STUDY TITLE: **Sex and Age Ultrasound Response to Differential Jugular Vein Pressure**

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CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER

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(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 currently being experienced for life-treatment of surviving victims. An externally-worn medical device (the Device) that applies mild jugular vein compression according to the principle of the Queckenstedt Maneuver, 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 and Fisher 2011, Smith and Fisher 2011, Smith 2012) has been approved for studies in humans (IRB 2013-2240) and the results indicate safety for use during high demand and maximal exertion activities. 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. Initial safety testing and early clinical trials indicate that the collar application is both safe and efficacious to prevent brain microstructure and neurophysiological changes in response to head impacts.

(2) PURPOSE:

Clinical trials have suggested that this device is effective in mitigating changes in brain structure and function in athlete populations. The purpose of the current study is to measure the response of the jugular vein to various pressures applied by a generic compression device across various ages and gender. The relative jugular vein response will be measured using ultrasound.

(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. Concussion in female high school soccer players have been noted to occur at a rate of 4.5 concussions per 10,000 athletic exposures (Comstock, Currie et al. 2015). We propose that *Slosh Theory* can explain these differences offering a mechanistic approach that could help shed light on further ways to alleviate the TBI burden on society. Note

that *Slosh Theory* teaches us that hydrodynamics (fluids moving within moving containers) contribute to, or are even the main etiology for, energy absorption of the cranial contents and that mitigation of *SLOSH* (increased compensatory reserve volume) may mitigate TBI.

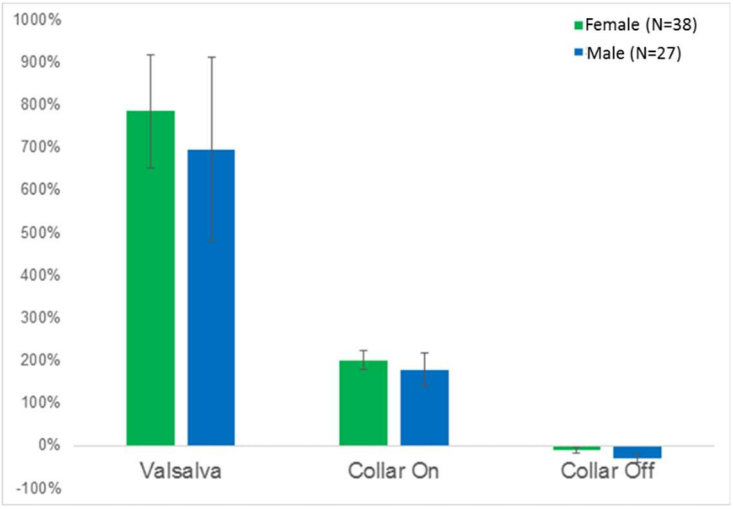
According to NASA, "The oscillation of a fluid caused by an external force, called sloshing, occurs in moving vehicles containing liquid masses, such as trucks, etc." This oscillation occurs when a vessel is only partially filled. It is hypothesized that the brain faces similar slosh energy absorption during external force impartation.(Turner, Naser et al. 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, Bailes et al. 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, Bailes et al. 2012, Turner, Naser et al. 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, Chin et al. 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, Bailes et al. 2012, Turner, Naser et al. 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. Initial safety testing and early (pre) clinical trials (detailed below) indicate that the collar application is both safe and efficacious to prevent brain microstructure and neurophysiological changes in response to head impacts. These data create the impetus better understand the jugular vein's response to collar application. Relative to the proposed investigation we have compared the ultrasound response to the standard collar in high school female and male athletes and have not seen a sex specific response. We are interested to learn more about the relative responsive of different ages and sex to the collar application and to determine the minimum relative pressure that is required to invoke the jugular vein response.



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, Edwards et al. 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, Edwards et al. 2013)

B. Magnetic Resonance Elastography was established at CCHMC in collaboration with The Mayo Clinic to support these studies (IRB: 2013-2240). 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, Duffin et al. 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, Laufer et al. 2014) For athletes in the non-intervention group, radial diffusivity (RD, DTI parameter associated with white matter structural integrity(Song, Sun et al. 2003, Song, Yoshino et al. 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 that it is possible to protect the brain from sports related head impacts.

F. 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: 2015-2205; PI: Gregory Myer). The *in vivo* clinical trial was performed in football players implementing the proposed intervention device used during sporting competitions to test its effect in ameliorating neuroanatomical changes to the brain using evidenced by diffusion tensor imaging (DTI), Based on pre-clinical data we hypothesized that collar imparted jugular compression that minimally restricts venous outflow to encourage cerebral venous sinus engorgement would reduce brain injury biomarkers in athletes exposed to head impacts during a competitive football season. This project utilized a prospective controlled trial to evaluate effects of mild jugular vein (i.e., neck) compression (collar; n=31) relative to controls (no-collar; n=30) during a competitive football season (males; 17.04 ± 0.67 years). Helmet sensors were used to collect daily impact data in excess of 20 g (games and practices) and the primary outcome measures, which included changes in white matter microstructure, were assessed by diffusion tensor imaging (DTI). Specifically, four DTI

measures including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were analyzed using a Tract-Based Spatial Statistics (TBSS) approach—a voxel based analysis. The final analyses included both an intent to treat (ITT) and per protocol evaluation of the collar intervention. The ITT analysis indicated a consistent vascular response by the athletes to collar compression, as indicated by internal jugular vein dilation (IJV) superior to its application ($p < .01$). Both groups experienced similar overall g-forces and total head impacts during the competitive football season (impacts > 20 g; collar 16983 vs no-collar 17750 ($p > .05$). Significant pre- to post-season reduction in MD, AD, and RD (corrected $p < .05$) was evidenced by extensive WM areas in the no-collar group, while no statistically significant longitudinal change was indicated for any of the DTI measures in any WM region in the collar group. Comparing the two groups, the no-collar group demonstrated significantly larger pre- to post-season DTI change in many WM regions (corrected $p < .05$). Correlation analysis also showed initial evidence of significant correlation between the change in AD in some WM regions and the number of impacts and/or the cumulative G-force experienced in the no-collar group (all $p < .05$). Per protocol, results were consistent with presented ITT findings with an expected increase in effect sizes noted in most voxel analyses. Our findings, based on four DTI measures known to relate to brain injury, indicate a consistent reduction of change in diffusivity parameters noted in the no-collar group at post-season. This is a literature driven sign of sub-threshold white matter injury due to repetitive head impacts during the competitive season. The smaller and statistically non-significant change in diffusivity in the collar group evidences a protective effect from the induced jugular outflow impedance. Restated, the approach to impede IVJ blood flow appears to have ameliorated the detrimental effects that resulted from a season of head impacts. The current study presents the first football related prospective longitudinal data and demonstrates a novel, in vivo, approach to protect the brain from football related head impacts. These results build on prior research and evidence the need for future work to determine if this novel method for brain injury prevention is both safe and effective. Understanding the intracranial mechanism of these potential protective effects is critical to further development.

G. 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: 2016-0988; PI: Gregory Myer). We aimed to investigate (1) whether repetitive head impact exposure during a soccer season induced significant functional changes in the brain network in female athletes; and (2) whether a neck collar that applies mild jugular vein compression to engorge the cranial reserve volume (to reduce brain slosh during head impact exposure) can ameliorate resultant change in brain functional network activation. Neuroimaging data was acquired prospectively prior to and immediately following a high school soccer season in female athletes. These athletes were assigned to the non-collar group ($n=12$, age = 15.61±1.00 years) and the collar group ($n=8$, age = 15.30±1.19 years, $p = 0.53$). Head impact exposures were recorded during all practices and games using X2's X-patch wearable sensor. A standard N-Back task was used to engage working memory during functional MRI at both pre- and post-season. On average, the athletes in the two groups experienced a similar number of impacts (145±91 vs. 143±23, $p=0.95$). Increased brain activation of working memory was observed from pre-season to post-season in the non-collar group ($p < .05$, corrected) but not in the collar group. Compared to the non-collar group, significantly lower alteration in fMRI brain activation ($p < .05$, corrected) was found in the collar group in the cingulate gyrus and the angular gyrus, both of which are known to be associated with memory functions. The current data indicate that repetitive head impact exposure

associated with participation in high school soccer is related to the altered functional brain network in female athletes. The significantly increased brain activation from pre- to post-season in the non-collar group suggested that greater effort was required for task completion. The absence of alteration of brain activation in the collar group suggests a potential protective effect, supporting the growing literature of mild jugular vein compression in brain injury protection in sports.

H. 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: 2015-2205; PI: Gregory Myer). We aimed to (1) quantify the longitudinal persistence of altered white matter (WM) integrity observed in one high school football season at 8 months post season; and (2) evaluate the long term effects of the jugular vein compression collar designed to ameliorate alterations in brain network. Prospective diffusion tensor imaging data from 23 male high school football athletes (10 non-collar; 13 collar) were acquired at three longitudinal time points: T_1 (pre-season),T_2 (post-season) and T_3 (following the off-season). The in-season time interval ($T_1 \rightarrow T_2$) was 4.24±0.52 months and the off-season interval ($T_2 \rightarrow T_3$) was 8.48±0.30 months. Tract Based Spatial Statistics approach was used to quantify change in the WM anisotropic diffusion properties between these time points. DTI remained unchanged across all time points in the collar group. Despite similar number/severity of head impact, the non-collar group showed significantly greater reduction than the collar group in mean, axial and radial diffusivity between $T_1 \rightarrow T_2$ in extensive WM regions (corrected $p<0.05$). During the presumed recovery off-season period without head impact exposure (T2→T3), DTI diffusivity values in the non-collar group increased significantly toward baseline, but remained significantly lower ($T_1>T_3$; all $p<0.05$).The non-collar group demonstrated WM recovery towards baseline during the off-season relative to post-season DTI alterations found following the competitive football season. However the persistence of significantly lower diffusion properties may be indicative of incomplete WM recovery. The lack of significant DTI change over time in the collar group suggests a protective effect may be afforded from the applied jugular compression.

I. 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: 2015-2205; PI: Gregory Myer). We sought to (1) identify brain networks in performance of a cognitive task, (2) evaluate whether longitudinal changes in performance are associated with alterations in brain network connectivity after a season of head contact competitive play, and (3) determine the effect of a jugular vein compression device on these relationships. Male high school football athletes were assigned to a collar (N=12, age=16.4±1.2) or non-collar group (N=13, age=16.2±1.6). Subject response times (RT) during a visual go/no-go test were recorded before and after the season. Neuroimaging data were acquired prospectively pre and post season. Functional networks were parcellated from preseason data via independent component analysis and intersected with the Harvard-Oxford brain atlas to form regions of interest. For all subjects at preseason, RT were positively correlated with connectivity within the salience network ($r=0.47$, $p=0.003$) but not any other network ($p>0.05$). Consequently, we evaluated associations between longitudinal changes in RT and connectivity within this network for each group; changes in RT were positively correlated with changes in connectivity for the non-collar group ($r=0.58$, $p=0.038$) but not the collar group ($r=0.38$, $p=0.221$).The salience network was associated with RT in a visual go/no-go task, consistent with its central role in motivation and a readiness to act. Associations between altered RT and network connectivity for only the non-collar group suggests not only that

exposure to head impacts may affect critical processing within the salience network, but that the collar may afford a protective effect in stabilizing brain network connectivity.

(4) STUDY DESIGN:

All testing will be performed in the SPORT Center, Division of Sports Medicine at Cincinnati Children's Hospital. Ultrasound testing will consist of measurement of dilation and compression of the jugular veins following the application of a generic jugular vein compression device. The ultrasound testing will be completed in 20 minutes or less.

(5) DURATION:

Each participant will participate in 1 planned study visit that may take up to 20 minutes. Data analysis will continue for a 6 month period following the final enrollment.

(6) SELECTION & RECRUITMENT OF PARTICIPANTS

We aim to recruit approximately 100 healthy volunteers divided equally between the sexes. The normal, healthy participants (age 7-60 years old) will be recruited from local school districts local sports clubs and teams, local colleges, adult sport leagues, and professional sports teams, through our well established network with area coaches and athletic trainers. To obtain the various age groups we will also recruit from that we may recruit from colleagues and staff members. All recruited participants will be made aware that participation is voluntary and will not be held against them if they decide not to participate. 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 (if subject under age of 18) who voluntarily agree to participate will be scheduled to complete the pre-participation testing. The participant and parent/guardian (if subject under the age of 18) 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. Additional Adult volunteers will be recruited via word of mouth or through affiliations with the teams/clubs noted above, through personal contacts, or through emails sent via Clinical Studies.

Inclusion criteria

- Normal healthy volunteer aged 7-60
- Able to provide written consent
- Able to tolerate hypercapnia for 1-2 minutes

Exclusion criteria

- 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. 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.

The participants 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/assent forms. It will be made clear to the patient and their parents that participation in the study is voluntary. Subjects over the age of 18 will complete the Adult Subject Consent Form.

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

Ultrasound Testing

The study coordinator will be responsible for providing the appropriate sized collar based on measured neck circumference. 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. Baseline measures with standard collar will be measured and recorded via ultrasound video following the methods described below.

Baseline ultra-sound imaging-Standard collar

Sitting upright, and facing forward, ultra-sound coupling gel is applied to the lateral neck, and the right side common carotid artery, and IJV in the transverse plane, are identified to verify normal anatomy. Collar positions will be marked on the neck using stickers or other temporary marking methods. The collar is then placed into proper position on the study volunteer's neck. To further evaluate responsiveness to the collar, a 15 s video clip is obtained, recording the collar in its proper position, the collar opened away from the neck, and the collar returned to its proper position. The largest transverse dimension at initial collar placement, and the smallest transverse dimension at opened collar view and again at proper collar replacement, will be used for IJV metrics.

IJV Compression ultra-sound imaging

With proper placement of IJV compression collar confirmed, pressure is increased in small intervals of pressure unilaterally until IJV compression is visually observed. The collar will then be rotated radially anterior and posterior to its initial position around the IJV. This process will be repeated at .2 increments of pressure until the 1.5 lbs pressure of the standard collar is achieved. The ultrasound technologist will record the jugular vein measurements relative to each indicated pressure level.

(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.

Statistical analyses will performed with SPSS statistical software (SPSS Inc, Chicago IL). Data regarding the descriptive information (such as mean and standard deviation) will be calculated for demographic, anthropometric and ultrasound variables of interest. Sex and age specific analysis will be compared between the test conditions (baseline vs. X pressure) using a paired student T-test.

(10) FACILITIES AND PERFORMANCE SITES:

All ultrasound testing will be performed in the SPORT Center in the Division of Sports Medicine.

(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, Quinn et al. 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 and Shipley 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, Buie et al. 1950, Torres and Ellington 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 and Ellington 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 and Grier 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, Moraine et al. 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, Eves et al. 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, Bailes et al. 2012, Turner, Naser et al. 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). As noted above the collar has been tested extensively in laboratory and field settings without reported adverse events.

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. 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.

Subject participation will 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:

Dr. Kate Berz will serve as a study monitor for this project for any incidental findings, 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 participant's 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 testing. Registration in the Clincard payment system requires a social security number, which will be acquired via a complete W-9 form for each participant. Participants will be compensated even if they are not able to complete the entire MRI session.

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