Quantitative Imaging of Blood-Brain Barrier Permeability Following Repetitive Mild Head Impacts

Joshua Leaston

Imaginostics, Inc., Cambridge, MA, United State

Abstract

This was an exploratory study designed to evaluate the feasibility of a recently established imaging modality, quantitative ultrashort time-to-echo contrast enhanced (QUTE-CE), to follow the early pathology and vulnerability of the blood brain barrier in response to single and repetitive mild head impacts. A closed-head, momentum exchange model was used to produce three consecutive mild head impacts aimed at the forebrain separated by 24 h each. Animals were measured at baseline and within 1 h of impact. Anatomical images were collected to assess the extent of structural damage. QUTE-CE biomarkers for BBB permeability were calculated on 420,000 voxels in the brain and were registered to a bilateral 3D brain atlas providing site-specific information on 118 anatomical regions. Blood brain barrier permeability was confirmed by extravasation of labeled dextran. All head impacts occurred in the absence of any structural brain damage. A single mild head impact had measurable effects on blood brain barrier permeability and was more significant after the second and third impacts. Affected regions included the prefrontal ctx, basal ganglia, hippocampus, amygdala, and brainstem. Our findings support the concerns raised by the healthcare community regarding mild head injuries in participants in organized contact sports and military personnel in basic training and combat. There is a growing concern and expanding literature on the behavioral and neurobiological consequences of repetitive mild head impacts or concussions incurred while playing organized sports or in military combat. Mild head impacts are estimated to account for 75% of all traumatic brain injuries .Concussion following a single incident is difficult to detect and any associated cognitive and behavioral problems can resolve within hours of insults However, a more pernicious, long-lasting condition arises when the brain is exposed to repeated mild head impacts.Repetitive head impacts induce cognitive, motor and behavioral deficits, which are more severe and protracted, and can last for months and even years with an increased risk of dementia, and chronic traumatic encephalopathy (CTE).Failure in the blood brain barrier (BBB) lies at the foundation of cerebrovascular dysfunction as first described by Ward law. BBB failure is characterized by hyper permeability of endothelial walls, damage to basement membranes, and enlargement of surrounding perivascular space allowing protein, macrophage, and lymphocyte invasion and β-amyloid (Aβ) deposition (11, Disruption in the BBB commonly occurs with moderate to severe traumatic brain injury (TBI)and the insult may persist for years contributing to the neuropathology of neurodegenerative diseases (18). Animal models of repetitive mild head impact report no effect on BBB permeability.or a modest increase that persists up to 3 days post insult (21, 22). Additionally, it has been documented in literarture that an early response to TBI may be a decrease in cerebral blood flow.and it is speculated that this may play an important role in inhibiting the recovery process of repetitive mild TBI (rmTBI).There are multiple imaging protocols for detecting the gross lesions that result from the neuropathological consequences of cerebral vascular injury, such as T2 Fluid Attenuated Inversion Recovery (FLAIR), Susceptibility Weighted Imaging (SWI), and Diffusion-Weighted Imaging (DWI). However, these methods cannot quantitatively assess BBB integrity (25). The most common way for assessing BBB leakage is dynamic contrast enhanced (DCE) MRI with gadolinium-based contrast agents (GBCAs) particularly with respect to BBB permeability following head injury.DCE-MRI is limited in error in the arterial input function (AIF) and significant variances are reported for rates of leakage .More recently, higher accuracy measurements have been achieved in rodents and humans however DCE-MRI remains limited to 2-dimensional imaging with thick slabs (1 mm in mice, 5 mm in humans)—in addition to requiring toxic GBCAs which have recently obtained an FDA black-box warning for brain retention in 2017. To address the need for safe, quantitative, whole-brain non-invasive precision medicine diagnostics for mild brain injury, we explored the use of a recently established alternative technique quantitative ultrashort time-to-echo contrast enhanced (QUTE-CE) MRI (35–39). This method has recently been utilized to map BBB leakage due to Type-2 Diabetes.Here, for the first time, we report the use of this technique to measure BBB leakage at the individual animal level, and for head injury, in a model of repeated mild impacts. Subjects were all adult male Sprague Dawley rats (n = 5), ~100 days of age and purchased from Charles River Laboratories (Wilmington, MA, USA). Animals were housed in Plexiglas cages and maintained in ambient temperature (22–24°C) on a 12:12 light-dark cycle (lights on at 07:00 a.m.). Food and water

were provided ad libitum. All methods and procedures described were approved by the Northeastern University Institutional Animal Care and Use Committee (IACUC). The Northeastern facility is AAALAC accredited with OLAW Assurance and is registered with the USDA. All housing, care, and use followed the Guide for the Care and Use of Laboratory Animals (8th Addition) and the Animal Welfare Act. The protocols used in this study adhere to the ARRIVE guidelines for reporting in vivo experiments in animal research.