Appendix B  

Publications arising from this thesis


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BIOMECHANICS OF A SHEEP MODEL OF AXONAL INJURY

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ABSTRACT
The aim of this project was to investigate the feasibility of using an animal model of axonal injury to study the biomechanics of the injury. The model utilises anaesthetised sheep that are mechanically ventilated and stabilised before being subjected to a single lateral impact from a captive bolt gun. The impact force was measured using a load cell mounted in the striker, and the resulting head acceleration was measured by means of a 9-accelerometer array which was rigidly mounted to the head of the sheep. Head kinematics were transformed to anatomical co-ordinates using stereo-radiography. High speed cine film (1000 fps) was used for the visualisation of gross head motion. After impact, each animal was allowed to survive for a predetermined period during which anaesthesia was maintained. A complement of physiological monitors was used to measure the physiological state of the animal at all times during the experiment. In one experiment, hypoxia was induced after the physical insult. After the survival period, the animal was sacrificed and the brain removed for histological processing. The brain was sectioned, processed and examined for axonal injury using the presence of amyloid precursor protein (APP) as an indicator of injury. The distribution of axonal injury in serial sections of the brain was mapped and quantified. Five experiments, displaying a range of injury responses, are reported on in this paper. In the future, the model will be used to study the biomechanics of axonal injury.

All experiments conform to the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes.

AMONG PERSONS SUSTAINING A HEAD INJURY, axonal injury is a major cause of mortality and morbidity (Gennarelli, 1984). There is evidence that it occurs across the spectrum of head injury severity (Blumbergs et al., 1994). Yet it remains unclear to what extent different mechanical parameters contribute to the incidence of axonal injury, and how post impact physiological changes relate to the eventual severity of axonal injury.

There have been many biological studies which have correlated the incidence of ‘diffuse type’ brain injuries (which includes axonal injury) with loading parameters. These types of studies have included isolated tissue studies, studies of single tracts of axons, direct percussion of the brains of small animals, and inertial loading of the head of larger animals. Animal models have the advantage that they are more likely to be better physiological representations of the human brain that isolated axon preparations. Isolated tissue studies are usually more simple to model biomechanically, however.

Several investigators have used utilised single axons or single bundles of axons to study the response of the axon to loading. These studies have shown that direct mechanical loading of axons can lead to physiological changes in the cell such as rises in intracellular calcium (Saatman and Thibault, 1991) and increased rate of glucose metabolism (Gennarelli et al., 1989). Such models have also produced clear evidence that applied loads that are less than that required to cause primary axotomy may result in marked histological changes (Gennarelli et al., 1989). If brain tissue deformation can produce

Presented at the 1997 International IRCOBI Conference on the biomechanics of impact, September 24-26, 1997, Hannover, Germany
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marked physiological as well as histological changes, it is important that animal models of axonal injury include monitoring and control of the animal’s pre- and post-impact physiology. Any physiological effects on the nature and extent of the resulting injury may then be measured and normalised.

Percussion and direct cortical impact models are animal models in which the cortex of the brain of the living animal is subjected to a pressure pulse, usually through a craniectomy. Insofar as they have been used for biomechanical analyses, these types of models have generally been used as part of an effort to study the injury response of brain tissue subjected to deformation (Ueno et al., 1991; Ueno et al., 1996; Meaney et al., 1994a).

Early studies using large animal models examined the relationship between the qualitative characteristics of inertial loading of the head, and the resulting ‘diffuse’ injury (Hirsch and Ommaya, 1970; Ommaya and Hirsch, 1971) or axonal injury (Gennarelli et al., 1982; Gennarelli et al., 1987). In some of these studies, axonal injury was not observed directly, but was inferred from other observations such as the duration of traumatic coma. More recent animal studies have examined the relationship between the kinematic parameters, the tissue level strains and the incidence of axonal injury (Margulies et al., 1990; Mends, 1992; Meaney et al., 1993; Meaney et al., 1994b; Meaney et al., 1996; Miller et al., 1996). Studies designed to examine brain tissue deformation have often used some form of numerical and/or physical modelling to estimate levels of strain. Some attempts have been made to compare the estimates of tissue strain and the resulting injury in the animal (Ueno et al., 1996; Meaney et al., 1994b). Early animal models used primates to maintain some anatomical fidelity with humans, and scaling laws were derived in an attempt to relate the results to human beings (see for example Ommaya et al., 1966; Ljung, 1980). However, advances in numerical modelling have meant that estimates of injury tolerance can now be made at the tissue level and have allowed other species to be used.

Several recent investigations have shown promising results in correlating the incidence of axonal injury with kinematic data and the estimated levels of strain in the brains of animals subjected to rapid dynamic loading. Meaney (1994b) used a physical model simulation of experiments in which a pig’s head was subjected to a coronal plane angular acceleration. They found that by incorporating the direction of axon bundles in the pig brain, to formulate what they described as a level of ‘oriented strain’, they were able to predict the incidence of injury in the animal to a reasonable degree. Analysing the same animal experiments, (Miller et al., 1996) quantified the extent and the severity of axonal injury. They were able to correlate the proportion of the tissue injured in certain regions of the brain with the peak angular acceleration and the maximum change in angular velocity.

New animal models of axonal injury are still required, even though the study of diffuse type brain injuries in living animals has been taking place for more than 30 years. Advances in kinematic measurement techniques, numerical modelling techniques, and the use of previously unavailable histological methods, have greatly enhanced the ability of researchers to investigate the mechanisms of axonal injury.

There has been no attempt thus far to examine the relationship between dynamic parameters and the severity and distribution of axonal injury in a large animal subjected to a concentrated impact loading to the head. In a study of real life traffic accidents, brain injury without some form of head contact was not seen (McLean, 1996). Any added effects of post impact physiology on the severity and distribution of axonal injury has also not been satisfactorily addressed in previous animal models. The development of the animal model presented in this paper was prompted, in part, by the paucity of information about the influence of these factors on the resulting injury.

AIM

The aim of this study is to examine the feasibility of developing a controlled and reproducible model of axonal injury due to impact loading of the head. The model will be used to study the biomechanics of axonal injury and the effect of post impact hypoxia on the extent and nature of the injury. This paper reports on the biomechanical development of the model, and presents the results of five experiments. In the last experiment, an attempt was made to impose a period of hypoxia upon the sheep after the impact.
EXPERIMENTAL PROTOCOL

Each experiment took place over three days; the first day was used to prepare the animal by implanting a sagittal sinus Doppler crystal for blood flow measurements. The head impact part of the experiment was performed after two days to allow the crystal to become adherent to the dural surface.

DAY ONE PROTOCOL - A two year old merino ewe was induced into anaesthesia with thiopental (15 mg/kg), and intubated. Anaesthesia was then maintained with 2 per cent isofluorane in 50 per cent oxygen and 50 per cent nitrogen, delivered via an endotracheal tube and controlled mechanical ventilation.

A craniotomy was performed and a Doppler crystal to measure blood flow was positioned over the superior sagittal sinus. The craniotomy was close and the isofluorane was withdrawn. Prior to the end of the procedure 1.5 ml of Finadyne was given for analgesia.

DAY THREE PROTOCOL - Anaesthesia was induced with diazepam (1 mg/kg), and ketamine, (4 mg/kg). The animal was then intubated. The animal was mechanically ventilated under isofluorane (2 per cent), until a ketamine intravenous line was established. The animal was ventilated with 100 per cent oxygen (3 l/min), until blood gases could be verified. Anaesthesia was maintained by an intravenous infusion of a ketamine/saline solution (15 mg/kg/hr) and isofluorane (1 per cent). Blood gas samples were taken at 10 minute intervals for the duration of the experiment. Ventilation was adjusted to maintain a target of 40 mmHg PaCO2 and a target of 110 ± 10 mmHg PaO2 (core temperature corrected values). Physiological parameters were digitally recorded throughout the experiment. The parameters monitored were cerebral blood flow (CBF), central venous pressure (CVP), arterial blood pressure (ABP), sagittal plane electrocardiogram (ECG), intracranial pressure (ICP), core temperature and fluid balance.

The accelerometer array was attached rigidly to the skull of the animal as described in the next section. The muzzle of a captive bolt gun was positioned so that the striker would predominantly contact the parietal bone and to a lesser extent the temporal bone (see Figure 1).

Once all physiological parameters were stabilised within tolerance limits, a 30 minute baseline period was commenced.

At the end of the baseline period an impact sequence was initiated. The captive bolt gun was fired and the resulting motion of the head was recorded on high speed film (HyCam, 1000 fps). All biomechanical measurements were captured via an A/D card installed in a digital computer. The animal was then repositioned, and the endotracheal tube reconnected immediately. Anaesthetic was continued for a further 2 to 4 hours and all physiological parameters were continuously monitored during this period.

In the last experiment, a period of hypoxia was imposed. The oxygen supply was altered so that the animal’s PaO2 was reduced to 15 mmHg for 15 minutes. During this period, blood gases were measured every two and a half minutes. After 15 minutes the oxygen supply and PaO2 were returned to normal target values.

At the end of the survival period each animal was sacrificed by perfusion fixation with 4
per cent para-formaldehyde. The skull was opened using a craniotome and the brain was removed. The brain was then placed in 4 per cent para-formaldehyde for two weeks.

The head was removed from the animal and the skull stripped of soft tissue using an enzyme solution. The skull was examined for fracture and stereo-radiographed in order to determine parameters for the subsequent biomechanical analysis.

BIOMECHANICAL MEASUREMENTS

CAPTIVE BOLT GUN - The impacts were delivered to the sheep’s head using a modified Schermer MKL captive bolt gun which can be mounted on a rigid frame. The modified captive bolt gun assembly is shown in Figure 2. The striker is powered by the expanding gases generated when a cartridge is detonated in the cartridge chamber. The striker is guided before striking the animal.

The gun was modified so that the dynamics of the striker could be measured; the impact force by a load cell mounted in the striker, and the relative striker velocity by an array of Hall-effect switches mounted in the muzzle. Four different charge strengths are available (“11”, “13”, “17” and “21”), allowing a range of striker velocities. Two versions of the striker were built and tested; the first is shown in the lower half of Figure 2 and the second, shown mounted in the captive bolt gun. The main difference between these two strikers was their mass. Both strikers present a domed surface of about 50 mm diameter.

In the initial experiments reported on here, the captive bolt gun was mounted on a rigid frame to minimise recoil velocity during firing. In later experiments the gun was hand held.

ACCELERATION MEASUREMENTS - An array of nine accelerometers may be so arranged so that the calculation of angular acceleration about each of the body-fixed axes at each time point is independent of any previous time points. This nine accelerometer array formation has been discussed extensively elsewhere (Padgaonkar et al., 1975; Mital and King, 1979; Alem and Holstein, 1977; Melvin and Shee, 1989; Boghani et al., 1989). The equations for the angular acceleration of such an array are:

\[
\dot{\omega}_x = \frac{(\ddot{z}_1 - \ddot{z}_0)}{2\rho_1} - \frac{(\ddot{y}_1 - \ddot{y}_0)}{2\rho_3}
\]

\[
\dot{\omega}_y = \frac{(\ddot{x}_1 - \ddot{x}_0)}{2\rho_3} - \frac{(\ddot{z}_1 - \ddot{z}_0)}{2\rho_2}
\]

\[
\dot{\omega}_z = \frac{(\ddot{y}_1 - \ddot{y}_0)}{2\rho_2} - \frac{(\ddot{x}_1 - \ddot{x}_0)}{2\rho_1}
\]

(Padgaonkar et al., 1975), where the symbol \(\rho\) denotes the array arm lengths, and the other variables denote acceleration measured at individual accelerometers within the array (see Figure 3). An accelerometer array that utilises the system of the above equations to measure rigid body motion was designed and built for this study (see Figure 3). The array base was milled from a solid block of aluminium, and nine piezo-electric accelerometers (Brüel & Kjær type 4901) were mounted on the base to measure the required accelerations. These accelerometers operate in the range 0.1 Hz-16 kHz making
them suitable for the measurement of the short impulsive accelerations experienced by the animals in this study.

COMPENSATION FOR NON-IDEAL ACCELEROMETER ARRAY CHARACTERISTICS - In the array configuration presented above, the seismic centres of the accelerometers are offset from the principal axes of the array. This is associated with a measurement error due to the centripetal accelerations experienced by accelerometers that have their sensitive axis perpendicular to, and displaced from the axis of rotation (DiMasi, 1995). This, in addition to the cross axis sensitivity, bias and placement errors of the accelerometers, is likely to add spurious components to the measurement of the actual acceleration of the array. The techniques for the calibration of this type of array have been discussed extensively by others (Boghani et al., 1989; DiMasi, 1995; Plank et al., 1989). For the accelerometer array presented above, many of the required compensation coefficients theoretically reduce to zero because each accelerometer's sensitive axis lies in one of the planes formed by the axes of the array. This means that there is effectively no misalignment of accelerometers insofar as the calculation of angular acceleration is concerned. Theoretically, the only compensation required is that for the linear acceleration measured at the origin of the array.

ACCELEROMETER ARRAY ATTACHMENT - A mounting system for the accelerometer array was manufactured such that the array could be rigidly attached to the sheep's head. The design allowed the plate to be reattached after the experiment when the skull of the animal had been cleaned, so that the relative position of the array with respect to the sheep's bony anatomy could be determined.

The mounting plate consists of a 3 mm plate of aluminium which extends over the cornual processes of the sheep skull. The plate extends forward and down, through a bend of 45˚, over the frontal bone (see Figures 1 and 4). Two dowels are incorporated into the plate to facilitate accurate alignment of the accelerometer array with the plate [RWG1].

The mounting plate underwent a series of modifications throughout the study, in an attempt to make the array to skull attachment as stiff as possible. These modifications included the removal of spacers, the inclusion of more screws and bone reinforcing.

TRANSFORMATION OF MEASURED ACCELERATIONS TO AN ANATOMICAL VECTOR BASE - The calculated accelerations were measured with respect to the array coordinate system. Anatomical coordinate systems were defined for each animal so that the experimental results were comparable, and so that they will be able to be more readily applied to a finite element model in the future.

To express the acceleration of the head in terms of a consistent anatomical coordinate system, the vector transformation between the array coordinate system and the anatomical coordinate system had to be determined for each experiment. This was achieved by attaching radio opaque markers and taking two orthogonal x-ray images of
the skull and array base plate, to define the relative orientation of the array and the skull. In summary, the technique to do this involved:

- the definition of an anatomical coordinate system by attaching radio opaque markers to conveniently chosen anatomical landmarks on the skull,
- the definition of the instrumentation coordinate system by the use of radio opaque markers,
- the use of stereo-radiography to measure the location of the above markers in the laboratory space,
- from these measurements, the derivation of a mathematical transformation that allows a vector defined in the instrumentation base to be defined in the anatomical base.

This transformation was then used to estimate the acceleration of the anatomical base from the array measurements. Similar techniques are described by Becker (1977) and Nusholtz et al., (1979).

This procedure was performed in vivo before the impact in the first two experiments. For the subsequent experiments, the procedure was performed in vitro, after the skull was removed and cleaned. The advantage of performing the procedure before the impact is that the plate does not have to be reattached after the experiment, minimising any realignment error. The disadvantage is that accurate marker placement on the anatomy in vivo is more difficult than placement in vitro. Another advantage of performing the procedure in vitro is that many more marker sites are available, with the whole bony anatomy exposed. The imaging is also more accurate, with less chance of the subject moving between exposures. For these reasons the in vitro procedure is preferable.

DATA ACQUISITION AND POST PROCESSING - All kinematic data was captured using an A/D expansion card and a simple acquisition program on a PC. These signals were then post-processed to calculate the force and acceleration histories.

NEUROPATHOLOGY

To assess the degree of axonal damage, a survey of axonal lesions was undertaken in each case and the distribution of axonal lesions, as defined by the presence of axonal amyloid precursor protein (APP), was mapped.

After the brain of the animal was completely fixed, it was cut into at least sixteen 5 mm coronal slices. Each slice was embedded in paraffin wax and five micron sections were cut and prepared for examination using standard H & E staining & anti-APP immuno-staining. Once stained, the brain sections were examined using light microscopy. A transparent grid of 4 mm squares was placed over the slide during microscopic examination. The coordinates of the APP positive squares were recorded.
At the time of writing, a simple quantification of the maps of the distribution of axonal injury has been performed. This method has been described previously by Miller et al. (1996). They used a grid to map the lesions on seven representative sections of the brain. They defined the Total Injury Score (TIS) as the number of positive grid squares in the seven representative sections. In the present study, the same score was used, except that in this study the size of each grid square was larger, and more sections (16) were examined. For this reason the TIS in Miller et al.’s study and the TIS in this study are not comparable. By dividing the TIS by the total number of squares which was required to cover all 16 sections of each brain, an estimate was made of the percentage of the brain injured in each animal.

RESULTS

Five experiments were performed as described above. The first two used the initial striker design and were allowed to survive for two hours. It was decided after this that a longer survival time would allow the observable characteristics of the axonal injury to develop more fully. In the final three experiments the survival time was increased to four hours. In the last experiment, a period of hypoxia was imposed on the animal, shortly after the impact. The animal did not survive this period, however.

FORCE AND KINEMATIC RESULTS - Measured kinematic data for each experiment are summarised in Table 2. The impacts were characterised by measured angular accelerations of up to 126 krad/s\(^2\) and linear accelerations of up to 16 km/s\(^2\). Impact force measurements were between 6.2 and 8.0 kN, and caused fracture in two cases. In addition to this data, high speed film was taken of all impacts.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Striker mass</th>
<th>Charge</th>
<th>F</th>
<th>Head kinematics</th>
<th>Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>g</td>
<td>kN</td>
<td>krad(^2)</td>
<td>km/s(^2)</td>
<td>rads(^1)</td>
</tr>
<tr>
<td>Sheep 1</td>
<td>654</td>
<td>‘13’</td>
<td>6.2</td>
<td>103</td>
<td>6.7</td>
</tr>
<tr>
<td>Sheep 2</td>
<td>654</td>
<td>‘17’</td>
<td>8.5</td>
<td>99</td>
<td>7.0</td>
</tr>
<tr>
<td>Sheep 3</td>
<td>385</td>
<td>‘21’</td>
<td>6.6</td>
<td>95</td>
<td>6.6</td>
</tr>
<tr>
<td>Sheep 4</td>
<td>385</td>
<td>‘21’</td>
<td>5.6</td>
<td>102</td>
<td>9.7</td>
</tr>
<tr>
<td>Sheep 5</td>
<td>385</td>
<td>‘21’</td>
<td>8.0</td>
<td>126</td>
<td>16.0</td>
</tr>
</tbody>
</table>

The force and resultant acceleration traces for each experiment are shown in Figures 5 through 9. Figure 10 shows the linear and angular acceleration components for Sheep 2. The general shape of the acceleration components recorded in this experiment were also characteristic of the other experiments.

In each experiment, a ‘bi-phasic’ acceleration characteristic was recorded; that is the acceleration phase, which was associated with the duration of the impact force, was followed by a large amplitude deceleration (see Figure 10 for example). These results seemed somewhat anomalous. As the head acceleration is brought about by an impact, it was expected that a large amplitude acceleration phase associated with the impact force would be seen, followed by a much longer, lower amplitude deceleration phase as the head of the animal was brought to rest under the influence of the restraining loads of the neck.

To examine the validity of the measured results, the acceleration data from each experiment was applied to a rigid body numerical (MADYMO) model of the skull-array system. The model consisted of two rigid bodies, representing the head and the array, joined by a bracket joint. The geometry of the model was determined from the stereo-radiographic measurements made for the coordinate transformation process. The displacement predicted by the MADYMO model was compared to the high speed film for each of the five experiments. In every case, the kinematics of the MADYMO model appeared to closely match the kinematics of the array, even up to 30 ms after the impact.

Presented at the 1997 International IRCOBI Conference on the biomechanics of impact, September 24-26, 1997, Hannover, Germany
However, careful examination of the first few milliseconds of motion in the numerical model and in the high speed film revealed that some complex array kinematics occurred during the period of maximum acceleration and deceleration, with the array velocity rapidly changing direction. It appeared that these complex kinematics were due to a combination of relative movement between the array and the skull, and skull bending during the impact. It is likely that the peak recorded acceleration values were associated with these non-rigid-body type motions.

PHYSIOLOGY

Physiological parameters were monitored in each experiment. In every case, the impact was followed by marked physiological changes. The responses were characterised by acute changes and this was sometimes followed by other changes which were delayed and occurred for varying periods throughout the survival period. The short term and long term trends are illustrated on the left and on the right of Figure 11, respectively.

The responses are illustrated for Sheep 1 and Sheep 3, which represent the least and the most severe responses, respectively, observed in the experiments reported on here. Note the large acute change in the intracranial pressure of Sheep 3, which is sustained for the entire survival period, and the decrease in mean arterial pressure. It is also interesting to note that the response of Sheep 1 was an acute decrease in heart rate, whereas the heart rate of Sheep 3 increased acutely.

Presented at the 1997 International IRCOBI Conference on the biomechanics of impact, September 24-26, 1997, Hannover, Germany
Figure 11. Physiological response for experiments Sheep 1 and Sheep 3 (a) up until 5 minutes after impact and (b) 2 hours after impact (1 minute averages)

NEUROPATHOLOGY - The principal pathological findings are summarised in Table 3. In Sheep 1 and Sheep 2 there was no skull fracture and on macroscopic examination the brains were essentially normal, apart from focal haemorrhage related to penetration of the subdural intracranial pressure monitor. There was no evidence of subarachnoid haemorrhage or contusion related to the impact. On microscopy, abnormal APP staining was identified in only a few sectors (TIS scores of 9 and 17), and much of this occurred around the track of the pressure monitor. These two animals were impacted using a "13" and "17" charge respectively.

Two animals (Sheep 3 and Sheep 5) sustained fractures. Associated with this was extensive subarachnoid haemorrhage at the left temporal impact site, extending around the brain stem and onto the cerebellum. In both animals fracture contusions occurred in the left temporal and parietal regions (extending through the cortex into digitate white matter) and in Sheep 5 there was a small contre coup contusion in the right parietal region. In both animals microscopy revealed widespread APP abnormalities throughout both cerebral hemispheres (TIS 304 and 135 respectively). These were most prominent around contusions, but also at a distance from vascular injuries, and in Sheep 3 extended into the brain stem. The TIS for Sheep 5 was considerably less than for Sheep 3. However, this animal was subjected to a concomitant hypoxic insult and died only 25 minutes after impact. Given this very short survival time it is likely that APP abnormalities
had not fully developed and had the animal survived for the intended 4 hours, the TIS would have been greater.

Table 3  Neuropathological scores

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Survival time</th>
<th>Total Injury Score</th>
<th>Percentage of brain injured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheep 1</td>
<td>2 hours</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Sheep 2</td>
<td>2 hours</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Sheep 3</td>
<td>4 hours</td>
<td>304</td>
<td>32</td>
</tr>
<tr>
<td>Sheep 4</td>
<td>4 hours</td>
<td>165</td>
<td>19</td>
</tr>
<tr>
<td>Sheep 5</td>
<td>25 min</td>
<td>135</td>
<td>16</td>
</tr>
</tbody>
</table>

In the remaining case (Sheep 4) extensive subarachnoid haemorrhage, contusion at the impact site and widespread APP abnormalities (TIS 163) similar to those in Sheep 3 and Sheep 5 were seen despite the absence of a fracture. This animal and the preceding two cases were subjected to an impact using a "21" charge.

DISCUSSION

The five experiments presented in this paper represent the development stage of a biomechanical model of axonal injury. As such they do not represent a homogeneous set of experiments from which general conclusions can be made. For instance, fractures occurred in two experiments, which may have altered the energy released into the brain from the impact. In the first two experiments, the survival time was two hours. The duration of this period was increased to four hours in the remaining experiments. In the last experiment, the animal underwent a deliberate period of hypoxia, which may have altered the way in which the cells of the brain were able to deal with the trauma of the impact. All these factors may have had a significant bearing on the observable injury. Nevertheless, some observations have been made regarding these experiments.

In the kinematic simulations, as in the high speed film, it was apparent that non-rigid body motions between the array and the skull were contributing to the measured acceleration. False acceleration measurements associated with skull bending have been encountered by others studying brain injury in an animal model subjected to direct impact (Nusholtz et al., 1984). With the levels of acceleration measured in this study, a fraction of a millimetre of relative movement between the array and the skull would introduce significant errors into the measurement of the acceleration of the head. This effect is unlikely to be unique to this study and care is needed to ensure that the measurements are meaningful in similar types of model. Validation techniques that are being explored for use in this model include the use of additional reference accelerometers rigidly mounted to the skull. By comparing the measured accelerations made using these accelerometers with those predicted from the array accelerations, an indication of the error in the estimation of the skull rigid body acceleration could be made. Additionally, the array itself is being redesigned to make the skull-array attachment stiffer, and to place the sensors closer to the attachment points. This should have the effect of reducing the amplitude of any relative motion measured by the array. Such enhancements should improve confidence in future kinematic results.

Neuropathological examination of these cases revealed a wide spectrum of severity of injury ranging from cases in which the brains were macroscopically normal with little histological evidence of axonal injury, to cases showing extensive subarachnoid haemorrhage, fracture contusions, contre coup contusion and very extensive axonal abnormalities on APP immunostaining. The wide spectrum of injury response is not explained by an inspection of the kinematic data. This may be due, in part, to the potential errors in the kinematic data as discussed above. However it is interesting to note that where there was a focal contusion, due to contact effects from the striker, there was a strong presence of axonal injury and the observable axonal injury was not restricted to the site of impact but was found throughout the brain. Although the number of experiments in this paper is too small to indicate a correlation, the results here imply that some measure of contact phenomena may be important in this model.

SUMMARY AND FUTURE WORK
This paper presents the development of an impact model of axonal injury using sheep which features detailed biomechanical and physiological measurements during the experiment, and a detailed neuropathological description. Five experiments have been reported here, covering a range of conditions and results. Relative motion between the nine accelerometer array and the skull of the sheep was identified as a possibly significant source of error in the measurement the kinematics of the head.

In future experiments, the biomechanical measurements will extend to include the measurement of the dynamic intracranial pressure changes during impact. Additionally, the nine accelerometer array is being redesigned in an attempt to further minimise relative motion between the skull and the array.

This model of axonal injury will be used to study the relationship between impact force, head kinematics and the resulting observed injury. The effect of post-impact physiology will also be examined. A finite element model is also being constructed to examine the relationship between the observed injury and estimated stresses and strains in the brain tissue.

REFERENCES


Presented at the 1997 International IRCOBI Conference on the biomechanics of impact, September 24-26, 1997, Hannover, Germany


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ABSTRACT

This paper investigates the relationship between the incidence of axonal injury and the tissue mechanics produced by an impact to the head in an animal model. The data are drawn from an experimental model of brain injury using sheep where the dynamics of the head impact are measured. Measurements include impact force, head acceleration and subdural pressures. A preliminary finite element model of the sheep skull and brain is presented. Simulations of selected experiments are used to estimate mechanics of the brain tissue during the impact. The resulting injury in the brain tissue was mapped using amyloid precursor protein as a marker for injury. A comparison is made between the von Mises’ stresses predicted by the finite element model, and the incidence of injury in various regions of the brain. The results of the model suggest that a trend exists between high levels of stress and the incidence of injury. All experiments conformed to the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes.

THE INVESTIGATION OF BRAIN INJURY MECHANISMS remains a crucial part of formulating criteria for the assessment of head injury risk. Despite many years of work, there is still no general agreement on a well founded method of determining the risk of injury to the human brain due to blunt impact to the head. Studying the biomechanics of brain injuries such as axonal injury in living animals can provide important insights into the mechanisms of injury. In a well defined animal model, it should be possible to relate the incidence of injury in the brain tissue of the animal to the output of a numerical model of the experiment. Such an analysis should provide a threshold of stress or strain above which injury is likely to occur. The threshold for injury may apply across species. If so, then the value of the threshold determined from such an experimental approach may be directly applied to numerical models of impact to the human head. The analysis of such models would be able to estimate the risk of injury for a given impact.

The validity of numerical techniques for modelling head impact can also be examined using this experimental approach. For example, different interface conditions between the skull and the brain can be applied to the model to examine their effects on the results of the model. Similarly, the inclusion of anatomical details can be investigated to determine how much detail is required in a numerical model to be able to correctly predict the dynamics of the brain in an impact.
In this paper we report on results of work which is designed to investigate the mechanisms of axonal injury produced by an impact in a sheep model of head injury. The paper describes new techniques for validating acceleration measurements, and techniques for controlling coordinate data. These techniques have improved our confidence in the acceleration measurements over those made in previous experiments (Anderson et al., 1997). We also present a preliminary finite element model, which is used to investigate injury thresholds in the animal model.

AIMS

The aims of this study were to:
• Characterise head impacts in an animal model of axonal injury
• Relate the incidence of injury to a preliminary finite element model of the impact.

METHODS

OVERVIEW - This study is comprised of several stages; they were
• the animal experiment which incorporated the biomechanical measurements,
• the application of the measured head dynamics to a finite element model of the experiment,
• the recording of the injury resulting from the impact, and
• a correlation between the observed injury and the output of the finite element model.

The biomechanics of the experiment were measured in a manner that allowed the dynamics to be accurately reproduced in the finite element model. The biomechanics of the impact were characterised by the linear and angular acceleration of the head about a defined set of axes, the impact force, the impact velocity, and the pressure in the cerebrospinal fluid at defined locations. The force and acceleration measurements were applied to a finite element model of the sheep's skull and brain and the pressure measurements were used to validate the output of the finite element model.

The axonal injury in each animal was recorded by taking coronal sections of the brain and applying histological techniques to identify the injury. To compare the results of the finite element model to the injury produced in the model, we needed to be able to identify the location of the coronal section in the model. This was made possible by producing magnetic resonance imaging (MRI) data and computed tomography (CT) data of the head of a single animal. These data consisted of geometrical information of the entire volume of the brain. These data were transformed so that the geometry of the head in each set of data was exactly aligned. The CT data was used as a basis for the finite element model and the MRI data was used to identify the location of each histology section (The MRI data contained finer anatomical details of the brain). Because the CT and MRI data were aligned, results data from the finite element model could be extracted on the same plane as the histology section.

The success of interchanging data between different stages of the study hinged on measuring coordinate data. In the experiments, measurements were made of the position and orientation of the striker and of all instrumentation on the head. These measurements were made in relation to anatomical features on the sheep's head. These anatomical features were also identified in the medical imaging data. This facilitated the application of the force and acceleration to the finite element model.

ANIMAL PREPARATION - All experiments conformed to the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (National Health and Medical Research Council, 1997). The animal was anaesthetised with diazepam (1 mg/
kg) and ketamine (4 mg/kg). The animal was then intubated and mechanically ventilated under isofluorane (2 per cent), until a ketamine intravenous line was established. Anaesthesia was maintained by an intravenous infusion of a ketamine/saline solution (15 mg/kg/hr) and isofluorane (1 per cent). The animal was ventilated with 100 per cent oxygen (3 l/min) until blood gases could be verified. Blood gas samples were then taken at 10 minute intervals for the duration of the experiment. Ventilation was adjusted to maintain PaCO$_2$ at 40 mmHg and PaO$_2$ at 110 ± 10 mmHg (core temperature corrected values). Other physiological parameters that were monitored and digitally recorded throughout the experiment were central venous pressure (CVP), arterial blood pressure (ABP), sagittal plane electrocardiogram (ECG), intracranial pressure (ICP), core temperature and fluid balance.

Once the animal had been instrumented for physiological measurements, biomechanical sensors were attached

ACCELEROMETER ARRAY - We have previously reported on an accelerometer array used to measure the head kinematics in this animal model (Anderson et al., 1997). The major source of error with the first array was found to be the presence of relative motion between the skull and the array. The design of an improved array (Figure 1) has several advantages over the previous design:

- the array attaches directly to the skull, eliminating the need for the attachment plate used in the first design
- spacers are not required, thereby eliminating a source of relative motion
- better attachment techniques are used
- the accelerometers are placed nearer to the attachment points, minimising the effects of any relative motion
- the array has a tenth accelerometer which is a ‘floating’ member of the array. This accelerometer is attached to the skull and acts as a reference, providing an independent measure of the validity of the acceleration measurement in each experiment.

If the acceleration of a rigid body is known, the acceleration at any known point on the rigid body can be calculated. This is the basis of the reference accelerometer concept. An accelerometer placed on the skull recorded the acceleration experienced by a single point on the head during the impact. The output of the array was used to predict the appropriate component of acceleration of the rigid body at that point. The cross correlation between the prediction of the array, and the acceleration measured by the

FIGURE 1. 3-2-2-2 array in position on the skull of the sheep

Presented at the 1999 International IRCOBI Conference on the Biomechanics of Impact, September 23-24, Sitges, Spain
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The reference accelerometer was computed. The cross correlation provides a statistical measure of the reliability of the acceleration measurement in any given experiment. A poor correlation may be a result of poor attachment of either the array or the reference. But if the predicted and measured acceleration correlate well, one can have a certain confidence that the array successfully measured the rigid body motion of the skull. This technique is useful in animal experiments because the ability of the array to measure the rigid body motion of the skull must be validated during the experiment itself; the quality of the attachment cannot be characterised generally.

The array was held in place with four orthopaedic self tapping screws; one near each horn bud at the rear of the array, and two above the distal end of the frontal bone, above the olfactory sinus. The array attachment points were chosen to sit above air sinuses in the sheep skull. Before attachment, and after the animal was anaesthetised and ventilated, a pneumatic surgical burr was used to open up the air sinus. A fast setting epoxy putty was forced into the sinus, forming a wedge and an anchor for the screws. Putty was added to provide adequate seating for the feet of the array. Once the putty had set, holes were drilled and tapped and the array was attached.

The reference accelerometer was attached to the posterior face of the right horn bud, roughly aligned with the direction of the impact. The aim was to measure a significant component of the acceleration of that region of the skull. The putty placed in the air sinus on the right side of the skull also provided an anchor for the screw that held the reference array in position.

DYNAMIC INTRACRANIAL PRESSURE MEASUREMENTS - The anatomy of the head of the sheep allows only a limited number of locations to be selected for the pressure measurements at the surface of the brain; only regions where the bones of the cranium are near the surface of the skin are accessible for mounting the devices.

Two locations were selected. One location was on the left of the midline of the brain, near the impact point, and the other was located on the right of the midline, toward the contra coup region of the brain (Figure 2). The locations of the pressure transducers were arbitrary and chosen with regard to other instrumentation that was mounted on the skull. The exact location of each transducer was measured relative to the anatomy of the skull using a three dimensional coordinate measuring arm (Microscribe-3DX, Immersion Corporation).

The transducers were Endevco 8514 pressure transducers with a range of 0 - 50 psi (0 - 345 kPa) that had been doped to resist slightly saline solutions. They were mounted using modified Camino intracranial pressure monitor bolts. The bolts are hollow and the sensor is inserted so that the tip of the sensor is flush with the end of the bolt. A collet, silicon ring and hollow nut provide a pressure seal. Holes, three millimetres in diameter, were drilled through the skull to the surface of the dura, and micro-operating

![FIGURE 2. Typical pressure transducer locations](image)
tools were used to cut and remove the dura directly underneath the hole. The lower edge of the hole was cleaned of any remaining bone, and any bone fragments were removed. Removal of the dura allowed the tip of the transducer to be in contact with the cerebrospinal fluid. The bolts were flushed with sterile saline before the pressure transducers were inserted with the aim of removing any air between the transducer and the cerebrospinal fluid.

**IMPACT DEVICE** - The impact to the sheep’s head was delivered by a modified Schermer MKL captive bolt gun. Our previous communication describes the mechanics and operation of the gun (Anderson et al., 1997). The striker’s mass is 395 g and the impact velocity can be varied up to 40 m/s. Typically, the measured impact force ranges between 5 and 8 kN over durations of 2 to 3 ms.

**COORDINATE SYSTEM CONTROL** - Multiple reference frames provided a means of relating the results from one phase of the study to the next. More specifically, loading measured in the experiment had to be applied to the finite element model and finite element model predictions needed to be related to locations of injury in the brain. The complex motion of the head and the three dimensional representation of the brain in the finite element model complicate this process. An anatomical coordinate system was the basis for recording coordinate data in this study. The coordinate system uses the point of bregma on the exterior of the skull and the two infraorbital notches on the zygomatic processes to define an anatomical coordinate system. This coordinate system could be identified during the surgical procedure on the living sheep, on the post mortem skull, and in the medical imaging data used to construct the finite element model (CT and MRI data). It was also indirectly accessible in the neuropathology data by identifying the cutting plane of the histology section in the MRI data.

A three dimensional coordinate measuring arm was used to relate physical coordinate systems to the anatomical coordinate system. Using the arm, coordinate transformation parameters were defined between any pertinent coordinate system and the positions of instrumentation; namely the array, the reference accelerometer and the pressure transducers. The impact point and the impact direction could also be related to the anatomical reference system. These positions could then be transformed to the coordinate system of the finite element model for application to the model. Figure 3 illustrates the typical coordinate system and instrumentation layout in a given experiment.

**KINEMATIC MEASUREMENTS** - All kinematic data was collected using a high speed digital acquisition system. Acceleration, force and pressure measurements were filtered with a 10 kHz analogue filter and subsequently filtered with a digital 4th order 3 kHz elliptical filter. Linear and angular acceleration were calculated in the manner described by Padgaonkar et al. (1975) and corrected where necessary by the methods described in Plank et al. (1989). The kinematics of the experiment was recorded using a high speed cine camera (1000 frames per second).

**NEUROPATHOLOGY** - After the impact, the animal continued to be monitored and supported physiologically for a further four hours. At the end of the survival period the animal was sacrificed using a perfusion of 4% paraformaldehyde which also fixed the brain tissue. The cranial cavity was opened using a craniotome, the dura was cut and the brain was removed intact. The brain was placed in a bath of the paraformaldehyde solution for a minimum period of one week to ensure complete fixation of the tissue.

Following fixation, the brain was sectioned in the coronal plane at 5 mm intervals. Each section was embedded in paraffin wax and histology sections were cut from each block and mounted on microscope slides. The mounted tissue was stained for the presence of amyloid precursor protein (APP), a reliable marker of axonal injury (Gentleman et al., 1993).
Each section was examined by placing a 4mm grid over the section. The grid provided a means of quantifying and describing the distribution of injury. A grading system (Table 1) was used in conjunction with the grid to map the distribution and the severity of the injury.

<table>
<thead>
<tr>
<th>Number of injured axons per 4x4 mm square</th>
<th>Injury grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 10</td>
<td>1+</td>
</tr>
<tr>
<td>&gt;10</td>
<td>2+</td>
</tr>
<tr>
<td>stain visible macroscopically</td>
<td>3+</td>
</tr>
</tbody>
</table>

EXPERIMENTAL RESULTS

MACROSCOPIC PATHOLOGY - In experiments in which there was no skull fracture, the brain of the animal often exhibited mild subarachnoid haemorrhage and isolated petichial haemorrhages in the cortex. In two experiments there was a linear fracture at the impact point. The macroscopic features of the pathology in these cases included patchy subarachnoid haemorrhage and, in one case, a contusion under the impact point (Experiment 0498). The contusion extended through the thickness of the cortex. Depressed fractures produced significant cortical contusions and associated subarachnoid haemorrhage. Often the contusions extended beyond the cortex and into the digitate white matter of the left hemisphere. In some cases of severe comminuted fracture, the brain tissue was lacerated at the site of the contusion. In several cases the subarachnoid haemorrhage was present around the brain stem and the base of the brain.

MICROSCOPIC PATHOLOGY - The brains of all animals contained widespread axonal injury of a severity of 1+. There was extensive 2+ injury in the mid-brain, along the margins of the lateral ventricles, and in tissue surrounding impact contusions. There was also 2+ injury to a lesser extent in some of the digitate white matter of the cortex.

BIOMECHANICS - A summary of the results is presented in Table 2. Cross correlation coefficients between the reference accelerometer and the array predictions provide a measure of the validity of the acceleration measurements. Excluding...
experiment number 0997, which had a poor cross correlation coefficient, the angular acceleration of the sheep heads were in the range of 97 to 199 krad.s\(^{-2}\).

Table 3 summarises the peak pressures (relative to atmospheric pressure) measured at the surface of the brain in the experiments. Pressure measurements were clipped in the first few experiments and only indications of their magnitude can be given here (indicated by the “>” sign).

Table 2: Summary of rigid body dynamic results

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Impact velocity (m.s(^{-1}))</th>
<th>Maximum force (kN)</th>
<th>Maximum linear acceleration of the head(a) (km.s(^{-2}))</th>
<th>Maximum angular acceleration of the head (krad.s(^{-2}))</th>
<th>(\rho_0), (\rho_{max})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0697</td>
<td>44.6</td>
<td>10.0</td>
<td>14.3</td>
<td>189</td>
<td>n.a.</td>
</tr>
<tr>
<td>0797</td>
<td>44.6</td>
<td>5.4</td>
<td>10.1</td>
<td>111</td>
<td>n.a.</td>
</tr>
<tr>
<td>0897</td>
<td>45.2</td>
<td>5.5</td>
<td>13.1</td>
<td>196</td>
<td>0.57, 0.88</td>
</tr>
<tr>
<td>0997</td>
<td>42.0</td>
<td>8.1</td>
<td>15.9</td>
<td>300</td>
<td>0.57, 0.88</td>
</tr>
<tr>
<td>1097</td>
<td>42.0</td>
<td>10.8</td>
<td>14.8</td>
<td>165</td>
<td>0.92, 0.92</td>
</tr>
<tr>
<td>0198</td>
<td>32.5</td>
<td>6.4</td>
<td>10.4</td>
<td>143</td>
<td>n.a.</td>
</tr>
<tr>
<td>0298</td>
<td>28.6</td>
<td>7.0</td>
<td>16.9</td>
<td>199</td>
<td>0.86, 0.89</td>
</tr>
<tr>
<td>0398</td>
<td>23.0</td>
<td>5.7</td>
<td>9.7</td>
<td>143</td>
<td>0.95, 0.98</td>
</tr>
<tr>
<td>0498</td>
<td>27.5</td>
<td>6.2</td>
<td>8.6</td>
<td>135</td>
<td>0.94, 0.95</td>
</tr>
<tr>
<td>0598</td>
<td>25.5</td>
<td>4.8</td>
<td>8.7</td>
<td>97</td>
<td>0.93, 0.93</td>
</tr>
</tbody>
</table>

Table 2: Summary of rigid body dynamic results

- a. measured at the origin of the anatomical coordinate system
- b. \(\rho_0\) = cross correlation between array prediction and reference reading at zero delay.
- c. \(\rho_{max}\) = maximum cross correlation between array prediction and reference reading.

Table 3: Relative pressure measurements in the experiments\(^a\)

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Fracture</th>
<th>Maximum near side pressure (KPa)</th>
<th>Minimum near side pressure (KPa)</th>
<th>Maximum far side pressure (KPa)</th>
<th>Minimum far side pressure (KPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0697</td>
<td>depressed</td>
<td>32</td>
<td>-26</td>
<td>41</td>
<td>-23.2</td>
</tr>
<tr>
<td>0797</td>
<td>depressed(^c)</td>
<td>&gt;115(^b)</td>
<td>-75</td>
<td>&gt;115(^b)</td>
<td>-29</td>
</tr>
<tr>
<td>0897</td>
<td>linear</td>
<td>&gt;690(^b)</td>
<td>-46</td>
<td>138</td>
<td>-100</td>
</tr>
<tr>
<td>0997</td>
<td>depressed(^c)</td>
<td>&gt;1150(^b)</td>
<td>-65</td>
<td>695</td>
<td>-23</td>
</tr>
<tr>
<td>1097</td>
<td>depressed(^c)</td>
<td>341</td>
<td>-26</td>
<td>&gt;350(^b)</td>
<td>-24</td>
</tr>
<tr>
<td>0198</td>
<td>depressed</td>
<td>552</td>
<td>-38</td>
<td>150</td>
<td>-75</td>
</tr>
<tr>
<td>0298</td>
<td>mild depressed</td>
<td>20</td>
<td>-96</td>
<td>196</td>
<td>-89</td>
</tr>
<tr>
<td>0398</td>
<td>none</td>
<td>69</td>
<td>-66</td>
<td>31</td>
<td>-61</td>
</tr>
<tr>
<td>0498</td>
<td>linear</td>
<td>43</td>
<td>-43</td>
<td>103</td>
<td>-91</td>
</tr>
<tr>
<td>0598</td>
<td>none</td>
<td>78</td>
<td>-44</td>
<td>104</td>
<td>-91</td>
</tr>
</tbody>
</table>

Table 3: Relative pressure measurements in the experiments\(^a\)

- a. Pressure measurements are quoted relative to atmospheric pressure (1 atm = 0)
- b. over range
- c. comminuted
FINITE ELEMENT MODEL

MODELLING PHILOSOPHY - The purpose of the finite element model was to predict the mechanics of the impact in the brain tissue. The model considers the skull as a container that transmits loads to the brain. The model is designed so that kinematics are directly applied to the skull as well as impact loads. It was clear from dynamic data collected in these experiments that the entire head does not act as a rigid and free body during impact and that loads transmitted to the skull from non-rigid components of the head affect the kinematic results. For the purposes of the model we have assumed that the skull may be approximated as rigid in regions that are immediately adjacent to the brain but that are remote from the impact site. We have assumed that the kinematics of this rigid region of the skull may be described by the kinematics measured by the accelerometer array that was mounted to the skull of the animal. The skull is modelled as deformable in the region of impact to allow transmission of contact loads to the brain. The model of the brain includes the left and right hemispheres partitioned from the cerebellum by the tentorium.

MESH GENERATION - One of the experimental animals was sacrificed to collect geometrical data for the mesh generation and the post processing of finite element model results. MRI images of an intact and freshly killed sheep were taken at 1 mm intervals over the volume of the head. The head was immediately removed, frozen and CT scanned over the same volume. The head was then partially dissected for direct measurements of the dural membranes.

The CT data was used to define the interior and exterior surfaces of the skull. Surfaces were extracted using a nodal projection technique within the software package Persona (Abbott and Netherway, 1991). These surfaces were exported to a 3D modelling package Amapi (Template Graphics Software, Inc.) where extra construction surfaces were defined in preparation for mesh generation. The mesh itself was generated in ANSYS and exported to LSDYNA. The tentorium and falx were modelled by making direct contour measurements of the frozen head with the three dimensional digitiser in Amapi and then by exporting the surfaces to ANSYS for final mesh generation. The CT data and the direct measurement data were aligned by using anatomical landmarks which were identifiable in the CT data and measured on the actual skull at the time that the dura was modelled.

Using the same landmarks, the coordinate transformation between the MRI and the CT data was defined. This allowed CT coordinate data (and hence finite element coordinate data) to be readily related to the anatomical detail visible in the MRI data.

The model consists of 1024 elements that represent the impact region of the skull, 1280 elements for the rigid body part of the skull, 2912 elements for the brain and 271 elements for the tentorium and falx (which is very small in the sheep). The model is illustrated in Figure 4.

MATERIAL PROPERTIES, BOUNDARY CONDITIONS AND FINITE ELEMENT MODEL VALIDATION

Published material properties for the tissues of the brain vary widely and satisfactory definitions of the brain/skull interface have yet to be demonstrated. Previous finite element models have either modelled the behaviour of brain tissue as linear elastic or as viscoelastic. These material characterisations have largely been based on work done some twenty five years ago (McElhaney et al., 1973; Shuck and Advani, 1972). More recently Mendis et al. (1995), characterised the behaviour of brain tissue by the strain energy density function of a hyperelastic material. They were able to model the behaviour of a sample of brain tissue over a range of loading conditions, including large

Presented at the 1999 International IRCOBI Conference on the Biomechanics of Impact, September 23-24, Sitges, Spain
strains. Other work shows that regional differences exist in the brain’s material properties. Arbogast and Margulies (1998) demonstrated that brain tissue in the brainstem is stiffer than that of the cerebral hemispheres and that the tissue exhibits anisotropic behaviour. We plan to incorporate some of these recent findings in our finite element model. However, as a first order of approximation, we have used a linear elastic model to describe the material properties of the brain. Claessens et al. (1997) showed that for short duration events and for certain viscoelastic characterisations, viscoelastic models gave very similar pressure results to a model that used a linear elastic characterisation. Table 4 lists the material properties used in the model.

Table 4: Material properties assigned to the finite element model

<table>
<thead>
<tr>
<th></th>
<th>Density (kg/m³)</th>
<th>Young's modulus (Pa)</th>
<th>Poisson's ratio</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>skull</td>
<td>3000</td>
<td>6.5 x 10⁹</td>
<td>0.22</td>
<td>Claessens (1997)</td>
</tr>
<tr>
<td>brain</td>
<td>1040</td>
<td>1.0 x 10⁵</td>
<td>0.48</td>
<td>Claessens (1997)</td>
</tr>
<tr>
<td>tentorium</td>
<td>1130</td>
<td>3.15 x 10⁷</td>
<td>0.45</td>
<td>Ruan et al. (1997)</td>
</tr>
</tbody>
</table>

In preliminary simulations, the boundary between the skull and the brain was modelled as fixed, and then as a simple contact that allowed separation and sliding. Some researchers have encountered problems when trying to define a realistic interface between the skull and the brain. The definition of a slip condition between the skull and
the brain can lead to problems with the two surfaces separating when the pressure at the interface reaches zero. The result of this is that these models do not represent the negative relative pressure behaviour seen in head impact experiments (see Claessens, 1997, and Miller et al., 1998 for recent examples). Our model also displayed this characteristic when the skull/brain interface was defined as a simple contact with sliding and separation. To capture the negative relative pressure behaviour, we fixed the brain nodes to the skull.

**MODEL PERFORMANCE**

Three experiments were selected for investigation using the finite element model. They were experiments 0398, 0498 and 0598. Experiment 0398 and 0598 were free from fractures and the animal in Experiment 0498 received a small linear fracture without tissue disruption or comminution. The experimentally recorded force and acceleration were applied to the model, and tracer particles were defined to measure the pressure at equivalent locations to those chosen in each experiment.

**PRESSURE RESULTS** - Figure 5 shows the pressures predicted by the model compared to that measured in each experiment. The model pressure histories are of similar magnitude to the experimental pressures. In the experiments, peaks of positive pressure were sometimes seen on the far side at the beginning of the impact. The model does not predict these peaks. A possible reason for this could be a rapid volume change in the skull; this change cannot be represented in the current finite element model because most of the skull is represented as a rigid entity.

![Figure 5](image-url)  
**FIGURE 5.** Pressures predicted by the finite element model and those recorded in Experiment 0398 (a), Experiment 0498 (b) and Experiment 0598 (c). Pressure 1 is the pressure measured on the near side and pressure 2 is that measured on the side further from the impact point.
MECHANICAL RESPONSE TO IMPACT - The model was examined at three coronal cross-sectional locations; one in the anterior region of the brain, one medial and one posterior in the occipital region of the brain. Each section was offset from the next by 10 mm. The cross-sections were chosen to match histology sections that had been examined for the presence of axonal injury. The location and orientation of the cross-section plane was found by matching the image of an oblique cut through the MRI data to the histology section. The equation of the plane was transformed to finite element coordinates and any element in the model cut by the plane was selected. This set of elements was interrogated further; the time histories of these elements were extracted from the finite element results and the maximum values of pressure, von Mises’ stress, first principal stress, maximum shear stress, first principal strain and maximum principal shear strain were recorded for each element. Contour plots were generated on the basis of these maxima and compared to the results of the histology.

MODEL PREDICTIONS

GENERAL CHARACTERISTICS - Peak pressures were generally seen under the impact location and on the side furthest from impact. Peak negative pressures were always seen in the contrecoup region. Peak pressures were around 100 kPa in the contrecoup regions of the brain and up to 170 kPa in the coup region of the brain, while negative pressures reached -140 kPa in the contrecoup region. These results are similar to those relative pressures measured in the non-fracture experiments, except for negative relative pressures, which were limited in the experiments to around -100 kPa (vaporisation pressure). The distribution of peak values were similar for von Mises’ stress, first principal strain, maximum shear stress and maximum shear strain. High values were seen in elements near the tentorium, and in the central part of the brain, in elements representing the left occipital lobe and in elements representing the parietal lobe. The distribution of peak values of first principal stress was somewhat different, with the highest regions of stress existing around the impact region and in the periphery of the brain generally.

MODEL PREDICTIONS AND OBSERVED INJURY - Figure 6 compares the output of the model to the observed injury distribution in two example sections. The contours are of von Mises’ stress and the injury distribution is of 1+ and 2+ injury. These two examples are typical in that there are similarities between regions of high von Mises’ stress and the incidence of 2+ injury within each slice. In the posterior section, the model predicts high von Mises’ stresses in the elements along the margins of the tentorium and in the left hemisphere generally, particularly in the superior region. We commonly observed injury in these regions, although in non-fracture cases, injury was bilateral and not necessarily more pronounced in the left hemisphere. In the medial section, injury was consistently concentrated in the central region of the brain; the model predicted the highest von Mises’ stress in the central region, although in regions that were superior to those found to have the most intense injury. The anterior section was consistently less severely injured, and the model also predicted much lower stresses in this region.

Although there appears to be some consistency between areas of higher von Mises’ stress and regions of injury in particular sections, when sections within the same brain are compared, similarities were not as strong. In general, the model predicted the highest von Mises’ stress in the posterior regions of the brain, but these regions were not necessarily more severely injured than other regions. Stresses which seemed to relate to 2+ injury in the medial section did not relate to the same severity of injury in the anterior section.

To explore this further, an analysis was performed to see if there was any relationship between the amount of injury observed in the brain and the proportion of the
DISCUSSION

The finite element model presented here is intended for use as a tool for preliminary investigation of the tissue mechanics during the impact with the head of the experimental animal. Simplified representations have been used for the material properties of the brain and the interface conditions between structures of the head. The only internal structure that has been included is the division between the cerebral hemispheres and the cerebellum by the tentorium. Although there is a suggestion from the data that the output of the finite element model may relate to injury observed in the animal model, such a relationship is not significantly apparent from the analyses performed thus far. On the basis of the distribution of injury, the model seems to overestimate the level of stress near the interface between the skull and the brain, relative to the rest of the model. This is apparent from the high levels of von Mises’ stress predicted in the occipital lobe. This region of the model is constrained along its margins to the skull and the tentorium, possibly creating higher shear stresses than those predicted for regions deeper inside the brain. A more realistic interface between the brain model that experienced high von Mises’ stress. Figure 7 plots the proportion of grid squares scoring an injury level of 2+ or greater against the proportion of the elements in the section that experienced a von Mises’ stress of more than 30 kPa. There seems to be a trend of increasing injury with predicted stress, although the relationship just fails to be statistically significant at the 0.05 level ($R(7) = 0.629, p > 0.05, R^2 = 0.3954$).
and the skull may improve this part of the model. Similarly, the model does not include the fissure between the hemispheres, nor the lateral ventricles, and these structures are likely to influence the distribution of stress in the model.

SUMMARY

The animal model of injury presented here has now progressed to a stage where we are able to measure the head kinematics during impact using an extension of the 3-2-2-2 accelerometer concept, which includes a reference accelerometer, that provides a means of validating acceleration measurements in situ. Additional accuracy is gained by the use of coordinate data throughout every stage of the study; three-dimensional coordinate data recorded in the experimental setting makes the accurate application of loads to the finite element model possible. Similarly, coupled coordinate data allow the extraction of finite element results in planes for which we have histological data.

In the animal model itself, a spectrum of injury is apparent after 4 hours survival. Axonal injury is more intense under the site of impact when the skull of the animal fractures.

The biomechanical data recorded in the experiments are being used to study the tissue mechanics during impact by applying them to a finite element model of the impact. The model presented in this paper is preliminary, and planned enhancements include more realistic material properties, the inclusion of a fluid layer between the skull and brain and better anatomical definition within the model. Other future work will include the simulation of as many sheep experiments as possible, using the methodology outlined in this paper.

It may be possible to relate the presence of injury in the brain to the predictions of the finite element model on a region by region basis, rather than over a whole slice, as presented in this paper. If so, it should be possible to determine a tissue level threshold of stress or strain, above which injury is likely to occur. Such an injury threshold may be useful as a threshold for injury in the analysis of human head impact.

ACKNOWLEDGEMENTS

This project was funded through a Unit grant from the National Health and Medical Research Council. The authors wish to thank staff from the Animal Care Services at the Institute of Medical and Veterinary Science, the Departments of Radiology at the Royal...
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