STUDY TITLE: **Concussion Prevention Device and Audiological Measures**

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CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER

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INVESTIGATOR INFORMATION:

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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 that applies mild jugular compression according to the principle of the Queckenstedt Maneuver (the Device) is being developed by Q30 Labs, LLC (Q30). Initial research suggests that the Device has the potential to reduce the likelihood of TBI. The rationale for OAE is that we need to evaluate the brain responses to mild jugular compression across multiple age groups. To determine this with MR imaging is currently cost prohibitive. Our pilot data from the parent IRB indicate a consistent response measured via otoacoustic emissions and reflectance in young adults. Therefore, a preliminary step to evaluate the safety and efficacy of the neck collar device is to employ OAE technology.

(2) PURPOSE: To monitor changes in audiological measures in a diverse population of individuals wearing the Device. The Device being tested has not been cleared or approved by the U.S. Food and Drug Administration for any intended use. The primary aim is to determine if the neck collar will influence similar responses across multiple age groups and help us establish age related normative values of expected change used to identify collar "activation."

(3) SIGNIFICANCE OF STUDY IN RELATION TO HUMAN HEALTH:

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"[1-3]. 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 and are also a concern for athletes who participate in a wide range of sports, including hockey, rugby and soccer.
According to NASA, "The oscillation of a fluid caused by 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. Similarly, the brain faces slosh peril during external force impartation. 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.

Woodpeckers, head ramming sheep and all mammals (including mankind) 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 Smith *et al.* have demonstrated that we can easily and safely facilitate this muscle's actions by a well engineered gentle compression over those muscles.

(4) PREVIOUS WORK DONE IN THIS AREA:

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 lumber 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"[4]. This incredibly simple principle can be employed to protect soldiers and athletes from TBI by safely, and reversibly, increasing intracranial volume and pressure. The Device is a simple elastic neck collar providing comfortable and precise jugular compression that potentially mitigates cerebral slosh and promises to significantly reduce the risk of TBI. The simplicity of the design of the Device makes it amenable to rapid deployment.

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, pressure increases proportionally. The pressure volume curve (Figure 1) demonstrates that the compliance of the cerebral system can be reduced by a mild increase in cerebral volume. Increasing cerebral blood volume and pressure safely and reversibly reduces compliance of the cerebral vascular tree and diminishes absorption of slosh energies. Jugular compression increases cerebral blood flow

almost instantaneously. As mentioned, this degree of increase has significantly mitigated slosh in laboratory animals and some wild animals are able to reflexively increase cerebral blood volume and pressure through jugular compression.

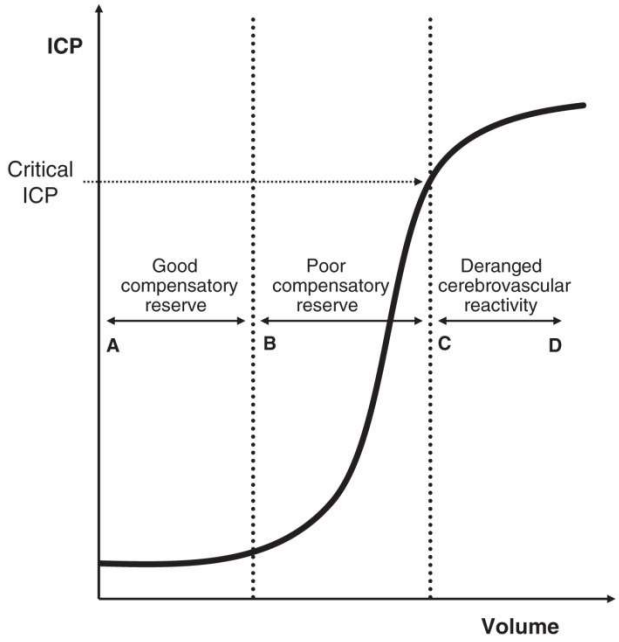


Figure 1. The pressure volume curve demonstrates that the compliance of the cerebral system can be reduced by a mild increase in cerebral volume

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 Precurser Proteins (APP) [5]. 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.

In the body, cerebral blood flow (CBF) is precisely controlled to meet the brain's metabolic needs. Intrinsic mechanisms within the vasculature buffer the effects of stresses on CBF to match actual blood flow to the brain's metabolic needs. This is referred to as cerebral autoregulation: the ability of the cerebral vasculature to maintain consistent blood flow despite fluctuations in cerebral perfusion pressure. With respect to blood pressure changes, autoregulation serves to protect the brain from oxygen deficit when perfusion pressures are low and from brain swelling when perfusion pressures are high [6].

CBF changes in response to a number of stimuli: PCO_2, pH, temperature, perfusion pressure, neuronal function, autonomic nervous system activity, and other factors such as drugs and chemical exposure [7-10] .The extent of response to these perturbations, termed cerebral vascular reactivity (CVR), is one indicator of the health of the control system. The best studied effector is the partial pressure of carbon dioxide in the arterial blood, $PaCO_2$. Under normal circumstances,

increasing $PaCO_2$ increases CBF by about 3% for each mmHg increase in $PaCO_2$ [11]. As $PaCO_2$ requires sampling of arterial blood, most studies use the end-expiratory partial pressure of carbon dioxide, $P_{ET}CO_2$, as a surrogate for $PaCO_2$.

Preliminary testing on 4 adults have been studied to date with 8 pending at the time of this application. fMRI and CO_2 reactivity were performed before and after application of jugular compression fashioned after the rat study conducted by Smith *et al*. Preliminary results before and after jugular compressions (with the Device) have yielded no alterations in O_2 uptake or glucose metabolism to any portion of the brain. The methods are utilized in prior approved IRB (2013-2240).

(5) SELECTION OF PARTICIPANTS

Normal healthy volunteers will be recruited by word of mouth. We aim to recruit approximately 500 healthy volunteers divided equally between the sexes aged 8-50 years. The primary aim is to determine if the neck collar will influence similar responses across multiple age groups and help us establish age related normative values of expected change used to identify collar "activation."

Inclusion criteria

- Normal healthy volunteer
- 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 head trauma
- Medical contraindications to limited hypercapnia or 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
- Known open eye injuries
- Neck injuries
- Any known airway obstruction
- Any known seizure disorder
- Any altered level of consciousness

(6) RECRUITMENT

We will recruit subjects via word of mouth from known contacts at local schools, organizations, and military.

(7) RANDOMIZATION

All subjects who meet the study criteria and volunteer to participate will be included in the study. During one testing session, the participants will be tested while wearing the restrictive neck device.

(8) STUDY PROCEDURES

For the testing sessions, subjects may either come to our testing site or we may bring the testing to their location (e.g. schools, work). The subjects will be fitted with a device around your neck, like a neck tie. The Device is a standard hockey neck guard, adapted for the purposes of this study. The Device incorporates two bulges localized over the site of the internal jugular veins bilaterally. Experiments performed with jugular Doppler ultrasound demonstrate that while wearing the Device, flows within the jugular veins are reduced, while flow within the carotid arteries and all portions of the cerebrum are preserved (JA Fisher, unpublished data). Thus, application of the Device to the subject will not cause any untoward health risks (IRB# 2013-2240 safety testing performed on this Device). The pressure exerted by the Device on the region of the neck superficial to the internal jugular vein is akin to the pressure felt when a person yawns or wears a snugly fitting necktie. The methods are utilized in prior approved IRB (2013-2240)..

Station I: Consent to Participate

Each participant will review the Institutional Review Board approved consent to participate form prior to data collection. They will be given an adequate amount of time to ask questions to the study coordinator, or the person obtaining consent, and then make their decision to participate or not participate. If they wish to participate, they will be asked to sign the informed consent form.

Station II: Device Fitting and Ultrasound

The subjects will be outfitted with the device by a staff member appropriately trained in fitting the device in the proper location. To ensure proper fitting and Device placement, ultrasound may be performed to examine the immediate effect of Device placement on venous return in the neck. Ultrasound frequency will be set at 6.0 MHz to 12 Mhz and the predicted exposure time per person is 5 minutes.

Station III: Distortion Product Testing of Oto-Acoustic Emissions

This station will help determine the effectiveness of the device by measuring the auditory response of a clicking noise that will be non-invasively imparted into the subject's ear. The rebounding sound emission will be monitored to provide information on the operation of the device. Recording microphones pick up the oto-acoustic emission coming back from the outer hair cells of the inner ear, and the computer averages and processes the responses in reference to a noise floor across a specified frequency range, displaying the results on the computer screen for the tester. Evidence indicates that distortion or transient or both oto-acoustic emission will be

altered with increased intracranial pressure and thus this simple, non-invasive exam will provide instant feedback on the effectiveness of the device.

During distortion product testing of oto-acoustic emissions testing the study participants will also be fitted with a compressive circumferential neck collar which can provide variable and specific levels of pressure. The pressure is achieved by inflatable pods that sit adjacent to the trachea affixed to a non-stretch adjustable collar. Manual inflation is regulated and monitored by an experience operator/ technician through a bulb style pump and an electronic gauge. Testing will occur without pressure and then with pressures applied up to 40mmHg.

(9) VULNERABLE POPULATIONS
n/a

(10) SURVEYS OR QUESTIONNAIRES
n/a

(11) BLOOD
n/a

(12) METHODS

Data Storage.
Data will be recorded on a form for each test and will be entered into a custom database. 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 that only pertinent research personnel have access. All data will be collected for research purposes.

Data Analysis.
Statistical analysis will be done with SPSS statistical software (SPSS Inc, Chicago IL). Qualitative analysis of frequency waveforms with standard error of the mean plotted will be used to determine frequencies most sensitive to the collar activation. The statistical test will be age and gender specific paired test of OAE at various frequencies. Up to 500 subjects will be needed to establish the age and sex specific analyses.

(13) 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.

(14) POTENTIAL RISKS, DISCOMFORTS, INCONVENIENCES AND PRECAUTIONS

The Device 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. These garments gently facilitate natural response mechanisms in 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. 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, 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 pressure and 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 spandex, Lycra or similar material and should be barely noticeable to the wearer.

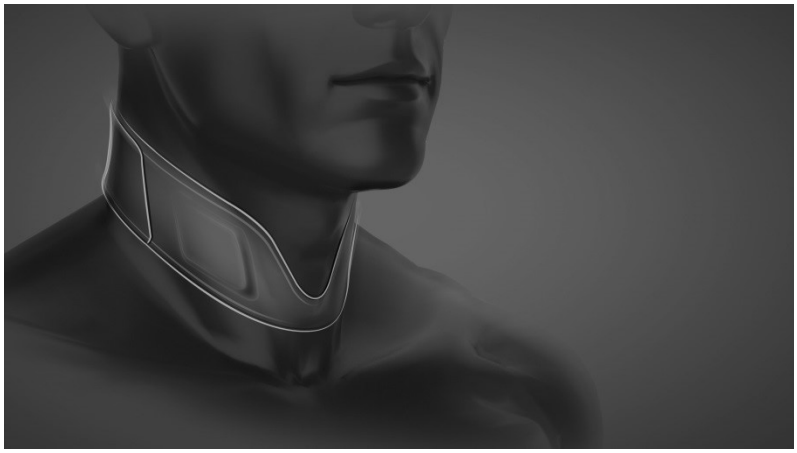
Careful MRI studies have confirmed an increase in blood volume in the brain but have also shown that there is no significant change in brain blood flow pattern with wearing a "tight necktie" [12].

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*."[13] 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 [14, 15]. This decline is urinary sodium is minimal.

There was no correlation between EEG changes and changes in systolic blood pressure occurring during jugular or carotid compression[15]. 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."[16]

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.[5, 17]

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). See the image below for an example of the device.



Data Storage. There is also a minimal risk that the data collected for each subject 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. In the case of an adverse event 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 subject 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 subject 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.

As a precautionary measure, a trained physician (M.D.) will be on-site during all data collection sessions to respond to any unanticipated medical events if they were to take place.

(15) RISK/BENEFIT ANALYSIS

Subjects 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 subject 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 subject.

The methods used 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.

(16) WITHDRAWALS

Subjects will be recruited from to ensure adequate and timely subject recruitment. The projected sample size for this study was calculated to account for potential subject drop-out and/or withdrawal.

Participation in this study is completely voluntary. Refusal of a subject to participate will involve no penalty or loss of benefits to which they are otherwise entitled.
The participant has the right to withdraw from this study for any reason and would do so simply by communicating this with the investigators. Depending on the investigators' findings, the investigators will inform the participant if there would be any reason why the participant would be jeopardized by withdrawing from the study.

(17) DATA SAFETY AND MONITORING

The Safety Officer (Dr. Nicholas Edwards) 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. Edwards 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 subject safety arise.

Dr. Nicholas Edwards, 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 subjects (see Risk/Benefit Analysis section (15)). Further assurances regarding subject safety and protection of private and confidential subject information have been outlined in the Potential Risks, Discomforts, Inconveniences and Precautions section (14), the Privacy section (18) and the Confidentiality section (19).

(18) PRIVACY

The subject has the right to privacy. The investigators will protect subject 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 subjects 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 subject identification code will be used on all data questionnaires.

(19) CONFIDENTIALITY

The results of this study will be kept confidential. No subject identification will be made public record in any form unless the subject gives his or her expressed written permission of release of subject'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.

(20) PAYMENT FOR STUDIES

n/a

(21) PROCESS OF OBTAINING CONSENT

Once a subject is identified as a potential subject, is contacted by a CHMC/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 subject at this time. The study coordinator will review the informed consent and the subjects will have an opportunity to ask any questions

regarding the study and/or the study protocol. At that time, the subject will be given time to decide whether or not they wish to participate and if so, then asked to sign the informed consent. Once the signature is obtained, the subject will be given a copy of the consent and testing will commence. At no time, will the subject be coerced into participation. Receiving the informed consent prior to enrollment will allow the subjects to review the study information prior to participation in the study. This will aid the subject to make an informed, unforced decision regarding election to participate in the study.

(22) ASSENT AND PARENTAL PERMISSION

Subjects under the age of 18 will complete an assent form and parents will complete and parental permission form.

(23)WAIVER OF CONSENT:

N/A

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