STUDY TITLE: Novel protection against potential brain injury during competitive football head impacts

IRB#: 2015-2205

NCT#: NCT02696200

Approval Date: 05/05/2015

CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER

STUDY TITLE: Novel protection against potential brain injury during competitive football head impacts

INVESTIGATOR INFORMATION:

Gregory D. Myer, PhD (513) 636-0249
Principal Investigator Name Telephone Number

CO-INVESTIGATORS:

Kim Barber Foss, MS ATC
Adam Kiefer, PhD

(1) ABSTRACT:

Significant morbidity, mortality, and related costs are caused by traumatic brain injury (TBI). A simple, effective, and lightweight device worn by athletes or war fighters in the field, designed to mitigate TBI resulting from blast trauma or concussive events, would save lives, and the huge costs incurred for life-treatment of surviving victims. An externally-worn medical device that applies mild jugular compression according to the principle of the Queckenstedt Maneuver (the Device) is being developed by Q30 Sports Science, LLC (Q30). Preliminary research suggests that the Device has the potential to reduce the likelihood of TBI. The currently developed collar (Smith 2009; Smith 2011; Smith 2011; Smith 2012) has been approved for studies in humans and the results indicate safety for use during high demand and maximal exertion activities, *Study ID: 2013-2240, Institutional Review Board - Federalwide Assurance #00002988).* Regarding safety, the externally worn collar is meticulously designed to mimic the body's own omohyoid muscle actions upon the jugular veins that will provide similar pressure and volume increases not to surpass that of a yawn or the mere act of just lying down.

This study will investigate the effectiveness of this device in high school athletes playing a collision sport such as football. The use of helmets during such a high-risk sport will allow for collision measurement devices to be embedded in the helmet and will not affect play or fit of equipment. Athletes participating in this study will be randomly assigned to one of two groups: 1) Device wearing during the season or 2) Non-device wearing during the season. By the nature of the sport selected, it is likely this pilot study will primarily include males, however if any female meets inclusion criteria on the team selected, she will be included in this investigation. The helmets of all participants will be outfitted with an accelerometer which will measure the magnitude of every impact to the head sustained by the athlete. Effectiveness of the device will be determined via differences in longitudinal brain imaging and functional testing following competitive football participation. A subset of athletes who report a diagnosed concussion will also receive additional brain neuroanatomical and neurophysiological testing within a week following the diagnosed concussive event. At each of these time points participants will also undergo various neurocognitive assessments outlined below.

(2) PURPOSE OF STUDY:

The purpose of the study is to monitor longitudinal changes in brain structure and function between the preseason and postseason, in a population of football playing athletes wearing the Device and compared to a similar population not wearing the device. Secondly, the purpose is to determine the protection of the device relative to amount and magnitude of sustained head impacts.

(3) BACKGROUND:

The Device has the promise of providing a novel mechanism for reducing or preventing the likelihood of TBI, and may be used in conjunction with other protective equipment. TBI is the leading cause of death in individuals under age 45. The cost of TBI in the U.S. is estimated at anywhere from $50 to $150 billion, annually. The January, 2008 New England Journal of Medicine reports, "Head and neck injuries, including severe brain trauma, have been reported in one quarter of service members who have been evacuated from Iraq and Afghanistan"(Okie 2005; Xydakis 2005; Hoge 2008). The vast majority of these injuries have resulted from exposure to improvised explosive device (IED) blast waves**.** Head injuries, concussions and the resulting trauma have been in public discussion recently as the National Football League (NFL) deals with a lawsuit regarding head injuries by about one-third of living former NFL players.

According to NASA, "The oscillation of a fluid caused by an external force, called sloshing, occurs in moving vehicles containing liquid masses, such as trucks, etc." This oscillation occurs when a vessel is only partially filled. It is hypothesized that the brain faces similar slosh energy absorption during external force impartation.(Turner 2012) Slosh permits external energies to be absorbed by the contents of a partially filled vessel or container by means of inelastic collisions. Tissues of differing densities can decelerate at different rates creating shear and cavitation. If the collisions between objects or molecules are elastic, the transfer of energies to those objects diminishes, minimizing the energies imparted by slosh.(Smith 2012)

Woodpeckers, head ramming sheep and all mammals (including humans) have small, little known and misunderstood muscles in their necks called the omohyoid muscles. Highly G-tolerant creatures of the forest have utilized these muscles to gently restrict outflow of the internal jugular veins thereby "taking up" the excess compliance of the cranial space and ultimately protecting themselves from TBI like tiny "airbags" in a motor vehicle. Rat studies by have demonstrated that we can easily and safely facilitate this muscle's actions by a well-engineered gentle compression over those muscles.(Smith 2012; Turner 2012)

The medical Queckenstedt Maneuver devised to detect spinal cord compression, gently places pressure over the external jugular veins to increase cerebral spinal volume and pressure. In this maneuver, the veins are compressed while a lumbar puncture monitors the intracranial pressure. "Normally, the pressure rise to the higher 'plateau' level occurs instantly upon jugular compression to fall again equally fast upon release of the compression"(Gilland 1969). This incredibly simple principle can be employed to protect soldiers and athletes from TBI by safely, and reversibly, increasing intracranial volume and pressure. The neck collar device is made of Outer collar - hytrel (thermoplastic elastomer),

Inner collar - TPSiV (thermoplastic elastomer), metal insert (stainless steel), and is fitted to the neck to provide a comfortable and precise jugular compression that potentially mitigates cerebral slosh (Figure 1).

Although the skull, blood, and brain are "almost incompressible," the vasculature tree of the cerebrum is quite reactive and compressible. As volume is added to the cranium, eventually the compensatory reserve volume is surpassed and the intracranial pressure increases slightly. Increasing cerebral blood volume by just 1-3% safely and reversibly reduces compliance of the cerebral vascular tree and diminishes absorption of slosh energies. Jugular compression increases cerebral blood volume almost instantaneously. As mentioned, this degree of increase has significantly mitigated slosh and TBI in laboratory animals and mimics the highly concussion resistant wild animals that are able to reflexively increase cerebral blood volume through natural jugular compression.

A landmark article, published in the *Journal of Neurosurgery*, used a standard acceleration-deceleration impact laboratory model of mild TBI. The study showed a successful and marked reduction of axonal injury following Internal Jugular Vein (IJV) compression as indicated by immunohistochemical staining of Amyloid Precursor Proteins (APP) (Smith 2012; Turner 2012). It is argued that IJV compression reduces slosh-mediated brain injury by increasing intracranial blood volume and reducing the compliance and potential for brain movement within the confines of the skull. The potential for such technique to mitigate both linear and rotational brain injury in humans by "internal protection" represents the most novel approach to mitigating TBI.

Summary of Prior Work

A. Safety testing in athletes has been approved by the local IRB and was completed in the Cincinnati Children's Hospital Human Performance Laboratory *(Study ID: 2013-2240; PI: Gregory Myer)*. Evaluation of monitored vital signs, biomechanics, cardiorespiratory capacity, postural control, dynamic stabilization, reactive index, concentration and cognition, memory, strength and power in a population of athletes showed no statistically significant adverse effect of wearing a mild jugular vein compressive neck collar compared to a sham arm band.(Myer 2013) Cumulatively, the pre and post safety measures indicate that neurologic parameters of executive function, eye hand coordination, balance, memory and reaction times were unchanged following two hours of physical testing wearing the collar prototype. Acceptance of the compression collar was not different in physiological biomarker response to the non-collared condition during maximal oxygen uptake and maximum effort power testing.(Myer 2013)

B. Magnetic Resonance Elastography was established at CCHMC in collaboration with The Mayo Clinic to support these studies. Under jugular vein compression with the collar, all participants tolerated the procedure without any untoward effects. The preliminary studies of dynamic shear strain showed no consistent pattern of wave propagation and elasticity placed upon the vascular and cranial tissues. Analysis of these data continues.

C. We studied 410 participants (ages 12 to 68 years of age) via a middle ear power analysis (MEPA) with and without the compression collar, and no complaints or untoward

effects were noted and no decline in the auditory perception was recorded. The expected changes of reduced Acoustic Reflectance of the inner ear and middle ear (indicative of reduced compliance) were noted only in subgroup analysis of those with jugular vein compression. The results of this study indicate that the neck compression collar prototype may have the potential to safely reduce energy impartation into cranial structures (i.e., the inner ear); however, further work is needed with advanced collar designs to establish this effect.

D. fMRI and CO_2 reactivity was performed on 12 adults before and after application of jugular vein compression. Results comparing before and after jugular vein compressions (with the collar) yielded no alterations in O_2 uptake or glucose metabolism to any portion of the brain.(Fisher 2013).

E. An *in vivo* clinical trial was approved by CCHMC IRB and was completed in the Cincinnati Children's Hospital Human Performance Laboratory and Radiology Department (Study ID: 2014-5009; PI: Gregory Myer) An *in vivo* clinical trial was performed in hockey players of the proposed intervention device used during sporting competitions to test its effect in ameliorating neuroanatomical and neurophysiological changes to the brain using two widely accepted techniques [diffusion tensor imaging (DTI), and event related potentials (ERPs) utilizing electroencephalography.](Reches 2014) For athletes in the non-intervention group, radial diffusivity (RD, DTI parameter associated with white matter structural integrity(Song 2003; Song 2005)) increased significantly from pre-season to mid-season. By comparison, the athletes in the intervention group did not show a significant change in RD with similar accumulated g-force head impacts. In kind, ERP analysis showed concomitant changes in brain network dynamics in the non-intervention group—the level of change was strongly correlated with the accumulated g-force of the collisions, whereas the intervention group showed no significant change. These group differences indicate that mild jugular vein compression may provide protection from the detrimental effects of collisions and resultant brain injury. These prospective longitudinal data utilized an internal (*in vivo*) approach and demonstrate, for the first time, that it is possible to protect the brain from sports related head impacts.

(4) STUDY DESIGN:

The current project will be designed following a prospective longitudinal study design. All MRI scanning will be performed on a 3 Tesla Philips Achieva MRI scanner located in Imaging Research Center (IRC) in the Cincinnati Children's Hospital Research Foundation (CCHRF). Sedation will not be used for any of the test visits. The entire MRI series, including anatomical imaging, DTI, resting state fMRI, SWI, HARDI, ASL and BOLD will be completed in 65 minutes or less (see Table 1 for detailed specifications). All functional and neurocognitive testing will be performed at the Cincinnati Children's Hospital Human Performance Laboratory.

Table 1. Image sequence, mode and analysis. Imaging will be completed in 60 minutes or less.

Sequence	Time (min)	Mode	Analysis
3D T1	5	Anatomy	Visual / Volumetrics
DTI	11	WM microstructure	Visual/ROI/TBSS or

			other
rs-fMRI	10	Connectivity/networks	Quantitative
SWI	6	Hemorrhagic Injury	Visual (Automated analysis)
HARDI	10-12	WM microstructure	Quantitative

(5) DURATION:

The study recruitment and intervention will occur during one season. Each participant will participate in 2 planned study visits that may take up to 2 hours. Data analysis will continue for a 2 year period following the final enrollment.

(6) SELECTION & RECRUITMENT OF PARTICIPANTS:

The purpose of the present study is to generate pilot data for effect size estimation and power analysis for future study. The group size proposed in the aims was determined empirically based on previous neuroimaging studies and study designs reported in the literature. The sample size proposed in this pilot study will not warrant extensive statistical analysis to test the listed hypothesis. This study is expected to lead to an accurate estimate of effect size and variability so that future studies can be designed more rigorously.

We will recruit up to 60 study participants. The participants (age 14-19 years old) will be recruited from a local school district and local sports clubs and teams. Participants will be recruited using a top-down approach. We have gained the consent and the cooperation of the school district administrations. Presentations and letters from the research team will be given to each participating school to detail the participation requirements and study risks. The high-risk sports which utilize helmets during competition will allow for measurement devices to be embedded in the headgear and will not affect play or fit of equipment. By the nature of the sports selected, it is likely this study will primarily include males, however if any female meets inclusion criteria on the team selected, she will be included in the investigation. Questions regarding participation will be answered during the presentations or through e-mail or phone. Participants will be contacted via telephone to further explain the study, answer any additional questions and to enroll them in the study. The participants and parents/guardians who voluntarily agree to participate will be scheduled to complete the pre-participation testing. The participant and parent/guardian will read and sign the "Consent to Participate in a Research Study" form, approved by the Institutional Review Board of Cincinnati Children's Hospital. If the participant and parent/guardian does not read or sign the form, they will not participate in the study. Once the potential study participants/school teams are identified, they will be allocated to one of two groups: 1) Device wearing during the season or 2) Non-device wearing during the season. This research does not mandate that the participant maintains participation in their sport. The desire to participate in the sporting event is an independent, personal decision separate from the decision to enter into this study. If any athlete choses to stop participation in the sporting activity then they will also be withdrawn from the study, due to no longer meeting inclusion criteria.

Inclusionary criteria include:

- Normal healthy volunteer
- Able to provide written consent

- Must be 14 years or older and a participant on varsity level high school football team

Exclusionary criteria include:

- Unable to provide written consent
- History of neurological deficits, previous cerebral infarction, or severe head trauma as indicated through pre-season screening:
- Medical contraindications to restriction of venous outflow via the internal jugular veins (known increased intracerebral pressure, metabolic acidosis or alkalosis)
- Glaucoma (Narrow Angle or Normal Tension)
- Hydrocephalus
- Recent penetrating brain trauma (within 6 months)
- Known carotid hypersensitivity
- Known increased intracranial pressure
- Central vein thrombosis
- Any known airway obstruction
- Any known seizure disorder

(7) PROCESS OF OBTAINING CONSENT

Once a participant is identified as a potential participant, is contacted by a CCHMC/Sports Medicine representative and verbally agrees to participate, the process to obtain consent will begin. A copy of the informed consent will be provided to the participant at this time. The study coordinator will review the informed consent and the participant will have an opportunity to ask any questions regarding the study and/or the study protocol. At that time, the participant will be given time to decide whether or not they wish to participate and if so, asked to sign the informed consent. Once the signature is obtained, the participant will be given a copy of the consent and testing will commence. At no time will the participant be coerced into participation. Receiving the informed consent prior to enrollment will allow the participants to review the study information prior to participation in the study. This will aid the participant to make an informed, unforced decision regarding election to participate in the study.

Because we will be testing teens, we will be using the Parent Consent Form to obtain both the participant assent and the parent consent. The participants and their parents will be given adequate time to review the study materials and ask questions. If they choose to participate, the patient and parent will sign the IRB approved consent forms. It will be made clear to the patient and their parents that participation in the study is voluntary.

In the event that a parent or guardian will not be present at the scheduled testing appointment, consent/assent forms will be provided ahead of time for review. The coordinator will ensure that all necessary forms have been signed prior to any data collection.

(8) STUDY PROCEDURES:

Location I – Brain Imaging-Performed at CCHMC Imagining Research Center

MR imaging data Acquisition

Magnetic Resonance Imaging (MRI), including sequences outlined in Table 1 are all based on the concept of using magnetic fields and radio waves to make chemical, anatomical and physiological assessments with in the living tissue. This technology has been utilized for diagnostic and research purposes since the early 1980s.

This testing will consist of a minimum of 2 MRI sessions (preseason, and post season) and additional scans following any clinically diagnosed concussions, all inside a 3T scanner at the CCHMC Imaging Research Center. During the acquisition of MR images, the study participants will lie on the scanner table. For most portions of MR acquisition, the study participants will only be instructed to lie still. For other parts of the acquisition, study participants will be asked to answer questions that will assess their cognitive ability and working memory. Participants will be allowed to communicate with the MR operator via an always-on, two-way intercom at any time. In addition, the participants have a hand-held air ball to squeeze in the event that they elect to be removed from the magnet immediately. The study participants have control over their presence in the magnet, which in turn tends to minimize feelings of claustrophobia. As magnetic resonance imaging employs the use of strong magnets, patients will receive a standard preoperative screening questionnaire regarding the potential for ferromagnetic objects within their bodies to ensure their safety during the study. Participants will be screened for MRI specific contraindications such as:

- Braces or permanent metal dental work
- Insulin pump
- Cardiac pacemaker
- Cochlear implants
- Hearing aids
- Aneurysm clips
- Orthopedic pins, wires, screws, or plates
- Any other exclusionary criteria as documented on the MRI safety screening poster included with recruitment materials

Those participants with any aforementioned contraindication will be excluded from the imaging portion of the study but will still be eligible to participate in the rest of the study procedures.

Location 2 -Physical and Cognitive Testing Performed at CCHMC Human Performance Laboratory

Station I: Anthropometric Measurements.

Anthropometric measures will be recorded at Station IV. Height, weight, leg length and body composition (bioelectrical impedance) will be recorded and body mass index (BMI) calculated.

Height: A measure of height will be recorded with a digital stadiometer (accurate to 0.25 cm).

Weight: A measure to the nearest 0.5 kg will be taken on a calibrated physician scale with the participants' shoes off.

Neck Measurement: We will measure the circumference of your neck with a measuring tape.

Station II – Neurocognitive Assessment

Neurocognitive testing will take place as participants will take the web version of ImPACT (Immediate Post-Concussion Assessment and Cognitive Testing). Neurocognitive testing is utilized in concussion management and ImPACT provides measures of verbal and visual memory, processing speed and reaction time. All participants will complete web-based ImPACT prior to participation in each experimental session and following any diagnosed concussion injury.

Station III - Reaction Time Testing on Smart Phone

The participants will be asked to perform simple visual and auditory reaction time testing using a customized smart phone application in which a tone plays/the screen changes color and the participant has to remove his finger as quickly as possible over 30 response trials.

Station IV – Occulomotor Assessment

All participants will sit in front of a desktop monitor. During this process, the participant will look at several points in order to calibrate the desk-top eye tracker (Tobii X2 60). All participants will participate in three oculomotor performance tests: (1) a reflexive saccade test, (2) a self-paced saccade test, and (3) a smooth-pursuit tracking test. All tests will be presented on a PC monitor approximately 1.5 m away from participant, and stimuli will be automated using customized *MATLAB* (Mathworks, Natick, MA) routines.

<u>*Reflexive Saccades*</u>. Reflexive saccades will be tested as participants track discrete target motion that will jump randomly by 14, 16, 18, 20, 22, or 24˚ on the screen in a horizontal direction, at intervals varying pseudo randomly between 1.0 and 2.0 s. The current fixation target will be extinguished at the same time as the next peripheral target appears. An auditory tone will also sound concurrently with each target jump. The test sequence will include 49 trials and all participants will be instructed to follow the targets as quickly and accurately as possible. Dependent measures for reflexive saccades will include: (1) saccade latency (ms), (2) saccade velocity (˚/s), (3) mean absolute position error of the final eye position, (4) gain of the primary saccade, and (4) gain of the final eye position.

<u>*Self-paced saccades*</u>. Self-paced saccades will be assessed as the participant glances back and forth as quickly and accurately as possible between two constantly visual targets at ± 15˚ horizontally from one another. This test will take 30 s per trial and the participant will perform 4 trials. The dependent measures will be: (1) the number of refixations within 30 s, and (2) the mean intersaccadic interval (ms).

<u>*Smooth pursuit tracking*</u>. Smooth pursuit tracking will be tested as the participant attempts to fixate and track the center of a horizontally moving stimulus on the computer screen. The stimulus will include a target moving in a predictable sinusoidal pattern with a peak velocity of 20, 40, and 60˚/s and a target moving in a random pattern with a mean peak velocity of 80˚/s. The duration of each test will be 40 s and this assessment will consist of six trials (2 per condition). Dependent measures for smooth pursuit tracking will include: (1)

average eye peak velocity (˚/s) after removal of all saccades from the tracking performance, and (2) the tracking lag (ms). Total oculomotor testing time will take approximately 10 minutes, and all eye data will be recorded using Tobii Studio software and will be sampled at 60 Hz.

Smooth pursuit tracking and occlusion. Smooth pursuit tracking will also be tested as the participant attempts to track the center of a horizontally moving stimulus prior to and after it becomes occluded as it moves on the computer screen. The stimulus will be the same as the smooth pursuit tracking mentioned above, however for 1000 ms, the target will become occluded and the participants will have to resume tracking the target object once it comes back out from behind the occluder.

Station V – Electroencephalogram (EEG)

The following cognitive tests will be performed while EEG/ERP data is collected:

Auditory oddball task. The oddball task is a classic EEG paradigm that has been extensively used for many years, in numerous studies and in many neurological patient populations. It is considered to involve executive functions, attention and memory processes. The main ERP components are N100 (low level stimulus processing) and P300 (attention allocation and stimulus evaluation), which is maximal at fronto-central areas for novel stimuli and centro-parietal for Target stimuli. In this task sounds are presented, at an average rate of 1 every 1.5sec. A total of 80% of the sounds ("standard') are tones of repeating frequency and intensity. A total of 10% of the sounds ("target") are tones of another frequency to which participants respond by pressing a button. The remaining 10% of sounds ("novel") are multi-frequency sounds, different for each trial. The test takes approximately 11 min to complete.

Go-No Go test. The Go-No Go paradigm is among the most well-established tests of response inhibition to perceptual stimuli. Go-No Go tasks involve the presentation of a continuous series of “Go” or target cues to which participants are asked to respond as quickly as possible, and “No Go” or distracter cues that require participants to inhibit motor responses. Studies involving ERP have identified a negative-going component occurring at 200 – 400 ms following the No Go stimulus known as the “No Go N2”, which occurs maximally at frontal-central scalp locations. On No Go trials, the N2 is followed by a positive-going shift. This positive complex, termed the “No Go P3”, also occurs maximally at frontal-central scalp sites and is typically seen 300 – 700 ms following the No Go stimulus. The Go-No Go task takes approximately 9 min to complete.

Resting EEG. 4 min resting EEG will be recorded at the end of the tasks, with participant fixating at the center of the screen, *2* min with eyes open and 2 min with eyes closed.

Injury Surveillance

Device and Compliance Acceptance: The study coordinator will be responsible for providing the appropriate intervention (device or no-device) to each team based on their random

assignment prior to the season onset. At first fitting of the collar a registered vascular technologist will utilize ultrasound to ensure that the collar fits correctly and is activated as prescribed. Following the initial fitting, each athlete will receive adequate instruction on how to properly use the device on a daily basis. Throughout the season, the coordinator will make routine visits to each team to monitor the proper usage and fitting of the device, tracking the use of the device by each athlete individually.

New Concussion Surveillance and Follow-up: Each helmet of the study participant will be instrumented with a GForce Tracker™ (GFT; gForceTracker, Markham, Ontario)) accelerometer device. The GFT will be affixed to the inside of each participant's helmet. The GFT is equipped with electronics that allow for the measurement of linear accelerations and rotational velocities of the head. The GFT measures 6 degrees of freedom by directly measuring three axes relative to linear acceleration and three axes relative to angular velocity. The GFT stores all impacts locally. These devices need to be connected physically to a computer, and data can only be accessed with a unique username and password only known to the research team. Accelerometer tracking and management will occur at every game and practice by the team Athletic Trainer (AT).

GFT is a small and durable device that is attached to or embedded in any helmet to track impacts, and it stores data for uploading to a PC. The GFT software converts tracker data in real-time for player and team analysis. This software accurately measures the severity of impacts by converting data such as high impact collision into usable reports. De-identified impact data are then transmitted to a cloud-based server, accessible only to researchers on this protocol via a unique username and password. GFT data will be used in final analysis to normalize the exposures to potential concussive events. All impact of greater than 10 g-force will be recorded and utilized in the post-season analyses. No one besides those approved by this IRB protocol will have access to any data. If available, video of games and practices will be used to validate and confirm head impacts recorded by accelerometers.

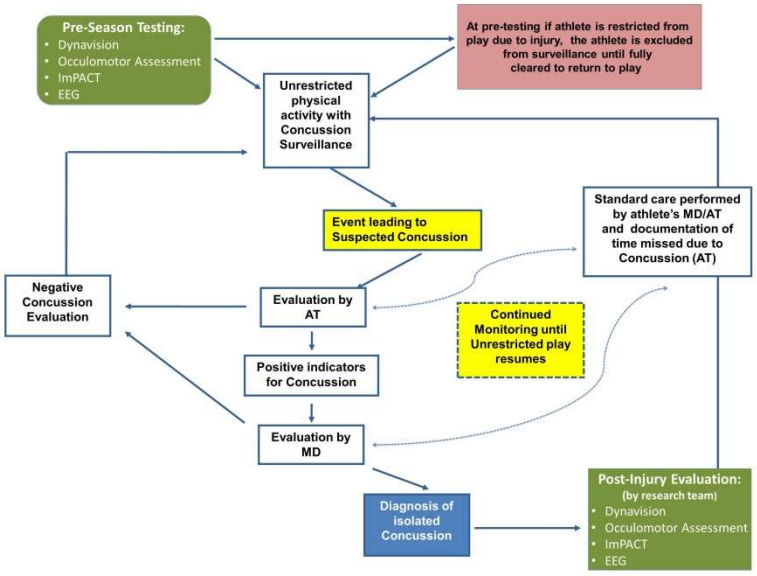

Figure 3. illustrates the steps that will be initiated when a concussive event is observed.

The study participants will also be monitored on a weekly basis for athletic exposures, and new concussion injury for a single season. Injury surveillance and concussion incidence will be monitored by the AT (K. Barber Foss) who will work directly with team athletes to visit each school and each team weekly following the initial screening. We will be monitoring injuries throughout the competitive sports season and collecting information about injuries from the school athletic trainer. Concussion will

be reported according to criteria outlined in recent multi-investigator consensus documents (McCrory, 2013). The incidence of concussion will be calculated in this study using cases identified through two primary mechanisms: 1) Monitoring of concussion injuries and time missed from planned physical activity by the AT for each team, and 2) weekly inquiries to each coach by the Study Coordinator as to whether any participants are missing time from activity due to concussion. This dual query approach enables the Study Coordinator to cross check the injury and exposure data collected to improve the accuracy of the data. The data secured from the coach regarding each athlete's participation in individual practices and games combined with accelerometer exposure to impacts allows the research team to capture robust individual athlete exposures rather than just combined team exposures.

The athletic trainer will evaluate any athlete for whom a concussive event has been observed (within 24 hours). If criteria for concussive sequelae are not met, the athlete is cleared for return to play. In the event of a positive concussion evaluation by the AT, an MD will perform a second evaluation. Should the MD concur with the AT on a positive evaluation, a diagnosis of isolated concussion is made and the athlete is removed from play and participant is referred for to a post-concussion evaluation. The diagnosing physician will be blinded to the experimental treatment of the study participants.

Post-concussion and post season testing consists of the same battery of tests as performed for pre-season testing, which allows for direct comparison between typical and concussed data. In addition, concussed athletes will complete the Post-Concussion Symptom Inventory (PCSI) questionnaire at the beginning of the testing session and repeated at the conclusion of this session. Additional neurologic testing is done on athletes with confirmed or suspected concussion to narrow down neuro-systems involved. Concussion evaluations will be repeated as needed until the MD is satisfied that the athlete has fully recovered from the concussion. This includes a return to baseline at rest, no exam abnormalities, and baseline symptoms with sports-specific exertion; whereupon the athlete will be cleared for return to activity. The amount of time the athlete was considered unfit to play will also be considered as one of the endpoints of this study. If any athlete choses to stop participation in the sporting activity following a concussion then they will also be withdrawn from the study, due to no longer meeting inclusion criteria.

(9) DATA ANALYSIS/METHODS:

Data Storage.
The personal demographic data for each participant will be blinded from the researchers, and a coded identification number will be used to track all collected data. Data will be stored on password-protected computers and only pertinent research personnel will have access. Data forms will be stored by coded identification number in a locked cabinet to which only pertinent research personnel have access. All data will be collected for research purposes only.

Data Analysis.
Data processing and analysis will be performed using a series of existing software including FSL (FMRIB's Diffusion Toolbox in FSL Software, Oxford, UK), AFNI (Cox, 1996) , SPM (Statistical Parametric Mapping analysis package, Wellcome Department of Cognitive

Neurology, London, UK), DTIStudio (John Hopkins University, Baltimore, MD; Jiang et al., 2006), as well as additional customized software written in Matlab or IDL.

DTI data will first be subjected to preprocessing to correct for Eddy current and head motion artifact, followed by calculation of the three diffusion eigenvectors and eigenvalues. DTI measures, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) will be calculated. The regions of interest will be manually determined in major white matter areas such as corpus callosum, internal capsule, and external capsule. After being normalized to a common template, voxel based group analysis can be performed to explore brain regions that present significant group difference or longitudinal changes. Fiber tracking can be performed to generate white matter tracts in different areas in the brain, e.g., cortico-spinal tract, different segments in corpus callosum, optic radiation, cingulum superior longitudinal fasciculus, and others.

Functional fMRI (resting state fMRI) will also be subjected to routine image pre-processing pipeline. Functional connectivity analysis will be performed, using the CONN toolbox, http://www.nitrc.org/projects/conn/) between all brain regions that are involved in the proper functioning of default mode network, sensory motor network, visual network, and a series of other networks that are known to be strongly functionally connected during resting state. SWI, HARDI and ASL BOLD will undergo standard image post-processing.

BNA Analysis EEG signals recorded will be cleaned by standard procedures, band pass filtered into overlapping physiological frequency bands, cut into epochs around sufficient pre and post stimulus onset times, and averaged to result with event related potentials (ERPs). For each band, the data is reduced into a set of discrete points that denote local extrema, the latencies and amplitudes of which are inputted to the algorithm. The algorithm then seeks a state-unique multi-sited spatiotemporal pattern. This is the BNA group network. Following that, a BNA score is computed for each participant individually. It is comprised of a set of similarity measures to a BNA group network or a group of BNA networks. Once normative data is established, patients who require assessment of their brain electrophysiological activity will undergo BNA analysis, and their scores will be compared to the BNA pattern of the normative data.

For the group analysis, the raw EEG of each participant undergoes three separate processing stages: (1) preprocessing (artifact removal, band-passing); (2) salient event extraction (discretization, normalization) and (3) network analysis (unitary events extraction, pair-pattern extraction) on all salient events gathered from all of the participants. The single participant level process involves three stages – the first two are identical to the first two stages of the group level process. In the third stage, the single participant activity is algorithmically compared to the set of patterns collected during the group analysis stage (see below).

The SIn (network) of a pair-pattern is 1 if it applies at all to a tested participant (i.e., the participant's electrode activity fulfilled the constraints set by the pair-pattern) and 0 if it does not. To assess the SIs (synchronicity) of all pair-patterns with an SIn of 1, the times of the discrete activity points of the individual participant are compared to the mean and SD of the activity times of the respective group pair-patterns. The SIa (amplitude) of the pair is

evaluated in a similar manner, by comparing the amplitudes of the activity points. The overall BNA score of the individual participant to each of the groups is computed by averaging the products WI (weight index) x SI (synchronicity index) of all pairs in all patterns of the group. For each participant, the classification score is computed separately for each similarity index such that three classification scores were computed: a network score, a synchronization score and an amplitude score:

$$Cnet = \frac{\sum_i (W_i * SIn_i)}{\sum_i W_i}, \quad Csync = \frac{\sum_i (W_i * SIs_i)}{\sum_i W_i},$$

$$Camp = \frac{\sum_i (W_i * SIa_i)}{\sum_i W_i}$$

Statistical considerations. The data analysis will begin with a review of descriptive statistics for all major variables and all major subgroupings of variables in the data set. For the inferential methods, we will use a number of different generalized linear modeling techniques, including linear regression models. All analyses will be conducted using SAS® version 9.3 (SAS Inst, Cary, NC), or Mplus (Muthén, 2007). Initial analyses will be undertaken to inspect data for errors, inconsistencies, and incomplete information. This will include examining the data with simple frequency tables and dot plots for univariate data and scatter plots and multi-way dot plots for bivariate and multivariate data. Data anomalies that cannot be resolved by the Biostatistical/data management team will be sent as queries via email to the project investigator for clarification and/or correction. During the verification process, outlying values will be corrected if necessary. Incomplete information will be corrected and the project investigator will receive updates. To summarize bivariate relationships among predictors and between predictors and outcomes, Chi-square of Fisher's exact test or Spearman's rank correlation coefficient, will be used, as appropriate. For reporting inferential statistics, such as differences in rates or means, 95 percent confidence intervals will be used extensively to quantify degree of clinical efficacy. Unless otherwise stated, statistical tests are considered two-sided and a .05 significance level is used. All models will be adjusted for potential independent predictor variables but will be limited to the number of predictors we can fit in a regression model while maintaining a valid and reliable model. Candidate predictors include amount of playing time, amount of practice time, previous mTBI, weight, age and height. Collinearity will be examined. Linearity assumptions will be checked and transformations examined. In those cases, a log transformation, polynomial terms, or restricted cubic splines will likely be used to relax the assumption of linearity in the regression models. We will remove the nonlinear terms or transformation only if the nonlinear test is non-significant with a $p \geq .10$. Additionally, overly-influential observations and distributional assumptions will be checked. Models will be interpreted graphically, predicted values will be examined, and appropriate significance tests will be utilized.

Statistical analyses. - Statistical analysis of outcomes measures will be done using SAS®, version 9.3 (SAS Institute, Cary, NC) and SPSS statistical software (SPSS Inc, Chicago IL). Comparisons between the testing conditions (collar vs. no collar) will be made using Analysis of Covariance, in order to control for time (pre vs post season) and condition (collar versus no collar). We will also conduct correlation analysis to test the association between imaging biomarkers (as described above) with the results obtained from the impact surveillance. The collision indices,

including total number of collisions, number of collisions from front, back, left, right, top, bottom, G force, and timing of each collision will all be recorded and tested in the analysis. Secondary analysis to compare the intervention with no intervention and calculate the rates would involve a Poisson model, using an offset to account for the playing time and exposure to concussive impact for each of the study participants. We will calculate the rate and the associated 95% confidence interval. SAS®, PROC GENMOD will be used for analysis, which allows us to account for the fixed and random effects, use the appropriate link function, and the offset for amount of playing time exposure.

Simple Reaction Time

A repeated measures mixed-model design will be employed. A total of up to three groups (Device vs. no device vs concussion) will be examined using a 3 x 2 (group by time point; pre-season vs. post-season) ANOVA.

Oculomotor Measures

Oculomotor control performance will also be compared using a 3 × 2 mixed-model ANOVA for each of the dependent variables. For smooth pursuit tracking performance, mean eye peak velocity and tracking lag will be submitted to separate 3 (group) × 2 (session) × 2 (random vs. sinusoidal task condition) mixed-model ANOVA.

(10) FACILITIES AND PERFORMANCE SITES:

All MRI scanning will be performed on a 3 Tesla Philips Achieva MRI scanner located in Imaging Research Center (IRC) in the Cincinnati Children's Hospital Research Foundation (CCHRF). Sedation will not be used for any of the test visits. The entire MRI series, including anatomical imaging, 3d T1, DTI, rs-fMRI, SWI, and HARDI will be completed in 60 minutes or less (see Table 1. below for detailed specifications). All functional and neurocognitive testing will be performed at the Cincinnati Children's Hospital Human Performance Laboratory.

(11) POTENTIAL BENEFITS:

Participants of this study will not receive any direct or immediate benefits by completing this study. However, they will be contributing to research involving the potential for major contributions to future TBI/concussion prevention strategies.

(12) POTENTIAL RISKS, DISCOMFORTS, INCONVENIENCES AND PRECAUTIONS:

The Device partially circumnavigates and compresses the neck in the same way that a compression garment (non-medical apparel) behaves, and very similar to the compression exerted by a necktie (although this device is open over the trachea and can be pulled off if inadvertently gripped). These garments have been shown to gently facilitate natural response mechanisms in several small neck muscles and tendons (the Omohyoids), which are universally present in mammals and birds.

The physiologies imparted by these Omohyoids (and further facilitated by these garments) merely approximate natural physiologies, which occur when individuals lie in the prone, or supine position, and are also comparable to the simple act of yawning (which has been shown to collapse the jugulars). The Device will intentionally deliver an exacting, but gentle compression to the Omohyoid muscles in the neck allowing these muscles to optimize blood

outflow of the neck vasculature. In the upright position (without the collar), the resultant vascular blood column siphons volume out of the neck, rapidly, creating a negative pressure on the cranium and resulting in a slight "under filling" and "sloshability" inside the skull.
The Omohyoid muscle raises the volume of the intracranial space by design. The Device does not contain any inherently rigid structures in its design. Similarly, neckties circumnavigate the neck, and safely raise intracranial pressure and volume comparable to the Device. The Device is manufactured of a soft rubber similar material and should be barely noticeable to the wearer. Careful MRI studies have confirmed an increase in blood volume in the brain but have also shown that there is no significant change in brain blood flow pattern with wearing a "tight necktie" (Rafferty 2010).

Although the venous jugular flow beneath the pressure cuff may be temporarily halted or slowed, the venous outflow from the cranium is never completely stopped, particularly from the anastomosis between the spinal vein and the basilar plexus and occipital sinuses *which are incompressible*."(Gregg 1944) Jugular compression has few known physiological effects besides the intended increase in cerebral blood volume and pressure. Only one innocuous physiology has ever been shown to alter with jugular compression. "Previous studies have shown that the decline in urinary sodium excretion which occurs normally in the sitting position, as compared with recumbency, can be partially but not completely prevented by compression of the neck (Lewis 1950; Torres 1970). This decline is urinary sodium excretion is minimal. There was no correlation between EEG changes and changes in systolic blood pressure occurring during jugular or carotid compression(Torres 1970). Further, studies on complete resection of the IJV note that, "the clinical observation that bilateral resection of the IJV is usually well tolerated suggests the presence of alternative, non-jugular pathways."(Gius 1950)

Effect of Body Position and Exercise on ICP: "At rest, compared with the reference 30-degree head-up position, the supine position increased intracranial pressure (ICP) by 6.21 mm Hg (35% with P<.01)."(Brimioulle 1997) Restated, just lying down increases ICP more than the Device (6.21mm Hg = 35% rise versus this device at only 25%). *Valsalva and raising ICP:* We define Valsalva, where a person tries to exhale forcibly with a closed glottis (windpipe), so that no air goes out through the mouth or nose. "When the Valsalva maneuver was performed during resistance exercise, the ICP rose to 31 mmHg (a rise of 138%). No complications were associated with participating in this investigation."(Haykowsky 2003) In other words, the Device facilitates the intended actions of the omohyoid with less pressure than the act of lying down or performing the Valsalva (holding one's breath and bearing down, which would be expected to occur regularly on a playing field).

Instead of letting three to five milliliters of blood rapidly flow out of one's brain upon standing, the Device will serve to retain that fluid inside the skull where it is believed to cushion the brain from external energy impacts and concussions. In rats, this simple action prevented 83% of TBI indicators during two 900 G impact studies at the West Virginia University.(Smith 2012; Turner 2012)Considering the above mentioned findings on jugular compression, this device can be considered not to meet the definition of a "significant risk device," as that term is defined in 21 C.F.R. § 812.3(m).

MR Imaging of the Brain: The risk the magnetic fields and the strengths, and radio waves is vanishingly small. Some patients can experience anxiety from the confined space of the magnet's bore. Therefore people with known claustrophobic tendencies will be excluded from the study. Another minor concern when using magnetic resonance technology is the noise the magnet makes when collecting data. Noise abatement measures are used; headphones and music with a selection of music options. Ferrous implants and or piercings can be affected in the magnetic field. Therefore participants will be advised to remove these and or scanned with a metal detector to screen for such objects.

Our colleague's previous experience with MRI experiments (who will be present and has a decade of experience with this technology) has provided confidence that there should be no psychological, physical, legal, or social risks involved with MRI experiments in general, though participants may be anxious about the scan, possibly causing them slight stress. The MRI scanning will be performed using the 3 T Siemens Trio MRI scanner. MRI does not involve ionizing radiation and scans up to 8 T are considered as non-significant risk. The risks common to all MRI scans can be described as: (1) ferromagnetic objects introduced into the magnetic field, (2) confinement in the scanner bore, (3) radio-frequency (RF) heat deposition in tissue which is monitored by the system to conform with FDA guidelines, and (4) acoustic noise. These risks are addressed below: Participants are allowed to communicate with the MR operator via an always-on, two-way intercom at any time. In addition, the participants have a hand-held air ball to squeeze in the event that they elect to be removed from the magnet immediately. Thus, the participants have control over their presence in the magnet, which in turn tends to minimize feelings of claustrophobia.

The MR imaging will be initially reviewed by a licensed radiologist just as it would be if it were being used as part of routine medical care. There is a possibility that while reviewing MR images we may see an abnormality that we did not expect to see in this study. In this event, we will notify the participant's legal representative (or participant is 18 years or older) if we see such an incidental finding. Depending on the type of incidental finding, we may contact the participant by mail or by phone. A member of the research team will discuss the incidental finding with the legal representative (or participant if over the age of 18 years). If the participant chooses, we will give information about this incidental finding to their primary doctor or we will refer them to an appropriate doctor for further evaluation. The costs for any care that will be needed to diagnose or treat an incidental finding would not be paid for by this research study.

Data Storage. There is also a minimal risk that the data collected for each participant may be viewed by individuals outside the research team. The risk that confidential data may be viewed is relevant for both the written forms and electronic databases. Precautions, such as password-protected computers, locked cabinets and coded identification numbers, are in place to minimize this risk.

Adverse Events. During the course of the investigation, injuries consistent with the sports being monitored are expected to occur (E.g. concussion, musculoskeletal injury, bone fractures). Care of all injuries will follow standard of care as directed by the team's athletic trainer and/or the participants treating physician. CCHMC will not be responsible for the

medical treatment of any injuries that are not directly related to wear of the Q-collar device. In the case of an adverse event that is determined to be directly related to the wear of the Q-collar during competitive play, the principal investigator will report such event to Cincinnati Children's Hospital Medical Center IRB as any future funding organizations in a manner consistent with the requirements of each organization. As described in the consent, if a participant believes they have sustained an injury as a result of the study then they are instructed to contact the principal investigator or director of social services who in turn will then contact CCHMC IRB and necessary funding institutions, as aforementioned. If a participant sustains an injury during testing they will be referred to the most appropriate medical facility or seek medical attention by the physician/medical specialist of their choice.

(13) RISK/BENEFIT ANALYSIS:

Participants will be approached for participation via the appropriate method. The purpose and the study protocol will be fully explained in conversation and with the informed consent process.

On the day of the study, the investigators will confirm that the volunteer participant has no health impairment as outlined in the exclusion criteria. Time will be taken to repeat the aims of the study, test protocol, and to answer any remaining questions posed by the participant. The methods described in this protocol have been used extensively in previous testing in the laboratory. During previous testing, there have been no reported injuries, adverse events or complications. Additionally, the investigators have considered potential risk for injury and have taken additional steps, described in the protocol, to minimize these risks.

A study participant may be withdrawn from the investigation if they demonstrate repeated alteration in their proper football tackling technique, such as adoption of spearing tackling tendencies. Subject participation will also be halted should an adverse event while wearing the collar, such as syncope, occur. Any adverse events will be immediately reported. The safety officer will evaluate all adverse events and will determine if early stopping of the study due to safety concerns is warranted. Given the study design and sample, we do not deem futility or efficacy stopping rules are warranted.

(14) DATA SAFETY & MONITORING:

The Safety Officer (Dr. Paul Gubanich, MD) who has extensive experience in the management of concussion at the professional, collegiate, high school and middle school level will act in an advisory capacity to the Principal Investigator (PI) to monitor patient safety and progress for the clinical trial, "Concussion Prevention Device". Dr. Gubanich will be the contact person for severe adverse event reporting.

The Safety Officer's responsibilities are to:

- review the research protocol, informed consent documents and plans for data safety and monitoring;
- evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the trial site, and other factors that can affect study outcome;

- consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- review study performance, make recommendations and assist in the resolution of problems reported by the PI;
- protect the safety of the study participants;
- report to the PI on the safety and progress of the trial;
- make recommendations to the PI concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- ensure the confidentiality of the trial data and the results of monitoring; and, assist the PI by commenting on any problems with study conduct, enrollment, sample size and/or data collection.

The Safety Officer and PI will hold meetings to review the data safety, the first of which will be held prior to initiation of the trial to discuss the protocol, approve the commencement of the trial, and approve the plans for monitoring the study. Meetings with the safety officer will be determined by the PI and will be closed to the public because of confidentiality considerations. An emergency meeting may be called at any time by the Safety Officer, or by the PI, should questions of participant safety arise.

Dr. Paul Gubanich, Division of Sports Medicine, will serve as a study monitor for this project, while the PI and study coordinators will be responsible for monitoring data quality and adverse events. The monitor will review adverse events and unanticipated events at the time they occur and will report his assessment of the event(s) to the PI.

This research study involves only minimal risk for participants (see Risk/Benefit Analysis section (15)). Further assurances regarding participant safety and protection of private and confidential participant information have been outlined in the Potential Risks, Discomforts, Inconveniences and Precautions section (14), the Privacy section (18) and the Confidentiality section (19). If during the, preliminary analyses the research team identifies strong evidence of harm from the Q-collar device the study will be stopped immediately.

(15) PRIVACY AND CONFIDENTIALITY:

The participant has the right to privacy. The investigators will protect participant privacy to the extent allowed by law. All facts about this study that can describe a participant's name will be kept private. Results of the study will be summarized regarding age, etc. but the investigators will take every precaution necessary to keep names private.

To maintain the privacy information of study participants, only pertinent research personnel will have access to participant information. Research personnel are employees of CCHMC and have been trained in human participants research and HIPAA compliance. To further insure privacy, all data will be analyzed and tracked using a coded identification number that does not use identifiable personal information. Personal information and identifiers will be securely recorded and filed by the administrative assistant. The data will be encrypted with a

password and stored on a personal computer and backed up on a network drive. The participant identification code will be used on all data questionnaires.

The results of this study will be kept confidential. No participant identification will be made public record in any form unless the participant gives his or her expressed written permission of release of participant's name, photograph or likeness captured on video. The investigators will be available for any questions that may arise.

To further insure confidentiality, only pertinent research personnel will have access to participant information. Research personnel are employees of CCHMC and have been trained in human subjects research and HIPAA compliance.

(16) COST OF PARTICIPATION:

Participants will endure no costs other than time and effort in participating in this study. Insurance will not be billed for any of the tests associated with this study.

(17) PAYMENT FOR PARTICIPATION:

Participants will be compensated for their time and effort in participating in this study. They will receive a $50 Clincard Mastercard® gift card for completing the first testing session and a $100 Clincard Mastercard® gift card for completing the final testing session. Participants who sustain a clinically diagnosed concussion will also receive $50 for each completed session following new concussion diagnosis.

References Cited

Reches A, Laufer I, Ziv K, Cukierman G, McEvoy K, Ettinger M, Knight R, Gazzaley A and Geva A (2014). "Network dynamics predict improvement in working memory performance following donepezil administration in healthy young adults." NeuroImage **88**: 228-241.

Fisher JA, Duffin J, Mikulis D and Sobczyk O (2013). "The effect of jugular vein compression on cerebral hemodynamics in healthy subjects." Unpublished Report.

Myer GD, Edwards NM and Clark JF (2013). "Safety and Tolerance of mild jugular compressive neck device during sports related exertional tasks." Unpublished Report.

Smith DW (2012). Methods and devices to reduce damaging effects of concussive or blast forces on a subject. Publication # WO/2012/054262, 26.04.2012, TBI Innovations LLC.

Smith DW, Bailes JE, Fisher JA, Robles J, Turner RC and Mills JD (2012). "Internal jugular vein compression mitigates traumatic axonal injury in a rat model by reducing the intracranial slosh effect." Neurosurgery **70**(3): 740-746.

Turner RC, Naser ZJ, Bailes JE, Smith DW, Fisher JA and Rosen CL (2012). "Effect of slosh mitigation on histologic markers of traumatic brain injury: laboratory investigation." J Neurosurg **117**(6): 1110-1118.

Smith DW and Fisher JA (2011). Methods and device to reduce slosh energy absorption effects by reducing blood flow from the cranium. Publication # WO/2012/054262, 26.04.2012.

Smith DW and Fisher JA (2011). Device to reduce slosh energy absorption and its damaging effects through reduction of the flow of one or more outflow vessels of the cranium. Publication # US20120197290 A1, 01.02.2011. USA, TBI Innovations LLC.

Rafferty M, Quinn TJ, Dawson J and Walters M (2010). "Neckties and cerebrovascular reactivity in young healthy males: a pilot randomised crossover trial." Stroke Res Treat **2011**: 692595.

Smith DW (2009). Method to reduce slosh energy absorption and its damaging effects through the reduction of inelastic collisions in an organism. . Publication # us2011/0065637 A1, 17.03.2009. USA, TBI Innovations LLC.

Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC and Castro CA (2008). "Mild Traumatic Brain Injury in U.S. Soldiers Returning from Iraq." New England Journal of Medicine **358**(5): 453-463.

Okie S (2005). "Traumatic brain injury in the war zone." N Engl J Med **352**(20): 2043-2047.

Song S-K, Yoshino J, Le TQ, Lin S-J, Sun S-W, Cross AH and Armstrong RC (2005). "Demyelination increases radial diffusivity in corpus callosum of mouse brain." Neuroimage **26**(1): 132-140.

Xydakis MS, Fravell MD, Nasser KE and Casler JD (2005). "Analysis of battlefield head and neck injuries in Iraq and Afghanistan." Otolaryngol Head Neck Surg **133**(4): 497-504.

Haykowsky MJ, Eves ND, DE RW and Findlay MJ (2003). "Resistance exercise, the Valsalva maneuver, and cerebrovascular transmural pressure." Med Sci Sports Exerc **35**(1): 65-68.

Song S-K, Sun S-W, Ju W-K, Lin S-J, Cross AH and Neufeld AH (2003). "Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia." Neuroimage **20**(3): 1714-1722.

Brimioulle S, Moraine JJ, Norrenberg D and Kahn RJ (1997). "Effects of positioning and exercise on intracranial pressure in a neurosurgical intensive care unit." Phys Ther **77**(12): 1682-1689.

Torres F and Ellington A (1970). "Changes in the electroencephalogram and in systemic blood pressure associated with caro0d compression." Neurology **20**(11).

Gilland O, Chin F, Anderson WB and Nelson JR (1969). "A cinemyelographic study of cerebrospinal fluid dynamics." Am J Roentgenol Radium Ther Nucl Med **106**(2): 369-375.

Gius JA and Grier DH (1950). "Venous adaptation following bilateral radical neck dissection with excision of the jugular veins." Surgery **28**(2): 305-321.

Lewis J, Buie R, Sevier S, Harrison T and TR H (1950). "The effects of posture and congestion of the head on sodium excretion in normal subjects." Circulation **2**.

Gregg D and Shipley R (1944). Experimental approaches to the study of the cerebral circulation. Fed. Proc.