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PAPER

PATHOLOGY/BIOLOGY

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Further Investigations into the Speed of Cerebral Swelling Following Blunt Cranial Trauma*

ABSTRACT: An anesthetized sheep model of traumatic brain injury (TBI) has been developed to assess early changes in intracranial pressure (ICP) following closed head injury. Immediately after TBI, a transient (<10 min) hypertensive response occurred, followed by significant and prolonged systemic hypotension. ICP demonstrated a biphasic response, being seven times baseline values of 8 ± 2 mm Hg 10 min after injury, decreasing to 25 ± 2 mm Hg by 30 min, and then increasing to values exceeding 30 mm Hg by 4 h postinjury. ICP was always significantly higher than baseline values, which combined with hypotension, reduced cerebral perfusion pressure to less than 60% of normal. This early and sustained increase in ICP after craniocerebral trauma acutely alters cerebral perfusion pressure and brain oxygenation and provides a potential pathophysiological explanation for immediate clinical manifestations in humans following significant TBI.

KEYWORDS: forensic science, traumatic brain injury, intracranial pressure, blunt craniocerebral trauma, lucid interval, impact, shaking

An important consideration in the evaluation of victims of blunt craniocerebral trauma in a forensic context is the speed with which symptoms and signs of raised intracranial pressure (ICP) develop. In previous work in a sheep model of traumatic brain injury (TBI), we have shown that increases in ICP could be detected by 30 min after blunt head trauma (1) and that ICP continued to increase as brain edema developed over the ensuing hours (2). These findings are particularly relevant to humans given that the sheep model successfully mimics several features that are found in human TBI, including similar ICP values, comparable falls in brain tissue oxygenation, as well as the development of significant diffuse axonal injury (2,3). In part, this may be related to the fact that sheep have gyrencephalic brains supported by a substantial bony and fibrous tentorium that is similar to humans (4), as opposed to the lissencephalic brains of rats that have little intracranial compartmentalization. Thus, sheep are better suited to reproduce the posttraumatic physiological state that exists in human TBI than rodents.

One challenge in obtaining early ICP changes after trauma is the speed with which ICP probes can be placed. Unfortunately, having a probe positioned before the induction of experimental trauma invariably results in probe-induced tissue damage that is not present in clinical TBI. Moreover, the presence of hemorrhage around a fixed ICP probe complicates interpretation of the ICP response, with the presence of a craniotomy defect altering both the response of the skull to impact and the physiological conditions experienced by the brain in what is normally a completely enclosed space. We have therefore focused on performing a craniotomy rapidly and placing the ICP probe as quickly as possible after experimental trauma and decreased the time required for this procedure to less than 10 min. The current study has therefore enabled us to more clearly delineate the nature and degree of acute changes in ICP that occur in the time immediately following blunt trauma.

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Materials and Methods

All studies were performed according to the guidelines established by the National Health and Medical Research Council, Australia, for the use of animals in experimental research and were approved by the Animal Ethics Committees of the Institute of Medical and Veterinary Science and The University of Adelaide, South Australia.

Eight 2-year-old sterilized male Merino sheep were anesthetized by an intravenous injection of thiopentone before intubation and ventilation (4 L/min) with oxygen enriched air (30–35% oxygen) containing 2.5% isoflurane. A femoral arterial catheter was implanted to continuously monitor mean arterial blood pressure (MABP) using a MACLAB data acquisition system (MacLab 2e; ADInstruments, Colorado Springs, CO), where a Statham-type pressure transducer (ADInstruments) was connected via a polyethylene tube to the animal's arterial cannula. The pressure trace (ADInstruments) was relayed from the transducer to the MACLAB via a bridge amp, and all data were recorded and stored using a personal computer. Arterial blood was taken every hour for gas analysis and adjustment of ventilation parameters as necessary. After placement of the catheter, isofluorane was lowered to 1.0–1.5% and an intravenous infusion of ketamine (4 mg/kg/h) was initiated. This regime provided an appropriate level of anesthesia for surgery with intact cardiovascular reflexes.

Injury was induced using a humane stunner according to standard methodology described in detail elsewhere (3,5). Briefly, the sheep were placed into a prone sphinx position and restrained to

the table, leaving the neck and head mobile relative to the body. Impact injury was induced at the midpoint between the left supraorbital process and the left external auditory meatus using a captive humane bolt stunner armed with a number 17 red charge (model KML; Karl Schermer & Co., Ettlingen, Germany). We have previously shown that this impact causes severe diffuse axonal injury (3,5). After injury, animals were stabilized and the heads restrained to the operating table to facilitate insertion of an ICP monitor probe within 10 min of trauma. Following exposure of the skull, a 2- to 2.5-mm burr hole was performed at a point 15 mm lateral to the sagittal midline on the ipsilateral side, just in front of the coronal suture. A #14 catheter (1.73 mm in diameter) was fixed into the burr hole, the dura mater opened, and a calibrated Codman Microsensor ICP transducer (Codman and Shurtleff, Inc., Warsaw, IN) inserted such that the tip of the sensor was 1.5 cm into the parenchyma of the left parietal lobe. The probe was attached to a Codman ICP Express monitoring system that was linked to an ADInstruments PowerLab® system where the data were postprocessed to provide averages of 10 sec epochs. After insertion of the probe, the burr hole was sealed using bone wax and the sheep monitored for another 4 h. A further eight animals were used as sham controls to establish baseline ICP values, where animals were surgically prepared and ICP monitoring initiated in the absence of any induced brain injury. Animals were euthanized by barbiturate overdose at the conclusion of the 4-h monitoring period.

Data are expressed as mean and SE of the mean and were analyzed by one-way analysis of variance (ANOVA) followed by Duncan's tests (PRISM; Graphpad Software, San Diego, CA). A p-value of <0.05 was considered significant.

Results

Baseline MABP prior to injury was 109 ± 4 mm Hg (Fig. 1*A*). Immediately after trauma, there was a highly significant ($p < 0.001$) increase in MABP to 176 ± 10 mm Hg, followed by a decline to normal levels within 10 min after trauma. MABP continued to decline with time with significant hypotension at 25 min posttrauma ($p < 0.05$) and achieved a minimum of 65 ± 8 mm Hg at 4 h after TBI ($p < 0.001$). Transient hypertension followed by sustained hypotension is typical of experimental TBI (3,6,7).

Normal ICP in sham (noninjured) animals was 8 ± 2 mm Hg (Fig. 1*B*). At 10 min after TBI, which was the earliest time point at which the craniotomy was completed and the ICP probe successfully implanted in all injured animals, ICP was 56 ± 7 mm Hg. The ICP gradually decreased to 25 ± 2 mm Hg by 60 min after TBI, before again increasing to 32 ± 2 mm Hg by 4 h after injury. The increase in ICP between 1 and 4 h after trauma has been previously associated with ongoing edema formation (1,2). ICP was significantly greater than baseline values at all time points ($0.001 < p < 0.05$).

Cerebral perfusion pressure (CPP), as determined by the difference between MABP and ICP, was 99 ± 6 mm Hg in sham (uninjured) animals. Immediately after ICP probe insertion, CPP was calculated as less than 60 mm Hg and continued to decline over the ensuing hours to be under 50 mm Hg by 4 h after injury (Fig. 1*C*).

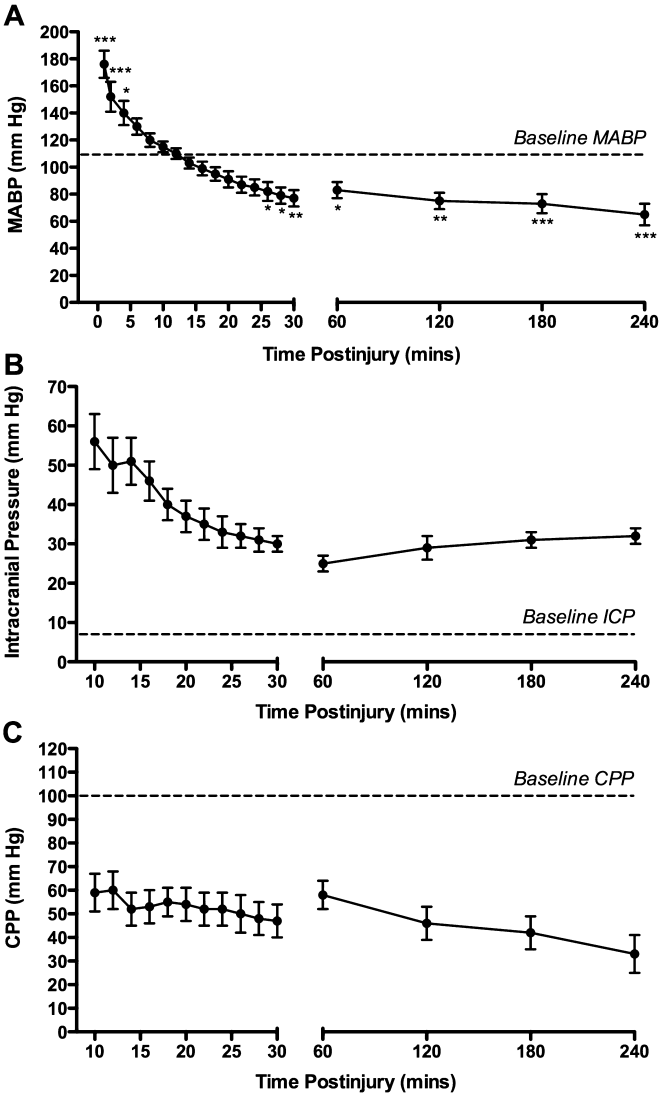

FIG. 1—*Changes in (A) mean arterial blood pressure (MABP), (B) intracranial pressure (ICP), and (C) cerebral perfusion pressure (CPP) in sheep subjected to blunt craniocerebral trauma. Raised ICP was present as early as 10 min after trauma, coincident with transient hypertension. All ICP values are significantly greater than baseline ($0.001 < p < 0.05$). *p < 0.05, **p < 0.01, ***p < 0.001 versus MABP baseline. CPP reduced to <60% of normal.*

Discussion

In previous studies by this group, blunt cranial trauma in the sheep model produced profound increases in ICP with concomitant reduction in cerebral oxygenation by 30 min after injury (1,2). This indicated that cerebral swelling could occur very soon after significant head injury. It was, however, difficult to obtain readings earlier than 30 min after trauma given the time necessary to implant the ICP probe. While the ICP probe could potentially be implanted prior to induction of injury, free movement of the head would have resulted in direct mechanical disruption of brain tissue from the inserted probes, with resultant hemorrhage. In the current study, we have focused on minimizing the time required to perform the craniotomy and correctly place the ICP probe and have managed to consistently complete the procedure in less than 10 min. In so doing, we have been able to demonstrate profound and highly significant increases in ICP occurring immediately after trauma. Comments on the behavioral responses to blunt head trauma were not possible, as all of the animals were anesthetized for the duration of the procedure and euthanized once the readings had been completed.

In cases of inflicted head injury in humans, an important forensic consideration is to determine a plausible temporal sequence for the development of symptoms and signs. For example, it is vigorously

debated whether an infant or young child who sustains a head injury that will ultimately prove to be lethal (without an epidural hemorrhage), ever appears normal after the injury (8,9). Those who favor the existence of a so-called lucid interval suggest that the clinical features may take some time to develop, as secondary manifestations such as cerebral swelling and axonal injury are not immediate. Unfortunately, in many of these studies, ''lucid interval'' has not always been clearly defined, autopsy examinations may not have been performed, and detailed clinical information is lacking (10–12). The alternative view is that once cases with epidural hematomas and incomplete or unverifiable histories have been excluded, that ''infants simply do not suffer massive head injury, show no significant symptoms for days, and then suddenly collapse and die'' (13). It is similarly asserted that ''an alert, well-appearing child has not already suffered a devastating acute injury that will become clinically obvious hours to days later'' (14).

In support of the latter position, animal studies using blunt cranial impact have shown that ICP rises very quickly after injury in sheep with an associated fall in brain oxygen (1,15). Within 5 min of blunt impact in piglets, ICP has increased significantly to 40 mm Hg, cerebral perfusion pressures have fallen from 85 to 40 mm Hg, and cerebral blood flow has dropped from 55 to 22 mL/min/100 gm (16).

The current study sheds further light on the nature of the changes in ICP immediately following blunt cranial trauma, as increases in ICP followed a biphasic pattern, with an initial sharp rise followed by a steady reduction to levels of around 25 mm Hg. Subsequently, there was a steady increase in ICP over the ensuing hours. The initial very rapid increase in ICP occurred within 10 min and was correlated with systemic hypertension and is most likely due to reactive vasodilatation, as significant edema may take some time to develop after an injury (17,18). The peak of ICP because of early vasodilatation then reduced, to be followed by slowly increasing pressures. This has been previously shown by positive immunohistochemical staining to be due to cerebral edema resulting from posttraumatic albumin extravasation (1). Throughout the entire monitoring period (from 10 min posttrauma), CPP in the injured sheep was <60% of normal values. Whether the immediate increase in MABP after the injury represents an attempt to maintain CPP in response to a significant increase in vasodilation-dependent ICP is unknown.

These observations demonstrate that blunt cranial trauma in the current model causes an almost immediate increase in ICP and a decrease in CPP, which we have previously shown to be associated with a reduction in cerebral oxygenation (2). Although ICP levels did reduce from an early peak, the mean values were always greater than 25 mm Hg, a level previously shown to be associated with increased mortality (19). In terms of a clinical response to such an injury, the marked changes in intracranial parameters would be more in keeping with an immediate and persistent alteration in behavior and/or conscious state because of consistently low cerebral oxygenation, rather than having a period of apparent normality prior to clinical decline. While some improvement occurred in measurements, at no stage did they approach normal levels after impact.

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