Quantification of Diffusion Tensor Changes in a Rat Model of Primary Blast-Induced Traumatic Brain Injury

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Target audience
This study is intended for researchers studying blast-induced traumatic brain injury (bTBI).

Purpose
Recently there has been a dramatic increase in the incidence of bTBI in United States military personnel. An estimated 15-20% of military personnel returning from Iraq and Afghanistan have suffered some form of bTBI1. Unfortunately, bTBI produces a heterogeneous injury that is often not grossly visible on CT or MRI, which makes diagnosis and treatment difficult. Blast exposure has three potential mechanisms of injury: (1) primary, caused by the blast pressure wave; (2) secondary, caused by debris accelerated by the blast; and (3) tertiary, resulting from rapid acceleration and deceleration of the head. Each of these mechanisms affect the brain in a different way, and therefore may benefit from different methods of prevention and mitigation. Recently, several groups have reported that diffusion tensor imaging (DTI) can detect and quantify bTBI in military personnel; however, it is often impossible to isolate a single form of bTBI in clinical populations because of simultaneous occurrence. Secondary and tertiary bTBI cause observable tissue damage, but the effects of primary bTBI have not been well characterized. Primary bTBI may lead to a wide range of subtle neurologic sequelae including increased rates of post-traumatic stress disorder2. A substantial need exists for a robust, quantifiable animal model of primary bTBI to study its effects and to help design measures to prevent or mitigate this damage. Currently, models of bTBI are assessed with myelin-stained histology, making whole brain screening and quantification difficult. In this study, we report quantitative changes in DTI tissue microstructural metrics in a rat model of primary bTBI.

Methods
We compared ex-vivo DTI images of normal rat brains to rat brains exposed to an air-blast designed to simulate isolated primary bTBI. We analyzed three groups of 10 adult male rats. Group 1 was a sham control. Group 2 was exposed to a 132-kPa air-blast. Group 3 was exposed to two, successive 132-kPa air blasts spaced one minute apart. Animals were perfusion fixed 72 hours post-injury with a mixture of 4% paraformaldehyde and a gadolinium-based MRI contrast agent (gadoteridol) to enhance MR signal. DTI datasets were acquired at 78-μm isotropic spatial resolution using a 3D spin echo pulse sequence (TR = 100 ms, TE = 16.2 ms, NEX = 1, FOV = 4 cm x 2 cm x 2 cm, matrix = 512 x 256 x 256, directions=6, b=1500 mm²/s). After tensor estimation and computation of DTI parametric maps (i.e. fractional anisotropy [FA], radial diffusivity [RD], axial diffusivity [AD], mean diffusivity [MD]), image data were spatially normalized using non-linear image registration to create an average brain template for voxelwise comparisons. We performed voxelwise analysis of DTI parameter changes in all three groups using SurfStat MATLAB tools.

Results
There was no gross pathology or tissue damage visible in unprocessed image volumes from any of the three experimental groups. We found no significant differences between single-blasted animals and controls; however, double-blasted animals had significantly lower FA than controls and single-blasted animals in several white matter regions including the deep cerebellar white matter, internal capsule, optic tracts, and anterior commissure. Areas of statistically significant decrease in FA are shown as a heat-mapped color overlay (left) displayed over coronal slices through the average brain template. All colored regions showed statistically significant decreases in FA, with hotter colors indicating increased statistical certainty. These results correlate with histological changes such as axon disruption and shearing.

Discussion
We have quantified microstructural changes in a rat model of primary bTBI using DTI. These results add to a mounting body of evidence suggesting that primary blast injury causes subtle tissue damage in the brain. Our results indicate that a double air-blast model produces a more robust and consistent injury than a single-blast model; however, increased sensitivity from improved tensor estimation accuracy, or in-vivo imaging may reveal statistically significant changes in the single-blast model.

Conclusions
This study demonstrates the feasibility of using DTI to quantify primary bTBI in preclinical models. We plan to use similar techniques to study the time course of primary bTBI injury and the efficacy of interventions designed to prevent or mitigate this injury.

References