pressure seen at severe head-injury levels was absent in mildly injured animals. The blood pressure of the animals subjected to the 450 gm-1 m impact decreased abruptly following trauma from a preinjury level of 104 ± 12 to 72 ± 18 mm Hg at 15 seconds after injury, and rapidly returned to control values within 2 minutes (Fig. 5).

Response of Heart Rate. In survivors of the severe head injury (450 gm-2 m impact), the heart rate decreased from a preinjury level of 321 ± 36 to 241 ± 61 beats/min by 1 minute postinjury. Thereafter, heart rate gradually returned toward the control level and was not significantly different from baseline by 10 minutes postinjury. In the five nonsurvivors of the 450 gm-2 m impact that died within the first few minutes of impact, marked bradycardia was observed and reached 50% of the control value by 2 minutes postinjury. This was followed by a gradual decrease in heart rate until

**TABLE 1**

<table>
<thead>
<tr>
<th>Impact</th>
<th>Anesthesia</th>
<th>Respiration</th>
<th>No. of Rats</th>
<th>Mortality Rate</th>
<th>Skull Fracture Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 gm-2 m</td>
<td>IP inj</td>
<td>non-intubated spontaneous</td>
<td>16</td>
<td>69.0%</td>
<td>31.0%</td>
</tr>
<tr>
<td>450 gm-2 m</td>
<td>IP inj</td>
<td>non-intubated spontaneous</td>
<td>16</td>
<td>44.0%</td>
<td>12.5%</td>
</tr>
<tr>
<td>450 gm-1 m</td>
<td>IP inj</td>
<td>non-intubated spontaneous</td>
<td>22</td>
<td>9%</td>
<td>0%</td>
</tr>
<tr>
<td>450 gm-2 m</td>
<td>inhalation</td>
<td>non-intubated spontaneous</td>
<td>58</td>
<td>58.6%</td>
<td>8.6%</td>
</tr>
<tr>
<td>450 gm-2 m</td>
<td>inhalation</td>
<td>intubated spontaneous</td>
<td>26</td>
<td>50.0%</td>
<td>3.8%</td>
</tr>
<tr>
<td>450 gm-2 m</td>
<td>inhalation</td>
<td>intubated mechanically assisted</td>
<td>23</td>
<td>8.7%</td>
<td>0%</td>
</tr>
</tbody>
</table>

* IP inj = intraperitoneal injection of alpha-chloralose; inhalation = inhalation of isoflurane.

Apneic lasting for up to 20 seconds immediately following impact, with a gradual slowing of respiration until death. Death occurred in five rats at a mean (± standard deviation) time of 4.2 ± 2.2 minutes postinjury; the other two rats died at 2 and 3 hours postinjury. The animals impacted at the 450 gm-1 m level also experienced a brief (5- to 10-second) apneic period but rapidly recovered to control respiratory rates.

Response of Blood Pressure. In survivors of the severe head injury (450 gm-2 m impact), the blood pressure increased from a mean preinjury level of 102 ± 16 mm Hg to a peak of 123 ± 37 mm Hg measured at 15 seconds after impact. This was immediately followed by a period of hypotension and gradual return toward normal by 30 minutes postimpact (Figs. 4 and 5). In nonsurvivors, the initial blood pressure profile was identical to that of survivors; however, more severe hypotension ensued without recovery.
TABLE 2
Blood gas changes in spontaneously breathing animals after mild and severe head injury*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Pretrauma</th>
<th>Posttrauma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 Min</td>
</tr>
<tr>
<td>pH</td>
<td>control</td>
<td>7.37 ± 0.06</td>
<td>7.37 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>mild injury</td>
<td>7.35 ± 0.03</td>
<td>7.35 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>severe injury</td>
<td>7.40 ± 0.01</td>
<td>7.34 ± 0.04</td>
</tr>
<tr>
<td>pO2</td>
<td>control</td>
<td>161.8 ± 12.7</td>
<td>152.8 ± 7.5</td>
</tr>
<tr>
<td></td>
<td>mild injury</td>
<td>170.4 ± 10.0</td>
<td>156.2 ± 7.0</td>
</tr>
<tr>
<td></td>
<td>severe injury</td>
<td>169.4 ± 12.7</td>
<td>147.4 ± 23.9</td>
</tr>
<tr>
<td>pCO2</td>
<td>control</td>
<td>48.9 ± 4.3</td>
<td>47.8 ± 4.4</td>
</tr>
<tr>
<td></td>
<td>mild injury</td>
<td>51.2 ± 6.0</td>
<td>49.3 ± 6.7</td>
</tr>
<tr>
<td></td>
<td>severe injury</td>
<td>47.7 ± 3.3</td>
<td>53.0 ± 4.0</td>
</tr>
<tr>
<td>HCO3−</td>
<td>control</td>
<td>32.3 ± 2.0</td>
<td>28.9 ± 4.7</td>
</tr>
<tr>
<td></td>
<td>mild injury</td>
<td>28.0 ± 3.7</td>
<td>27.0 ± 2.9</td>
</tr>
<tr>
<td></td>
<td>severe injury</td>
<td>29.0 ± 1.8</td>
<td>28.5 ± 1.7</td>
</tr>
</tbody>
</table>

* Mild injury = 450 gm-1 m impact; severe injury = 450 gm-2 m impact. Values are mean ± standard deviation. Statistical significance of difference: † = p = 0.007; ‡ = p = 0.044.

death. In the two animals that died within a few hours, there was an increase in heart rate from a preinjury level of 323 ± 47 to 450 to 480 beats/min, and this tachycardia was sustained until death. In animals subjected to the 450 gm-1 m trauma, there was no significant change in heart rate from preinjury baseline levels.

Response of Blood Gases. In Group 2D (spontaneously breathing) rats, all control and mildly head-injured (450 gm-1 m impact) animals survived, while only six of 14 severely head-injured (450 gm-2 m impact) animals survived the trauma. Changes in blood gas levels after mild head trauma were similar to those in control animals (Table 2). However, a progressive increase in pCO2 levels was observed in the survivors of severe head injury (p < 0.05). In the four animals that died within 7 to 10 minutes after severe trauma (450 gm-2 m impact), pCO2 dramatically increased and pO2 decreased 5 minutes after impact (Table 3). In contrast, all severely head-injured animals in the mechanically ventilated group (Group 2E) survived the trauma, and the blood gas changes in this group were similar to those in the control rats (Table 4).

Neurological Response

In addition to the apnea experienced immediately after injury, the animals exposed to the 450 gm-2 m impact developed severe generalized convulsions lasting

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**TABLE 3**
Blood gas changes in spontaneously breathing animals that died 7 to 10 minutes after severe head trauma*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Pretrauma</th>
<th>5 Min Posttrauma</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of rats</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.41 ± 0.022</td>
<td>7.11 ± 0.062</td>
<td></td>
</tr>
<tr>
<td>pO2</td>
<td>182.5 ± 17.99</td>
<td>34.03 ± 12.93</td>
<td></td>
</tr>
<tr>
<td>pCO2</td>
<td>44.78 ± 2.89</td>
<td>90.98 ± 10.14</td>
<td></td>
</tr>
<tr>
<td>HCO3−*</td>
<td>28.2 ± 0.86</td>
<td>28.8 ± 2.41</td>
<td></td>
</tr>
</tbody>
</table>

* Severe trauma = 450 gm-2 m impact. Values are mean ± standard deviation.

**TABLE 4**
Changes in blood gas levels in the mechanically ventilated animals following severe head trauma*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Pretrauma</th>
<th>Posttrauma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>15 Min</td>
</tr>
<tr>
<td>pH</td>
<td>control</td>
<td>7.45 ± 0.007</td>
<td>7.43 ± 0.008</td>
</tr>
<tr>
<td></td>
<td>severe injury</td>
<td>7.46 ± 0.012</td>
<td>7.43 ± 0.025</td>
</tr>
<tr>
<td>pO2</td>
<td>control</td>
<td>133.5 ± 2.96</td>
<td>127.7 ± 3.9</td>
</tr>
<tr>
<td></td>
<td>severe injury</td>
<td>134.5 ± 4.8</td>
<td>114.2 ± 9.3</td>
</tr>
<tr>
<td>pCO2</td>
<td>control</td>
<td>35.7 ± 1.2</td>
<td>36.5 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>severe injury</td>
<td>34.6 ± 1.4</td>
<td>37.7 ± 3.2</td>
</tr>
</tbody>
</table>

* Severe trauma = 450 gm-2 m impact. Values are mean ± standard deviation.

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**FIG. 5.** Graph showing blood pressure (BP) response following mild (450 gm-1 m) and severe (450 gm-2 m) head injury. In the severely head-injured animals (open circles), a moderate transient elevation in blood pressure is followed by a hypotensive period prior to baseline return. The hypertensive surge is not seen in animals with mild head injury (closed circles) or in control rats (diamonds).
15 to 30 seconds; those seizures were confined to the immediate postinjury period. Survivors in this group as well as the mildly head-injured animals developed decortication flexion deformity of the forelimbs. Seizures in the animals subjected to the 450 gm-1 m injury were less frequent, less severe, and lasted for only several seconds.

**Group 2 Study**

**Mortality and Respiratory Support.** Table 1 summarizes the changes in the mortality rate and the incidence of skull fracture related to the severity of impact and the type of respiration employed during and after the impact. In the 58 non-intubated spontaneously breathing animals (Group 2A), an impact of 450 gm-2 m resulted in death in 34 animals (58.6%). Five nonsurvivors (8.6%) had evidence of skull fracture. Thirty-one animals died within a few minutes following impact and three died after prolonged behavioral suppression lasting for up to 3 hours. All animals that suffered a 450 gm-2 m impact had a 10- to 20-second period of apnea associated with severe generalized convulsions for 15 to 30 seconds. In Group 2B (intubated nonventilated) animals, 26 rats were impacted at the 450 gm-2 m level. A total of 13 (50%) survived and 13 (50%) died, with only one (3.8%) of the non-survivors found to have a skull fracture. In the 23 Group 2C (intubated and mechanically ventilated) rats, all animals survived the 450 gm-2 m impact except for two animals with skull fracture (8.7%).

Electroencephalographic (EEG) studies in the animals that survived the 450 gm-2 m impact showed the development of cortical paroxysmal discharges for 40 to 60 seconds after impact, followed by a depression in the electrical activity of the brain for 10 minutes. The EEG recordings gradually returned to the preimpact control level by 30 minutes postimpact.

**Biomechanical Analysis**

**Skull Acceleration.** Since the force from the spring acts on both masses in proportion to their relative displacement and the damper yields a force on each mass proportional to its relative velocity, the following differential equations are found:

\[
M_1 \ddot{x}_1 + B_1 (x_1 - x_2) + K_1 (x_1 - x_2) = 0, \tag{1}
\]

\[
M_2 \ddot{x}_2 + B_2 \dot{x}_2 + B_1 (x_2 - x_1) + K_2 x_2 + K_1 (x_2 - x_1) = 0, \tag{2}
\]

where \( M_1 \) = mass of impactor, helmet, and skull, \( M_2 \) = mass of the foam, \( x_1 \) = position of top surface of the rat's head, \( x_2 \) = position of bottom surface of the rat's head, \( K_1 \) = stiffness of the rat's head (696,200 N/m), and \( K_2 \) = stiffness of the foam (2500 N/m); prime and double-prime symbols represent first and second derivative, respectively. The temporal course of acceleration corresponding to the 450 gm-2 m and 450 gm-1 m injuries is shown in Fig. 6. The results indicate that a peak acceleration of 900 G (1 G = 980 radians/sec/sec) was formed by the 2-m injury at the instant of impact, then rapidly dissipated within 0.20 msec. The 1-m injury produced a 630-G acceleration, with a similar pattern of decline.

**Estimated Magnitude of Skull Compression.** The computer results indicated that the skull is depressed upon impact and, since the foam has negligible resistance to acceleration, the base of the skull continues to descend without being compressed significantly. Ac-
Diffuse brain injury model

cording to the model, virtually all compression is the result of displacement of the vertex. Both the impactor and the skull descend in unison for a period equal to the time of contact between the impactor and the skull. The contact duration was determined by establishing a small electrical potential between electrodes connected to the impactor and the skull and measuring the electrical current on an oscilloscope; the time of contact was found to be 40 msec. On inserting these data into the model, the impactor continues to descend with the skull for approximately one-half the contact duration. At the 20-msec time point (one-half the contact duration) compression is at a maximum (Fig. 7). Following this cycle, the impactor and the skull move upward together, returning to zero displacement. When the impactor and the skull change direction and ascend, the acceleration is in the opposite direction and the skull base moves faster than the vertex, thereby exposing the brain surface opposite the impact site to a high acceleration gradient. Experimentally, multiple contact was eliminated by simply moving the rat from under the cylinder while the impactor was ascending. This simplified the model considerably. Based on this analysis, the skull undergoes a maximum compression of 0.28 mm for the 450 gm-2 m injury and 0.20 mm for the 450 gm-1 m injury.

Discussion

This report describes the development of a simple, reproducible, and practical model of rodent closed head injury that has certain advantages over other models. First, a lethal level of closed head injury can be achieved without predominant brain-stem damage as seen with direct dural impact. Second, at lethal levels, the transient rise in blood pressure seen in closed head injury immediately postimpact is mild and does not reach levels consistent with breakthrough of cerebral blood flow autoregulation or blood-brain barrier compromise. Thus, the effect of trauma in the absence of posttraumatic hypertension can be isolated. Third, data from our companion paper show that the model produces a pronounced diffuse axonal injury consistent with the features of human diffuse axonal injury described by Adams, et al. Finally, posttraumatic ventriculomegaly is observed in survivors of severe closed head injury at 4 to 6 weeks postinjury (unpublished data), which also mirrors the experience in human head injury.

Closed Head Injury in the Rat

Over the past 20 years, numerous investigators have studied the response of the rat to experimental closed head injury. In a study of head injury by Beckman and Bean, the heads of hand-held, nonanesthetized rats cushioned with a sponge rubber were impacted with a bolt. In those animals that did not survive the impact injury, the heart rate was found to decrease significantly, cases of pulmonary edema were noticeably more severe, lung weight:body weight ratios were significantly higher, and contusions, subarachnoid hemorrage (SAH), and subdural hemorrhage were frequently found in the brain. Hand-held rats were impacted with padded darts from a pistol in a study by West, et al., investigating concussion and EEG response. One-third of the rats displayed severe concussion with impairment of consciousness and apnea, associated with depressed EEG amplitudes lasting until recovery approximately 2 hours after impact. Huger and Patrick injured rats using a hinge-drop impact mechanism. Hypterventilation, convulsions, and SAH were noted effects of concussion. Although tyrosine and dopamine levels and synthesis rates were increased in the traumatized rats, there was no significant difference between the effects in traumatized rats and in those undergoing a sham drop, suggesting that catecholamine level changes were due to stress in the nonanesthetized animals.

A similar study on the effects of closed head injury in which mice were impacted with a sliding bolt striking the immobilized head was conducted by Nelson, et al. However, unlike the previous three studies mentioned in which constant amounts of energy were imparted to the rats' heads, the experiment by Nelson and coworkers included an adjustable impactor for the purpose of producing graded trauma. Shapira, et al., introduced another model for closed head injury in rats using a weight-drop impact to one side of the unprotected skull. This model produced an ipsilateral focal brain contusion and a blood pressure rise for more than 10 minutes posttrauma, and thus would be suitable for studying the focal but not the diffuse forms of brain injury.

In our study, the cortical paroxysmal discharges observed in the EEG recordings of severely head-injured animals during the first minute after impact correlate with the severe generalized convulsion observed in those animals immediately after trauma. On the other hand, the subsequent depression in EEG amplitude would explain the delayed recovery from anesthesia in these animals, which was prolonged compared to the recovery in control rats.

Fracture Threshold of the Rodent Skull

Studies by Nilsson and colleagues were directed toward an investigation into the physiological response of closed head injury in the rat. A piston accelerated by compressed gas was used to impact the supine rat in the region of the occipital protuberance. The velocity of the piston at impact was adjustable, thereby eliciting concussion (defined as the loss of reaction to pain stimuli) of variable severity: at 6 m/sec, no concussion resulted; at 9 m/sec, the concussive interval lasted for 3 to 10 minutes; and at 10 m/sec, the rats were comatose for long periods. The mortality rate was similarly related to impact velocity, ranging from 10% (two of 20 rats) at 7 m/sec to 67% (four of six rats) at 11 m/sec. Gross pathological examination revealed SAH in the occipital cistern at the velocity corresponding to concussion threshold (7 m/sec), with more extensive brain-stem hemorrhage at higher velocities. However, these
studies as well as those by Bakay, et al.,7 in which a pendulum device was used to cause concussion, found thin linear fractures at moderate concussion levels (9 m/sec) and shattering fractures at impactor velocities causing greater than 50% mortality. The rodent skull at the vertex is extremely thin and almost transparent. Thus, the ability to produce concussive closed head injury without fracture was the first objective of this study. Our results show that the protection offered by the stainless-steel helmet was sufficient to prevent fracture and achieve high kinetic energy levels at impact delivery. The impact and resultant high transient acceleration was sufficient to produce a severe brain injury without extensive brain-stem damage. Of interest was the fact that the acceleration in this model was confined generally to the sagittal plane. A distinction between rotational and translational acceleration has been made in at least one biological model28,23 in which it was found that visible brain lesions resulted from injuries caused by both translation and rotational acceleration, with a greater frequency and severity after rotation. The development of a rodent acceleration model, similar to that used by the Gennarelli group,6 is extremely difficult because of the relatively small brain mass of the rodent (2 gm). Levels of acceleration necessary to produce diffuse axonal injury by acceleration alone would be excessively high. From studies of diffuse axonal injury produced by our model, it appears that this is overcome with the combination impact.

Effect of Impact

A considerable effort was made in the preliminary stages of development of this model to select the optimum support for the rodent skull. We selected a foam of known spring constant based on the following consideration: dynamic loading of the head can be divided into impact and inertial effects, the former associated with the generation of transient stress waves in the tissue and skull and the latter with differential acceleration of tissue (regional gradients) and skull. Thus, the degree to which head motion is restricted is of chief importance in determining the relative contribution of impact and inertial components in head trauma.6 That is, when an impactor strikes the head, the compression effects and associated “contact phenomena” are most damaging whereas, if the head is free to move following impact, the shear forces between tissues are predominant. The size of the impactor relative to the skull is also important in determining the relative importance of contact and acceleration effects. A small high-velocity object causes the head to move very little and thus its kinetic energy is dissipated primarily through contact phenomena, while a large, blunt object primarily acts to accelerate the head with minimum contact effects.6 For this reason, we focused our experiment in the 400- to 500-gm weight range, and selected foam to provide reasonable support while allowing the head to accelerate.

Absence of Posttraumatic Hypertension in Rodent Closed Head Injury

Of importance is the response of blood pressure immediately following impact (Fig. 5). The fluid-percussion model and others involving direct dural impact result in a significant hypertension produced immediately following injury. With fluid percussion, blood pressure exceeds 180 mm Hg and does not recover for several minutes.31 This results in pressure breakthrough, loss of autoregulation, and a dramatic increase in cerebral blood flow.3 In contrast, closed head injury in the rat results in only a small elevation of blood pressure with hypotension developing within 1 minute of impact. Thus, as hypertension is not a feature of rodent closed head injury, it allows the investigator to isolate more clearly the effects of trauma upon barrier function and autoregulation.

Respiratory Depression in Closed Head Injury

We attribute the major cause of death due to impact to respiratory depression followed by an ensuing hypotension. Posttraumatic apnea and respiratory depression are observations consistently seen in both clinical and experimental head injury.20,26,27,31 In our experimental studies of spontaneously breathing animals, impact was immediately followed by apnea lasting for up to 20 seconds and a gradual slowing of respiration. In these animals, death occurred within minutes of impact as a result of severe hypoxia and hypercapnia. Tracheal intubation alone did not improve the mortality rate in these animals (Group 2B). When animals were intubated and mechanically ventilated during and for a few minutes after impact, the mortality rate decreased from more than 50% to less than 10%. These observations and those reported by others26 suggest a central rather than a peripheral mechanism accounting for this respiratory depression. The transient apnea may be explained by the transient changes in brain-stem auditory evoked potentials (BAEP’s) demonstrated by van den Brink, et al.28 In these studies, although BAEP’s remained intact, wave IV was less consistent in the severely injured rats than in the mildly injured or the control animals. Thus, we suspect that the respiratory depression seen in animals without respiratory support is caused by a transient brain-stem physiological dysfunction that can be overcome with mechanical ventilation. These results emphasize the need for early respiratory support in severely head-injured patients.

Mathematical Analysis of the Weight-Drop Model

One advantage of mathematical models is the ability to predict the kinetic energy transfer and acceleration profiles for different weight-height combinations, as demonstrated in this report. Previous models of impact acceleration injury have considered various methods through which the kinetic energy of the impacting device may be lost or transformed into injury-causing forces. One such model characterizes the uniaxial impact of a material with mechanical properties described in terms of ideal elastic, viscous, and inertial elements,
Diffuse brain injury model

that is, the spring, dash pot, and mass, respectively. This type of model is expressed mathematically in terms of a set of linear ordinary differential equations, thus resulting in solutions that are relatively simple to implement. However, the disadvantage of the lumped parameter model is that it cannot reveal the time history of stresses and strains occurring within the material. Models that describe the energy transformation more specifically (as a combination of deformation, stress, and pressure wave propagation, and contact phenomena throughout the head) are, for certain idealized geometries, able to predict the distribution of strains within the system.

As a starting point in our analysis, we elected to model the impact-acceleration system using the lumped parameter (spring-mass-dash pot) method. Our objective was to utilize this model to describe “whole head” motion. Based upon several simple measurements of the impact dynamics of our model and the relationship between loading duration and the comparative extent to which impact and impulse effects contribute to a given head injury, we believe that the inherent limitation of the spring-dash pot model may be mitigated in the context of our model. As described by Ommaya and Gennarelli,24 the impact component of dynamic loading is associated with skull bending or fracture and the propagation of shock waves through skull and tissue. The impulse component of dynamic loading, on the other hand, consists of “whole head” motion in either translational or rotational directions. Although the impact and impulse components of head injury are both ultimately manifested as tissue strains (shear, tensile, or compressive), it is known that, as the impact duration increases, the relative amount of tissue strain due to impact effects decreases and the tissue strain due to impulse effects increases. More extensive studies of contact duration are necessary to resolve the degree to which impact effects predominate.

Conclusions

A new practical and simple model of head injury in the rat has been developed with several features similar to the experience in the clinical setting. It is hoped that with continued investigation this model will contribute to our understanding of human head injury.

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