INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of death and disability, affecting 1.7 million Americans annually, 50,000 of whom die [1]. Victims who survive the initial injury often suffer debilitating neurologic deficits. The total annual cost of TBI in the United States has been estimated at $60 billion [2]. While damage to brain tissue is of primary concern in TBI, nearly all head trauma includes some element of vascular injury or dysfunction [3], putting neural tissue uninjured in the primary event at subsequent risk. Contusion, which includes injury to both brain and vessel tissue in the cortex, is considered the hallmark of head injury, but little is known about the specific mechanisms of vascular injury in contusion. Previous efforts to elucidate mechanisms and thresholds for contusion, including inanimate gel, animal, and computational models [e.g. 4-7], have defined bulk tissue deformations that are associated with contusion, but the relationship to vascular injury is not clear. In order to address this question, our laboratory is studying acute disruption of the blood-brain barrier using a controlled cortical impact (CCI) mouse model. The objective of this study was to compare acute vascular injury in CCI with cortical mechanics predicted by a computational model of the experiment. This comparison is then discussed in the context of results from isolated vessels testing in our laboratory.

METHODS

Controlled cortical impact is commonly used to produce contusion in an experimental animal. It uses a pneumatically or electrically driven piston to impact the exposed dura at a controlled velocity and penetration depth to create a contusion injury. In the experiments reported here, C57BL/6J mice were anesthetized using an isoflurane vaporizer and immobilized stereotaxically. A 3.5 mm craniotomy centered at +2.0 mm forward of bregma and 2.0 mm lateral of midline was then performed to expose the dura over the left cerebral hemisphere. The intact dura was then struck by an electrically driven piston at a velocity of 4.6 meters/sec and a penetration depth of 1.0 mm. At one and 24 hour time points, animals were sacrificed by isoflurane overdose and cardiac perfusion and brains were extracted and fixed in 4% paraformaldehyde. Fifty-micron thick serial sections from the impact point and surrounding tissue were then cut and examined using immunohistological techniques to determine the extent of injury. In particular, extravasation of IgG, a natural blood protein, was used to determine extent of blood-brain barrier breakdown. AF-594 conjugated GtxMs IgG1 was used to visualize results using fluorescence microscopy.

To quantify brain deformations associated with experimental impact conditions, a finite element (FE) model of the mouse brain was constructed. The outer contours of 37 serial coronal section images from the brain of a 51 day old C57BL/6J mouse (obtained from The Mouse Brain Library, http://www.mbl.org/) were digitized, imported into SolidWorks, and lofted together to form a 3D body. HyperMesh was used for FE preprocessing. Brain tissue was meshed with 235,437 hexahedral brick elements. Following [7], a single layer of rigid brick elements, created by duplicating the outer elements of the brain tissue, were offset to represent the skull, and a hole was created to model the CCI craniotomy. Dura and pia-arachnoid were similarly generated but were modeled as single layers of shell elements. The impactor was meshed with rigid brick elements. Contact interactions were specified between the impactor and the dura, between the skull and the dura, and between the dura and the pia-arachnoid. The pia-arachnoid shared nodes with the outer layer of brain tissue. Material properties were taken from [7]; no internal brain structures were modeled separately in this initial model, so the homogeneous brain was given properties of gray matter since the focus of this study was cortical injury. With these
definitions made, the skull was fixed and the impactor was constrained to move as in the experiment. The model was run using the LS-Dyna explicit solver. Results were viewed using LS-PrePost. Predictions of mechanical parameters were compared to histological section images to estimate the level of tissue deformation required to cause blood-brain barrier disruption and subsequent secondary brain injury.

RESULTS AND DISCUSSION

Figure 1 illustrates FE-predicted measures of stress and strain at maximum deformation plotted on an undeformed coronal section passing through the center of the impact. Figure 2 shows the distribution of IgG in a section at approximately the same location from a mouse euthanized 1 hour after injury. The image shows a distinct increase in fluorescence in the region of the impact, superior to the ventricle, with some focal areas of particular brightness in portions of the cortex. Longer animal survival times showed similar IgG profiles but with severe degradation of tissue integrity, likely as a result of inflammatory processes occurring post-injury.

Not surprisingly, there appears to be good qualitative correlation between both FE-predicted measures and the level of fluorescence (amount of IgG). In particular, the brightest regions appear to correspond with the highest stresses and strains. It is also interesting to note that peak stress and strain are predicted to occur below the surface of the brain in some locations and that the greatest fluorescence in the injured brain occurs below the cortical surface. These possible correlations need more investigation, as does which measure of severity (or combination) correlates best with vessel injury.

Isolated vessel testing from our laboratory (unpublished) has shown that rat middle cerebral arteries typically fail at a Green-Lagrange axial strain value of approximately 0.4, which corresponds to the transition between blue and green in the strain results. The distinctly bright, injured region in Fig. 2 appears to include a larger portion of the brain than what is predicted to experience a strain of 0.4 (or greater) in Fig. 1. This may be due to the smaller parenchymal vessels having lower failure strains or to failure mechanisms other than just axial stretch playing a role, but these questions need further investigation.

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REFERENCES