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Elucidating the Role of Compression Waves and Impact Duration for Generating mild Traumatic Brain Injury in Rats

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Abstract

3 million concussions occur each year in the United States. The mechanisms linking acute injury to chronic deficits are poorly understood. Mild traumatic brain injury has been described clinically in terms of acute functional deficits, but the underlying histopathologic changes that occur are relatively unknown due to limited high-function imaging modalities. In order to improve our understanding of acute injury mechanisms, appropriately designed preclinical models must be utilized. The clinical relevance of compression wave injury models revolves around the ability to produce consistent histopathologic deficits. Repetitive mild traumatic brain injuries activate similar neuroinflammatory cascades, cell death markers, and increases in amyloid precursor protein in both humans and rodents. Humans however infrequently succumb to mild traumatic brain injuries and therefore the intensity and magnitude of impacts must be inferred.

Understanding compression wave properties and mechanical loading could help link the histopathologic deficits seen in rodents to what might be happening in human brains following repetitive concussions. Advances in mathematical and computer modeling can help characterize the wave properties generated by the compression wave model. While this concept of linking duration and intensity of impact to subsequent histopathologic deficits makes sense, numerical modeling of compression waves has not been performed in this context. In this collaborative interdisciplinary work, numerical simulations were performed to study the creation of compression waves in our experimental model. This work was conducted in conjunction with a repetitive compression wave injury paradigm in rats in order to better understand how the wave generation correlates with validated histopathologic deficits.

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Keywords

Finite Volume Modeling; Compression Wave; Traumatic Brain Injury; Apoptosis; Pre-clinical Model

Introduction

It has been estimated that 1.7 to 3.4 million concussions occur each year in the United States¹. How mechanical forces cause brain injury and initiate injury cascades is poorly elucidated. Therefore, a diagnosis of concussion is primarily based on observable symptomatic changes². It is currently unknown how many athletes and soldiers are at risk for developing chronic traumatic encephalopathy³. Chronic traumatic encephalopathy is a degenerative tauopathy characterized by mood disorders and cognitive deficits⁴. The biochemical mechanisms linking acute injury to behavioral deficits and the development of neurodegeneration over time warrants further investigation⁵. Banks and colleagues are conducting the first prospective cohort study to determine the incidence of chronic traumatic encephalopathy in mixed martial arts fighters⁶. Laboratory research can also provide important discoveries for how acute injury contributes to tauopathy. Most importantly, laboratory studies allow for a comparison of mechanical loading to observed physiologic changes post-injury⁷.

In order to improve our understanding of mild traumatic brain injury, it is necessary to utilize pre-clinical models that produce relevant pathologic changes consistent with human brain injury. In previous papers, we have described acute biochemical changes that occur within a rat's brain following compression-wave injury. These changes include blood brain barrier disruption, endoplasmic reticulum stress, and oxidative stress⁸⁻¹⁰. Recently, we discovered that these acute pathways are implicated in the development of tauopathy, and contribute to long-term cognitive and behavioral deficits¹¹. These deficits in humans can manifest as post-traumatic epilepsy, sleep disturbances, and increased risk for suicide¹²⁻¹⁴. In this multidisciplinary project, we sought to delineate the wave dynamics associated with our clinically relevant model and correlate the wave properties to observed histopathologic changes within the rat's brain post-injury. Simulation and numerical modeling can be used to enhance our understanding of the wave properties and how the rat's skull interacts with this wave. These properties are critical for determining how mechanical injury causes lasting damage that ultimately leads to behavior changes.

Methods

Tabletop model

The model consists of steel driven and driver section with a mylar membrane sandwiched in-between. The driven and driver section are screwed tight prior to rupturing the membrane. The apparatus is securely attached to a table and the 0.005" membrane was scored with a hand press prior to use. The intensity of the compression wave was determined by a pressure gage attached to a regulator. Nitrogen gas was used to rupture the membrane. The pressure was allowed to build via a needle nose attachment and regulator prior to rupture. The

compression tube has a short driver section in order to generate a short-duration wave. Piezoelectric sensors (Model 102AO5; PCB Piezotronics) were placed in the reflected and two incident positions near the exit of the shock tube to produce a linear configuration as shown in Figure 1. To test for planarity, the three sensors were placed at the edge of the tube. Data was recorded using a sensor signal conditioner (482C Series; PCB Piezotronics) and a data acquisition board (DAQ 23GF; National Instruments). A computer program written with LabView version 12.0 (National Instruments) was used for analysis. The anesthetized rats head was placed at the same position as sensor two. A polyvinyl tube to protect the thoracic cavity from wave exposure protected the body.

Numerical Approach

Numerical simulations are used to reconcile pressure profiles with the experimental setup in order to characterize wave formation. The tube and the surrounding air may generally be modeled by the compressible Navier-Stokes equations describing fluid flow. The flow produces a shock wave and an expansion wave propagating into stationary flow at atmospheric conditions. The timescales of both phenomena are small relative to the timescale of the viscous/diffusive terms within the Navier-Stokes equations. It follows that the boundary layers formed near the interior of the compression tube will have a minimal influence on the flow. Thus, the non-viscous Euler equations are used to simulate the compression waves generated from the tabletop compression tube.

The Euler equations listed in conservation form are:

$$\frac{\partial \mathbf{U}}{\partial t} + \frac{\partial \mathbf{F}_x(\mathbf{U})}{\partial x} + \frac{\partial \mathbf{F}_y(\mathbf{U})}{\partial y} = 0.$$

where,

$$\mathbf{U} = \begin{Bmatrix} \rho \\ \rho u \\ \rho v \\ \rho e_T \end{Bmatrix}, \mathbf{F}_x = \begin{Bmatrix} \rho u \\ \rho u^2 + p \\ \rho uv \\ (\rho e_T + p)u \end{Bmatrix}, \mathbf{F}_y = \begin{Bmatrix} \rho v \\ \rho uv \\ \rho v^2 + p \\ (\rho e_T + p)v \end{Bmatrix}.$$

The conservative variables inside the vector $\mathbf{U}$ represent density, ρ , x-momentum, ρu , y-momentum, ρv , and total energy, ρe_T . The total energy per unit mass may be defined as the summation of the internal and kinetic energy:

$$e_T = \frac{p}{\rho(\gamma - 1)} + \frac{1}{2}(u^2 + v^2).$$

An ideal gas equation of state $P = \rho R_{air} T$ is used to close the system of equations.

The compression tube is modeled using an axisymmetric geometry, which reduces computation time by solving for a three-dimensional flow field on a two-dimensional domain. The computational domain illustrated in figure 2 shows the compression tube with a large domain at the compression tube exit to capture the propagation of the blast wave after it exits the tube. The surrounding fluid region is chosen to be large enough to capture the transient evolution of the compression wave past the sensor two location without experiencing any interactions with the domain boundaries until much later.

The burst of the diaphragm is modeled by using a discontinuous initial condition where the pressure is higher in the driver section and lower outside. The initial velocity is zero and the initial temperature is 20°C everywhere. The initial conditions across the diaphragm are 110 psi in the driver section at atmospheric conditions, with 14.7 psi in the driven section and the domain outside the tube.

The governing equations are solved numerically using Star-CCM+. The Weiss-Smith Precondition Roe's Scheme ¹⁵ is used to discretize the physical domain into cells, and the governing equations are solved with a finite volume scheme. The scheme uses a multidimensional linear reconstruction to calculate the fluxes at each cell edge. The reconstruction uses a Taylor series expansion at the cell face to retain higher order accuracy. A multiple stage Runge-Kutta second order explicit scheme is utilized for the time integration ¹⁶. The time-step used in each simulation is determined using the Courant-Freidrich-Lewis (CFL) number. The CFL number is defined

$$CFL = (u + c) \frac{\Delta t}{\Delta x},$$

where u and c are local fluid velocity. The maximum CFL inside the domain was used to choose the time-step. The CFL number used for the simulations in this work is 0.5.

A range of grid spacing is used in this work and range from 0.3175 cm to 0.0595 cm. A grid sensitivity study is performed to ensure that the solution is not grid dependent. Computing the L_2 norm assesses grid sensitivity. The L_2 error is typically calculated by comparing the solution for the different mesh refinements to an exact solution. Since no exact solution is available, the solution with the finest mesh is used as an exact solution.

The L_2 error may be represented as,

$$L_2 = \left(\int (P_{\text{Mesh}} - P_{\text{Exact}})^2 dx \right)^{0.5}$$

The L_2 error value represents the error over an entire domain with individual contributions from each cell.

Animals

The Institutional Animal Care and Use Committee at West Virginia University approved all experiments involving animals. The experiments were conducted in accordance with the *Guide for the Care and Use of Laboratory Animals*. Sixteen (16) young-adult male Sprague dawley rats (Hilltop Lab Animals, Inc.) were used for immunohistochemistry (IHC). The rats were divided into two groups: repeat injury (6 compression waves every other day over 2 weeks) and anesthetized (4% isoflurane with 2% maintenance) control. Repeat injury exposure was performed with the 0.005" membrane according to the methods previously described¹⁷. A power analysis was conducted (DSS Research) with the equation $n=1+[2C(s/d)^2]$, where C is a value dependent upon the a and b values chosen. For this study a=0.05 and b=0.2 for a power of 1-b=0.8. $C_{(0.05, 0.8)}=7.85$ (obtained from table). The number needed is based on effect size and standard deviation, which was estimated from previous work. Rats were housed with a 12h:12h light to dark cycle and food and water available *ad libitum*.

Immunohistochemistry

Animals were anesthetized as described above followed by decapitation. The brain was removed and immediately flash frozen in isopentane and stored at -80°C. Brains were sliced to a thickness of 20µm using a cryostat. Standard Hematoxylin and Eosin, Fluorojade B, Thioflavin, and DAB (Sigma Aldrich) staining protocols were utilized to stain for cellular morphology and Amyloid precursor protein (APP) (Cell Signaling).

Images were obtained from a blinded observer using a Zeiss Axio Imager 2 and an Olympus MVX10 for brightfield and fluorescent imaging. For immunohistological DAB stains, 100 total cells were counted in the stereologic selected region of interest within the prefrontal cortex and determined to be either expressing or non-expressing. The ratios between groups were compared using chi-squared analysis. For fluorescent stains, a blinded observer used image J quantification. The measurements were adjusted for background giving corrected total cell fluorescence. The total cell fluorescence was compared between groups.

Statistical Analysis

Data were analyzed using GraphPad Prism version 4.0. An observer blinded to experimental group did imaging quantification. A student's t-test was used to compare across control and repeat injury groups for fluorescent imaging. A χ^2 analysis was used for DAB staining. A p-value of <0.05 was considered statistically significant for all studies.

Results

Compression Wave Formation

Figure 2 shows a sequence of pressure contours, which illustrate the formation and propagation of a traditional blast wave. At t=0, the diaphragm separates the fluid inside the driver section from the fluid inside the driven section. The fluid inside the driver section is at higher pressure than the atmospheric pressure in the driven section. Once the diaphragm bursts, the t = 0.1 ms frame shows that a shock wave moves to the left and an expansion wave moves to the right. At t=0.3 ms the shock wave has exited the tube and expands in all

directions. The exit of the shock wave creates an expansion wave that moves inside the shock tube. The induced flow from the shock wave as it propagates to the left further away from the compression tube creates a low-pressure region behind the shock wave. This region is where the pressure drops below atmospheric pressure.

A one-dimensional axis is selected down the center of the compression tube to evaluate the error. The pressure values along the axis are compared between different mesh refinements at a physical time of 1 ms. Figure 3 shows the L_2 error as a function of grid spacing on a log-log scale. The solution with the finest resolution is used as an exact solution. Figure 3 also shows that the slope is 1.841, which indicates that the solution is converging at a rate between first and second order accuracy. This convergence rate is consistent with the scheme's accuracy since the reconstruction step makes the solution second order accurate everywhere except for discontinuities such as shocks and contact discontinuities.

Figure 4 shows a contour plot of pressure on an x-t diagram using the solution data located along the axis in the center of the compression tube. The green dashed lines in figure 4 represent the analytical solution for an ideal one-dimensional compression tube. Looking exclusively at the shock wave and the head of the expansion wave propagation, both phenomena are represented relatively accurately compared to a purely 1-D shock tube case. It may also be seen that the expansion wave reflects off the driver wall at $t = 0.4$ ms and begins propagating in the direction of the shock wave. The solid blue lines represent the end of the compression tube and the initial diaphragm location. When the shock exits the compression tube at $t = 0.149$ ms an expansion wave is created as the wave expands radially outward in all directions. The contour shows that the pressure behind the transmitted compression wave decays with distance from the tube exit. The red dashed lines represent the locations of each of the pressure transducers in the experiment.

Pressure Sensors

Pressure readings are obtained using pressure taps at specific locations within the compression tube and at the location where the rat will be placed. Figure 1 provides the geometry and location of each of the sensors from the experiment. The pressures versus time profiles were analyzed for each pressure sensor placed linearly. The waves were mapped and quantified with MATLAB as previously published¹⁷. Three transducers were then placed in the same plane at the edge of the tube. These three transducers showed variation in the pressure histories, which suggests that non-planar shock waves are produced. This non-planar wave behavior is likely caused by inconsistent burst patterns of the diaphragm. The diaphragms are scored in similar patterns with a press to improve the planarity of the wave. Since there is some planar variability in pressure histories from case to case, an average pressure history is calculated using 7 membrane ruptures. The averaged pressure histories are then readily compared with the simulation results.

Pressure Profiles

The pressure profiles for each sensor are shown in figure 5 for both the averaged experimental data and the numerical simulation. The pressure histories of the experimental data were shifted to match time of peak pressure occurrence. The time shift allows an

average between pressure profiles and direct comparison between the averaged experiment and the simulation.

The third sensor shows the same general trend between the experiment and the simulation. The over-pressure does not reach the peak value observed in the simulation and the rise time is finite. The lower peak pressure and more gradual pressure increase indicate a wave that more closely resembles a strong compression wave. This is likely due to incomplete or partial diaphragm rupture. However, since the pressure ratio across the diaphragm is sufficiently large to create a shock (approximately 7.5), the wave created inside of the tube from the diaphragm burst will still be regarded as a shock wave. It can also be seen that the time scale of the pressure recovery matches between the simulation and the experiment. This pressure recovery occurs from the shock exiting the tube and the expansion wave travels inside.

The first sensor is near the exit of the tube and shows a similar behavior between the experiment and the simulation. The peak of the simulation is almost twice the magnitude of the experiment. Similar to the third sensor, the first sensor pressure recovery timescale is consistent between the experiment and the simulation.

The second pressure sensor is oriented for the experiment as a reflected sensor where the pressure transducer is pointed into the flow direction. The pressure tap is held within a large metal plate approximately 2 inches from the end of the shock tube. As can be expected, the pressure trace for sensor two shows that the experiment and numerical model are consistent on the arrival time of the blast wave at the transducer two location. Beyond this time the two pressure histories deviate because the numerical simulation does not model a reflecting plate. Instead, the numerical simulation measures what the pressure profile would be in the absence of an object that alters the wave profile. In the experiment, the pressure rises much higher and retains that high pressure for approximately 1.5 ms. This higher pressure rise occurs because of the wave reflection that occurs at sensor 2 from the wall plate. It should be noted that the reflection of the wave alters the wave profile to make the wave duration much longer than an unobstructed wave. This suggests that very different pressure histories may be recorded for the same compression wave depending upon the pressure transducer placement and geometry.

Immunohistochemistry

Compression wave TBI can lead to long-term changes in the brain. Neurons are acutely injured and can undergo apoptosis or survive with aggregated proteins. We show nuclear fragmentation, pyknotic nuclei, blebbing, and chromatolysis in the contralateral prefrontal cortex of repeat TBI animals compared to control animals (Figure 6 A-B). A significant increase in amyloid precursor protein was also seen 72 hours post repeat TBI (41/100) compared to controls (2/100) in the contralateral prefrontal cortex $\chi^2 = 81$, $p < 0.001$ (Figure 6 C-D). In addition to apoptosis, damaged tissue can degenerate over time. Fluor Jade B was used to mark early signs of neurodegeneration. We found a significant increase in the contralateral prefrontal cortex at 72 hours post repeat TBI compared to controls $t = 8.96$, $p < 0.001$ (Figure 7 A-B). We also found a significant increase in fluor Jade B in the contralateral hippocampus 72 hours post repeat TBI compared to controls $t = 3.22$, $p < 0.01$.

(Figure 7 C-D). The compression wave caused significant degeneration in the contralateral hemisphere due to large inertial wave forces. Finally, a significant increase in thioflavin staining was seen in the prefrontal cortex following repetitive TBI 72 hours post-injury compared to controls $t=3.636$, $p<0.01$ (Figure 7 E-F). Thioflavin marks increased tau hyperphosphorylation and protein aggregation.

Discussion

Panzer and colleagues recently urged for better understanding of pre-clinical TBI models and how these models produce head injury¹⁸. Gupta proposed that the most clinically relevant understanding of TBI is to determine how compression waves penetrate into tissue¹⁹. The numerical simulations contained in this work show that the tabletop model produces a pressure wave consistent with a compression wave. The expansion wave is created after the shock wave exits the shock tube and combines with the shock wave to produce the compression wave. The simulation results correlated well with the model recordings for sensor one and sensor three. The wave duration for the numerical simulation at the sensor two location was five times shorter than that observed from the averaged pressure transducer history. This suggests that obstacles in the flow can significantly alter incident wave profiles. Compression waves such as these can contribute to damage at density gradients within the brain²⁰. This type of injury from compression waves is most frequently seen in clinics due to athletic concussions and motor vehicle collisions²¹. In this multidisciplinary paper, we show that the tabletop model creates compression waves and that these waves cause significant injury as measured with immunohistochemistry.

The waves may potentially be causing shearing of vessels and axons²². We observed significant increases in amyloid precursor protein and thioflavin after repetitive TBI indicating potential damage from axonal shearing and persistent neuronal injury. Likewise H&E and fluorojade B staining revealed increased cell death and nuclear damage. The damage was particularly pronounced at the white/grey junction within the cortex and the hippocampus. Additionally, Readnower and colleagues observed substantial disruption of the blood brain barrier on the ipsilateral hemisphere following blast exposure likely due to a longer duration compression wave²⁴. We observe the disruption in the BBB on the contralateral hemisphere where the brain collides acutely with the skull⁸. The injury is reproducible and consistent, however a potential limitation is translating the findings to humans. The rodent brain is agyric and is situated in a different type of cranial vault compared to the human brain. A more complete understanding of pressure gradients, deformation and movement of the brain, and the significance of sulcal depth and gyral crest regions will be required to more fully appreciate how neurodegeneration may develop following neurotrauma.

Going forward, the use of advanced animal imaging can help determine the extent and progression of injury over time following exposure to repetitive compression waves²⁶. Advanced animal imaging can be more directly compared to human clinical imaging mitigating some of the limitations of histology. Functional magnetic resonance imaging would help detect some of the more subtle differences produced by the injury that is not as readily detected by traditional assays. These changes could then be mapped in conjunction

with advanced simulation techniques. Finite element and finite volume modeling are needed to further map the waves progression through the skull and into the brain²⁷. Combining the computational modeling with *in vivo* injury data will continue to require interdisciplinary collaboration²⁸. The development of these multidisciplinary teams is necessary to address the complexities of neurotrauma. By developing better understanding of pre-clinical models, important injury factors relevant to the brain such as duration until degeneration, number of impacts needed for cognitive decline, and the time scale of acute injury cascades initiated post-injury can be determined. We provide evidence that compression waves cause reproducible injuries. With the advent of more sophisticated imaging modalities, we can more successfully evaluate the relevance to TBI that is seen clinically in humans.

Conclusion

The use of numerical modeling provides a unique understanding of the wave dynamics generated by our TBI model. The model reliably produces compression waves. The injury profile outlined by immunohistochemistry confirms that cell death, axonal shearing, and tau hyperphosphorylation occurs following repetitive injury. These injury patterns may provide important clues for what is occurring in the brains of athletes following repetitive injuries. The use of advanced imaging will improve the ability to correlate between pre-clinical models and human pathology.

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Figure 1.
Geometry of Sensor Layout. A two dimensional representation shows the geometrical configuration of the problem.

Figure 2. Contour Plot 2D Pressure. Domain pressure profile shown at different times provides initial conditions and follows the shock and expansion wave development and propagation.

Figure 3. L_2 Error. A log-log plot shows converging simulation results with increasing grid resolution.

Figure 4. x-t Diagram. An x-t pressure contour plot shows the evolution of the shock and expansion waves after the diaphragm bursts.

Figure 5.

Pressure vs. Time by Sensor. A line plot provides a comparison between experiment and simulation. The experiment uses pressure taps to measure gage pressure while the simulation uses a point probe to measure static pressure.

Figure 6. Acute Pathophysiology. H&E staining reveals nuclear enlargement and fragmentation in the contralateral prefrontal cortex 72 hours post repetitive TBI. A significant increase in APP was also observed $\chi^2 = 81$, $p < 0.001$. Scale bar = 20 μ m.

Figure 7.

Neuronal Degeneration. A significant increase in fluorojade B was seen in the contralateral prefrontal cortex and hippocampus 72 hours following repetitive TBI. Thioflavin shows tau hyperphosphorylation and protein aggregation 72 hours following repetitive TBI.

= $p < 0.01$, *= $p < 0.001$. Scale bar = 50µm.