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Internal Jugular Vein Compression: A Novel Approach to Mitigate Blast Induced Hearing Injury

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Hypothesis: Internal jugular vein (IJV) compression before blast injury will lead to reduced risk of traumatic hearing injury following exposure to a blast injury.
Background: IJV compression and its effects on not only intracranial, but also intracochlear pressure may potentiate blast induced hearing injury, therefore, precluding its use as a prophylactic therapy for blast induced traumatic brain injury.
Methods: Twenty Sprague Dawley rats were exposed to a 17.9 ± 0.4 PSI (195.8 dB SPL) right sided shock wave in which 10 had application of a custom IJV compression collar before injury. All rodents received baseline and post blast injury otoacoustic emission (OAE) and auditory brainstem response (ABR) testing followed by cochlear histology.
Results: IJV compression was shown to significantly reduce ABR and OAE threshold shifts in comparison to the non-intervention group by: 14.9 ± 4.8 dB (right ear ABR 0.5 kHz Day 1 post blast, $p = 0.01$), 13.1 ± 4.9 dB (right ear ABR 4 kHz Day 1 post blast, $p = 0.04$), 16.5 ± 4.5 dB (right ear ABR click Day 1 post blast, $p = 0.003$), 12.1 ± 4.6 dB (right ear ABR click Day 6 post blast, $p = 0.04$), and 14.0 ± 3.2 dB (both ears OAE 3.2–10 kHz, $p < 0.0001$). Also, those animals with collar application had a greater number of total hair cells per mm from 70 to 100% distance from the cochlear apex following blast injury in comparison to those without intervention (blast: 211.8 ± 27.5 versus blast+collar: 355.5 ± 39.5 [$p = 0.0002$]).
Conclusion: This study supports the use of IJV compression in a pre-clinical model as a new prophylactic mechanism to combat blast induced hearing injury. **Key Words:** Blast—Internal jugular vein compression—Traumtic hearing injury.

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Internal jugular vein (IJV) compression has been proposed as a prophylactic measure to diminish the microscopic and macroscopic injuries associated with traumatic brain injury (TBI). The preeminent theory is that a TBI is due to the differential acceleration/deceleration of the viscoelastic cerebrum within the skull leading to stretch and strain forces upon the cells, white matter, and blood vessels (1–6). These forces cause initial primary axotomy and hemorrhage along with an initiation of a complex neurometabolic and vascular response leading to alterations in neuronal functioning (7–13). Prophylactic mild IJV compression engorges the cranial venous system, enlarges the brain, and increases brain turgor, therefore, reducing relative motion of the cerebrum within the skull (14). Preclinical studies in IJV compression before injury exposure have demonstrated its ability to reduce not only microscopic neuronal injury, but also the propensity for hemorrhagic extension (3,4,15). Recently, two clinical studies have successfully made the translational leap to demonstrate that use of an IJV compression collar in high school football and hockey players provided a significant reduction in sub-concussive axonal injury on diffusion tensor imaging following a season of play (16,17).

Application of this technology has been suggested for use in military personnel to combat military blast TBI, but concerns have been raised due to its potential consequences on blast induced hearing injury. Specifically, since IJV compression causes mild increases in intracranial volume and pressure and subsequently intracochlear pressure, what would be the effect of prophylactic IJV compression on traumatic hearing injury in those service members exposed to a blast injury (18–22)? With the already high prevalence of hearing deficits in military

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service members, any therapeutic modality that could potentially increase prevalence or worsen its morbidity would not be clinically feasible (23).

This study attempts to address if IJV compression before blast injury will lead to increased or reduced risk of traumatic hearing injury following exposure to a blast injury, to evaluate the collar's potential as a means for TBI prophylaxis in the military. If suggestive of a therapeutic effect, outcomes of this study have the potential to revolutionize our approach to improving protection of our military personal during operational theaters.

METHODS

Experimental Design Overview

To assess the effect of IJV compression on traumatic hearing injury, we exposed 20 rats to a right sided 18.0 PSI overpressure blast in which half of the animals had preblast application of a specialized IJV compression collar (blast+collar) and the other half did not (blast). All animals had baseline and post injury otoacoustic emissions (OAE) and auditory brainstem response (ABR) testing to assess functional injury of the cochlea and eighth cranial nerve, followed by structural evaluation via cochlear histology after euthanasia 9 days after injury.

Animals

Twenty male adult (3–6 months old) Sprague Dawley rats (Charles River Laboratories, Wilmington, MA) weighing between 350 and 400 g were delivered 5 days before initial testing in order for acclimatization. The group was heterogeneous regarding inner ear anatomy like hair cell density, ear canal length etc., but maintaining comparable age and weight ranges along with randomization was assumed to provide for these differences. All animals were housed in the hospital animal facility with appropriate feed and water and maintained on normal night/day cycles. Animals were monitored daily by trained animal technicians by the oversight of the hospital veterinarian and all care, and the entirety of the experimental protocol was approved by the NorthShore Evanston Institutional Animal Care and Use Committee (EH15–391).

Therapeutic IJV Compression Collar

To apply mild IJV compression, a customized collar, modeled from Smith et al. (4), was comprised of elastic with properly placed plastic beads to ensure compression of the bilateral IJV and avoid tracheal compromise or carotid stimulation. Before the clinical experiment, proper collar design (bead location and collar tightness) was determined by the trial of different collar prototypes in concert with invasive intracranial and non-invasive intraocular pressure monitoring. This also assured that proper collar application could be assessed experimentally through non-invasive measures without the need to alter the intracranial milieu through invasive monitoring.

All animals before blast injury received intraocular pressure (IOP) monitoring every 30 seconds for a total of 3 minutes. For those animals that were randomized to collar application before blast injury, the customized IJV compression collar was applied and IOP (Icare TONOLAB #TL-1, Colonial Medical Supply, Windham, NH) was again measured every 30 seconds for 3 minutes. The collar was re-adjusted and replaced for those animals that did not demonstrate immediate increases in intraocular pressure.

Blast Induced Hearing Injury

For blast induced hearing injury, the animals were anesthetized with isoflurane (2–5% for induction and 1–3% for maintenance) along with one dose of buprenorphine (0.05 mg/kg) for analgesia. Once anesthetized, the animals received IOP recordings and collar application (if appropriate), followed by placement into a small steel cylinder surrounded by foam padding to protect the thorax and eliminate barotrauma. Attention was focused on maintaining a constant location for the head to be exposed, being at the craniocervical junction just distal to the ears. The animal was then positioned in an upright manner, perpendicular to the front of the blast tube opening to receive a right lateralized blast. All animals' heads were positioned an equal distance from the blast tube exit site, roughly 2 cm.

The shock tube apparatus used to recreate blast induced traumatic hearing injury has been validated in previous studies (24–26). To create a blast wave with this tube, compressed helium gas is pumped into the driver section that is sealed by mylar membrane (McMaster Carr, Elmhurst, IL). At a given pressure, based on the thickness of the mylar, the membrane will rupture sending a shock wave down the driven section, striking the animal that is situated at the open end of the chamber. Three piezoresistive pressure transducers (8530B-200, Endevco Meggitt, Irvine, CA) are situated at the end of the blast tube to record blast overpressure and duration. Verified before the experimental study, one 0.010″ mylar membrane produces a 17 to 18 PSI blast overpressure with a duration of 0.4 ms. This level was chosen to reproduce a typical IED blast overpressure (between 7 and 145 PSI) and not to exceed the recommended rodent scaled blast duration of 0.3 to 3 ms; but, while also reducing traumatic tympanic membrane rupture (26–29). All animals had visual inspection of their tympanic membranes under light microscopy following blast exposure, and those with tympanic membrane rupture were removed from the final OAE analysis.

Auditory Brainstem Reponses

ABRs were performed the day previous (baseline), 1-day post, and 6-day post blast injury using Nihon Kodhen (Irvine, CA) MEE clinical evoked potential system. All animals were anesthetized with inhaled isoflurane, placed on a warming pad within a sound insulating container, and received continuous pulse oximetry and heart rate monitoring for the duration of testing. Following successful sedation, three subdermal scalp recording electrodes were placed in sterile fashion at the vertex and at both ears. Sound click and toneburst stimuli were delivered with foam inserts fitted tightly in the ear canal. Broadband (range of 3–8 kHz range, peak of 3–4 kHz) rarefraction clicks of 0.1 ms duration were delivered at 27.1 stimuli per second, and scalp responses (Cz-Ai) averaged over 200 to 2000 stimuli, depending on the signal to noise ratio. Similarly, two frequencies of toneburst stimuli were delivered at 27.1 stimuli/s: 500 Hz burst of 4 ms duration (2 ms rise, 0 ms plateau, 2 ms decay), and 4000 Hz wave of 6 ms duration (3 ms rise, 0 ms plateau, 3 ms decay). Contralateral masking noise was used for all ABRs. ABR thresholds were determined visually for 500 Hz toneburst, 4000 Hz toneburst, and broadband clicks for each ear by following Wave II response down from 80 dB and noting the intensity when it disappeared. ABR threshold shifts were calculated by subtracting post exposure from baseline testing values.

Distortion Product Otoacoustic Emissions

OAEs were performed the day prior (baseline), 5-minutes post, 1-day post, and 6-day post blast injury. Animals were

again prepared in similar fashion as the ABR testing. Following sedation, single ear rubber tipped ear inserts were placed, assuring a tight fit within the ear canal. Through the use of the Interacoustics Titan DPOAE440 (e3 Gordon Stowe, Birmingham, AL), cochlear emissions were measured from 2 to 10 kHz using two primary tones, f1 and f2 levels of L1 of L2 = 65 of 55 dB with a ratio f2 of f1 = 1.22. OAE levels were calculated by subtracting pre and post OAE levels. Also, the noise floor level was used for calculating OAE level changes in those that fell below the noise level floor for a specific frequency.

Histological Examination

Following completion of testing, the rats were euthanized by decapitation under deep anesthesia 9 days following blast exposure. Twelve total animals (six blast+collar and six blast) were randomly selected for cochlear histology. The temporal bones were quickly removed and fixed in 10% neutral buffered formalin for 2 to 5 days. The cochlear basilar membrane was dissected out under a dissection microscope, and stained with Harris' hematoxylin solution for 5 minutes. To remove the undesirable coloration, specimens were differentiated with 0.3% acid alcohol for few seconds, and then the samples were rinsed with running tap water to convert the color into violet blue. The cochlear basilar membrane was further trimmed and mounted in glycerin on glass slides as a flat surface preparation. The stereocilia, cuticular plate, and nucleus of hair cells were identified under a Zeiss microscope at 400 times magnification. The number of inner and outer hair cells was counted over successive 0.24 mm segments along the entire length of the cochlear basilar membrane. Hair cell density was computed into 10% segments of the cochlea from apex to base, and these values were normalized to lab standards based on hair cell counts from six young, healthy rats. A cochleogram was constructed by plotting the percent inner and outer hair cell loss as a function of the percent distance from the apex of the cochlea. For analysis, individual cochleograms were grouped to generate a mean cochleogram for each experimental condition using the custom software.

Statistical Analysis

A linear mixed effect model was used to assess the effects of experimental factors on both ABR and OAE threshold level shifts relative to baseline levels. Treatment (blast+collar versus blast) was modeled as a between-subject fixed effect; ear (right/left), test day, and ABR/OAE test frequency were modeled as within-subject fixed effects; and rat was modeled as a subject random effect. Type III tests of fixed effects and sub-effects in the model were evaluated using F tests. Collar minus control differences in response were evaluated using t statistics, with adjustment of p values and confidence intervals within logical groupings of tests using Sidak's method to maintain group wise significance levels of 0.05.

A generalized linear mixed effect models with Poisson errors (IHC hair counts) or Negative Binomial errors (OHC hair counts) were used to assess the effects of experimental factors on cochlear hair counts. Treatment (blast+collar versus blast) was modeled as a between-subject fixed effect; ear (right/left), and distance along the cochlea were modeled as within-subject fixed effects; and rat was modeled as a subject random effect. Average distance-specific hair counts from six healthy control animals were used as offsets in each model, allowing experimental factor means to be interpreted as the proportion of cells counted relative to ''ideal'' hair counts from typical healthy rats. Type III tests of fixed effects and sub-effects in the model were evaluated using F tests. Collar versus control ratios of mean standardized responses (hair count proportions) were evaluated using t statistics, with adjustment of p values and confidence intervals within logical groupings of tests using Sidak's method to maintain groupwise significance levels of 0.05.

Lastly, blast pressure, blast duration, and IOP are expressed as mean ± standard deviation while ABR, OAE, and cochlear histology is expressed as mean ± standard error of the mean.

RESULTS

Blast Exposure ± Collar

Following anesthesia, all animals received IOP pressure monitoring for 3 minutes to determine a baseline IOP of 13.1 ± 2.5 mm Hg. After application of our customized IJV compression collar, the IOP increased to 24.3 ± 1.8 mm Hg. All animals tolerated application of the IJV compression collar without any alterations in monitored pulse oximetry measurements.

The 20 animals were then exposed to a 17.9 ± 0.4 PSI (195.8 dB SPL) blast overpressure with a duration of 0.4 ± 0.03 ms followed by immediate removal of the IJV collar. There was no statistical difference in blast wave mechanics between the blast+collar and blast group (blast amplitude or duration). With this blast over pressure, none of the animals had a ruptured tympanic membrane in the left ear, but one (blast+collar) and three (blast) animals had a right ear tympanic membrane rupture (not statistically significant). These animals were removed from the final OAE analysis.

ABR Threshold Shifts

The left ear (farthest from the blast wave), showed no statistically significant difference between the blast+collar and blast animals. Interestingly, all ABR stimuli (500, 4000 Hz, and click) presented to the right ear showed a statistically significant improvement in threshold shifts in those animals with blast+collar 1 day following blast injury. In more detail, collar application reduced the ABR threshold shift by 14.9 ± 4.8 dB (0.5 kHz, $p = 0.01$), 13.1 ± 4.9 dB (4 kHz, $p = 0.04$), and 16.5 ± 4.5 dB (click, $p = 0.003$). Six days following the blast injury, threshold level shifts of 500, 4000 Hz, and click demonstrated partial recovery in the blast animals and almost complete return to baseline in the blast+collar animals. Six days following injury, the click ABR stimuli still demonstrated a statistically significant reduction in threshold shift between the blast and blast+collar animals by 12.1 ± 4.6 ($p < 0.05$), but the 500 and 4000 Hz lost significance. The persistent difference seen in the click stimuli is likely due to the broadband frequency and its ability to assess a wider range of hair cells compensating for the improved temporary threshold shifts.

OAE Threshold Shifts

A graphical analysis demonstrating the baseline OAEs followed by OAEs obtained 5 minutes, 1 day, and 6 days

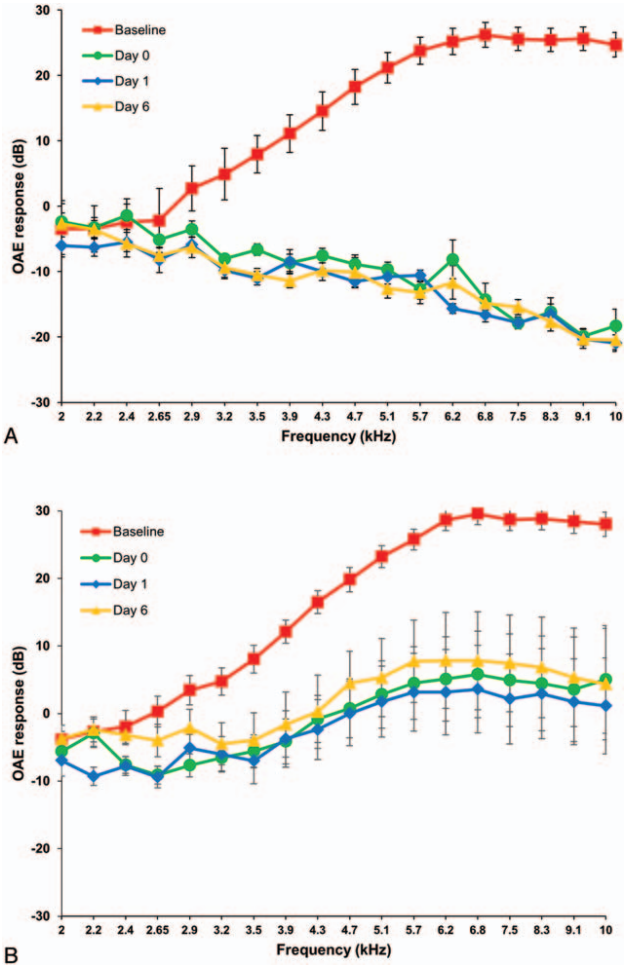

FIG. 1. OAE responses at baseline (pre-blast), 5 minutes (Day 0), 1 day, and 6 days post blast in the right ear (blast side). *A*, Blast (n = 7) and *B*, blast+collar (n = 9). OAE indicates otoacoustic emission.

post blast injury in both right and left ears of the blast and blast+collar animals is depicted in Figures 1 and 2. Of note, the Sprague Dawley rats used for this experiment were shown to not have significant OAE responses below 3.2 kHz. There was a non-statistically significant trend of OAE threshold shifts to worsen from the assessment immediately following the blast injury to Day 1, but then appeared to improve at Day 6. This observation in threshold shift has been previously published (30). Figure 3 shows the total OAE threshold level shifts from baseline to Day 6 in both the right and left ears of the blast and blast+collar animals. Statistical significance is depicted on the graphs as $^{*}<0.05$, $^{**}<0.01$, and $^{***}<0.001$. Averaged over 3.2 to 10 kHz (the frequencies with substantial OAE responses at baseline in this cohort of Spraque Dawley rats), there was a statistically significant reduction in OAE threshold shifts in the blast+collar compared with the blast groups by 12.5 ± 3.3 dB ($p < 0.005$) in the left ear, 15.5 ± 3.3 dB ($p < 0.0001$) in the right ear, or 14.0 ± 3.2 ($p < 0.0001$) in both ears favoring the blast+collar group.

Histology

Following euthanasia at 9 days post blast injury, the cochleograms demonstrated a significant reduction in inner (IHC) and outer (OHC) hair cell loss specifically at the location closest to the oval window of the cochlea, corresponding to higher frequencies (roughly 32 kHz).

For the left ear, the blast+collar had a significant reduction in IHC loss compared with the blast animals located at a distance of 90 to 100% from the apex (blast 62% versus blast+collar 10%, $p < 0.0001$). Statistical significance was also seen at 80 to 90% and 90 to 100% distance from the apex in outer hair cell loss between the two groups (80 to 90% cochlear distance: blast 78% versus blast+collar 20%, $p < 0.0001$, 90 to 100% cochlear distance: blast 100% versus 39%, $p < 0.05$) (Fig. 4).

For the right ear, the blast animals had a significant higher percentage of IHC loss located between 90 and 100% of the distance from the apex (blast 61% versus blast+collar 27%, $p < 0.0001$). Statistical significance was also seen at 80 to 90% and 90 to 100% distance from the apex in outer hair cell loss between the two

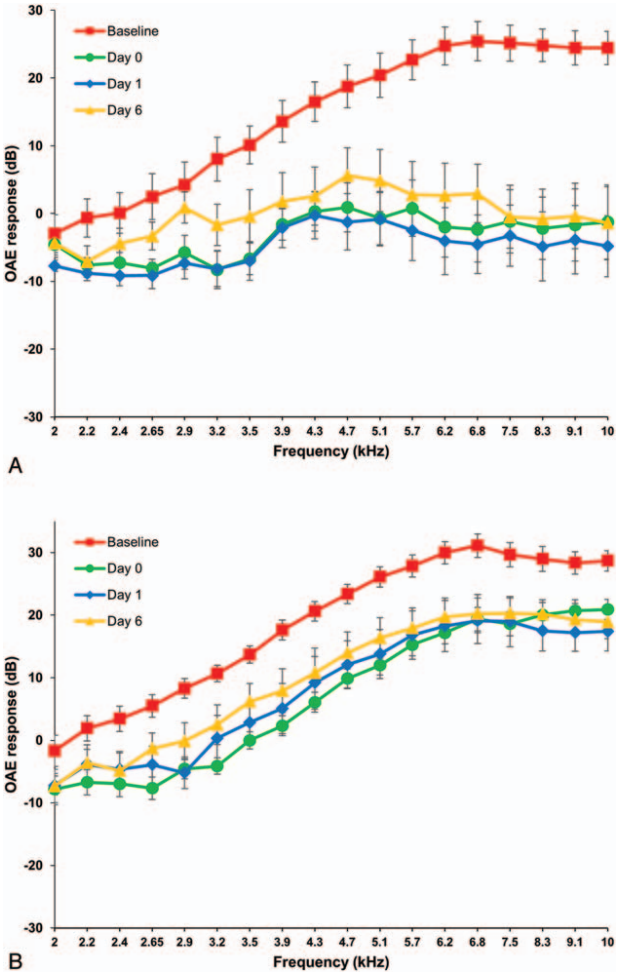

FIG. 2. OAE responses at baseline (pre-blast), 5 minutes (Day 0), 1 day, and 6 days post blast in the left ear (opposite blast side). *A*, Blast (n = 10) and *B*, blast+collar (n = 10). OAE indicates otoacoustic emission.

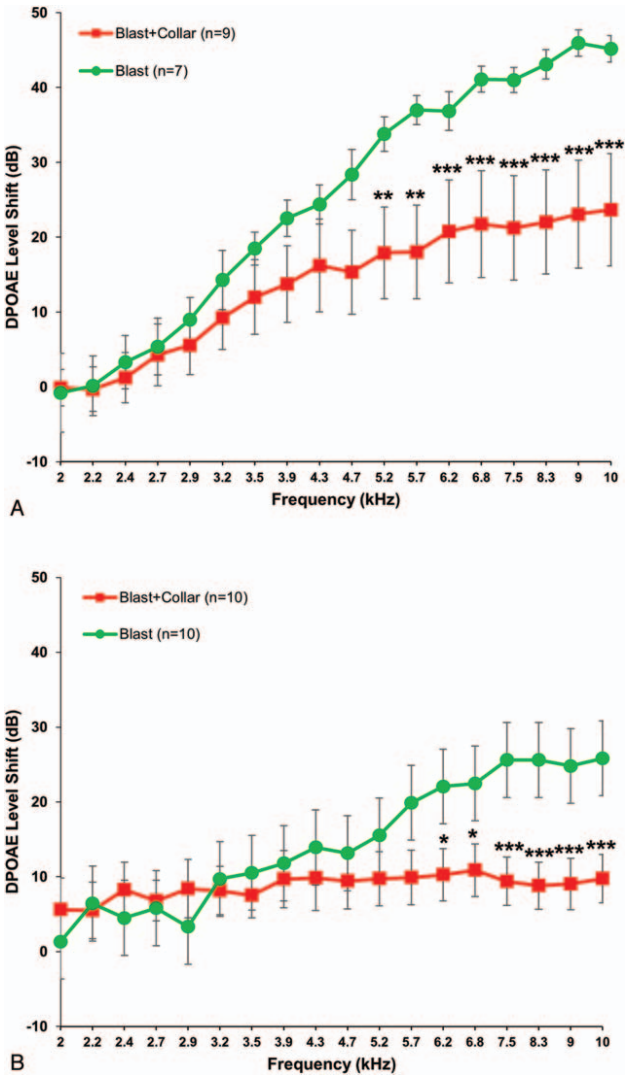

FIG. 3. OAE threshold shifts from baseline to Day 6 post blast in the *A*, right ear (blast side) and *B*, left ear (opposite blast side). $^{*}p < 0.05$ versus blast, $^{**}p < 0.01$ versus blast, $^{***}p < 0.001$ versus blast. OAE indicates otoacoustic emission.

groups (80–90% cochlear distance: blast 77% versus blast+collar 44%, $p < 0.0001$, 90–100% cochlear distance: blast 100% versus 62%, $p < 0.05$) (Figs. 4 and 5).

If specifically analyzing the 70 to 100% distance from the apex in the blast+collar compared with the blast group in all ears, there is a greater number of total hair cells (IHC+OHC) per mm in the blast+collar versus blast group following exposure (blast: 211.8 ± 27.5 versus blast+collar: 355.5 ± 39.5 [$p = 0.0002$]). In comparison to six control animals, the blast+collar group did not have a statistically different total number of hair cells per mm at the 70 to 100% distance (blast+collar: 355.5 ± 39.5 versus control: 463.72 ± 5.1 [$p > 0.05$]) (Fig. 6).

DISCUSSION

IJV compression has been shown in preclinical and clinical studies to have a potential benefit in mitigating the injury that occurs in TBI, and therefore has further been proposed for use in military blast TBI. This study specifically attempted to determine if prophylactic IJV compression, and resultant changes in intracranial and, potentially, intracochlear pressure, would improve or worsen traumatic blast audiological injury. In this study, it was demonstrated that IJV compression before injury did not increase the functional thresholds (ABR and OAE) or exacerbate structural (cochlear histology) inner ear pathology following a blast injury. Interestingly, this novel therapy was actually shown to dramatically reduce traumatic hearing injury in the rodent model based on ABR, OAE, and cochlear histology. Though difficult to compare to Li et al.'s (31) study assessing hearing injury in guinea pigs with ear inserts exposed to a shock wave due to differing methods (blast PSI, animal and blast model, time frame ABR obtained post blast, and

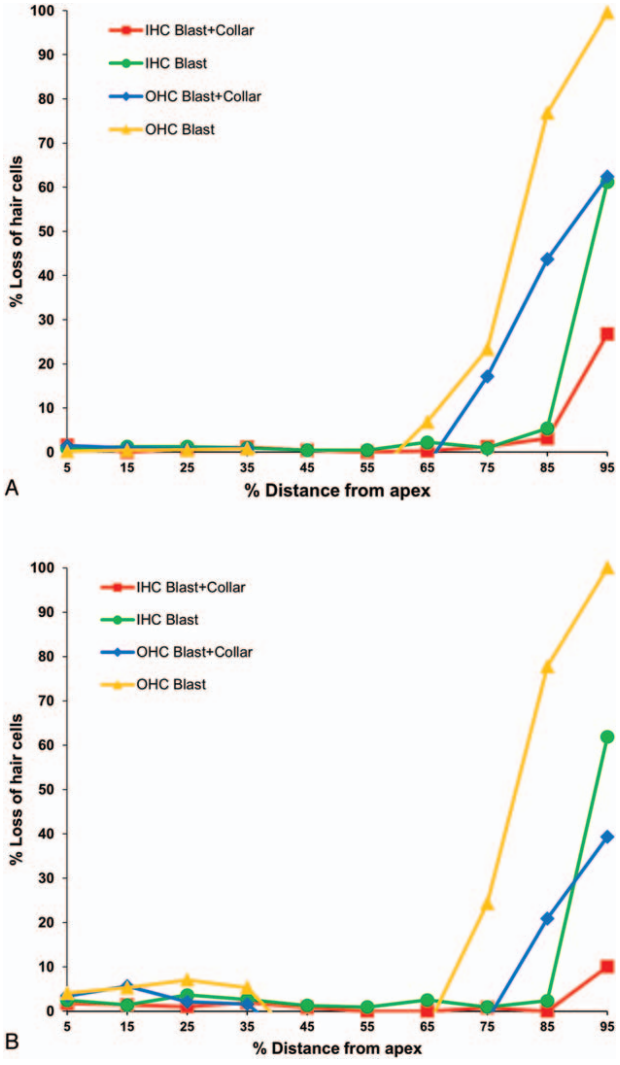

FIG. 4. Percent outer hair cell (OHC) and inner hair cell (IHC) loss compared with normal control graphed as a percent distance from the apex of the cochlea in the blast+collar and blast animals following euthanasia 9 days post blast injury. *A*, Right ear (blast side) and *B*, left ear (opposite blast side).

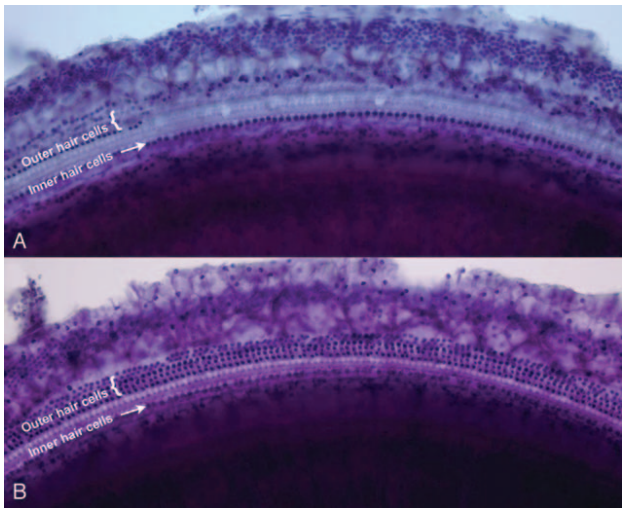

FIG. 5. Typical cochlear histology obtained from *A*, blast and *B*, blast+collar groups. Note the dramatic IHC and OHC loss seen in the blast animal. Images shown are from right ear (blast side) in the region 60 to 80% from apex. IHC indicates inner hair cell; OHC, outer hair cell.

euthanasia dates for histology), the similar and in some cases inferior outcomes of ear inserts compared with IJV compression has the potential to completely revolutionize our approach to prophylactic mitigation of blast traumatic hearing injury (31).

Communication from the intracranial to the intracochlear space has been demonstrated in animal models likely through a widely patent cochlear aqueduct (18–22,32–35). Presumably, IJV compression resulting in mild increases in intracranial volume and pressure could be transmitted to the cochlea via this route. The resultant change in intracochlear dynamics potentially may offer either mechanical impedance against the acoustic or shock wave, or may alter the stiffness of the sensory epithelium resulting in reduced movement and tearing of hair cells as the wave travels through the cochlea (36–38). Though inspection of tympanic membranes was performed to assess for gross rupture, it is not possible to exclude micro-perforation. Therefore, postulating whether hair cell injury occurs due to the blast shock wave (rupturing the tympanic membrane) or acoustic sound wave (causing vibration of the tympanic membrane) traveling through the cochlea is not able to be determined. But, it is interesting that our change to the cochlear histology was significant for a reduction in hair cell loss occurring closest to the oval window where the shock wave would first enter the cochlea and cause substantial injury.

Though this research has the potential to dramatically alter our approach to hearing protection, the translatability of these findings from preclinical to clinical subjects is uncertain due to the possible differences in temporal bone anatomy. An anatomical dissection of human temporal bones performed by Allen et al. (39) demonstrated that only 34% had a patent cochlear aqueduct, 59% had a lumen which was filled with connective tissue, and only 7% had either complete obliteration or occlusion by bone. It is unknown to what extent intracranial pressure modifies intracochlear pressure specifically in those patients with connective tissue filling the lumen. Therefore, the viability of IJV compression via this mechanism could potentially only benefit 34%, but may also benefit 93% of humans. Though the patency of the cochlear aqueduct in humans is questioned (20,38–45), multiple clinical studies have demonstrated alterations in inner ear pathology (OAE threshold changes and tympanic membrane displacement) in patients with elevated intracranial pressure (46–49). Due to these positive findings, non-invasive acoustic tests have been suggested for use as an indirect measure of intracranial pressure in patients suffering from traumatic brain injury or hydrocephalus (21,46–49). Until further research is done, the conduit (cochlear aqueduct, cochlear vein, perineural space, endolymphatic sac, etc.) between the intracranial and intracochlear space in humans can only be speculated (20,21,39,50). But, this discussion is futile because a connection does appear to exist, whatever that may be, to transmit ICP to the cochlea, making the hypothesis that IJV compression would also be feasible in clinical studies of traumatic hearing loss mitigation.

Aside from the preclinical nature of our rodent model, other limitations to this study include the lack of scientific inquiry into the mechanism of IJV compression, cochlear physiology, and its effects on shock and acoustic waves. For this reason, we can only provide speculation for these. Secondly, our functional and structural findings do not correlate with each other. Specifically, the statistically significant differences in OAE findings from roughly 5 to 10 kHz in the right and left ears did not show any significant pathology on cochlear histology. Due to the preliminary nature of this data, an early euthanasia time point was chosen. For this reason, lack of corresponding cochlear histology may be due to euthanasia that proceeded completion of hair cell death. Alternatively, sufficient time may have elapsed for hair cell atrophy and sloughing, but these findings could be suggestive of a recoverable functional injury occurring

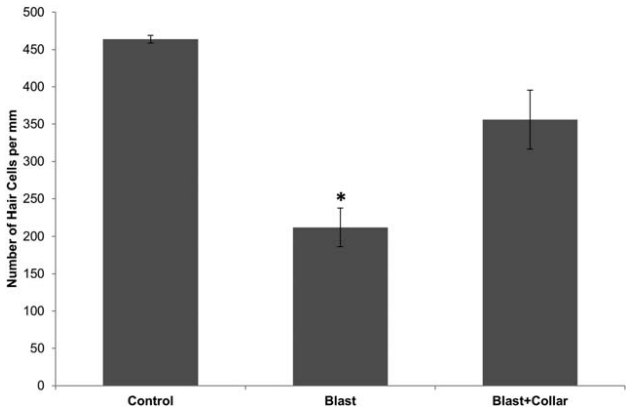

FIG. 6. Total hair cell count per mm at a distance of 70 to 100% from the cochlear apex in the blast+collar (n = 12), blast (n = 12), and control (n = 6). $*p < 0.01$ versus blast.

at 5 to 10 kHz, i.e., temporary threshold shift. Follow-up studies will require acute and chronic time points to evaluate these questions.

CONCLUSION

IJV compression before blast induced hearing injury was shown to reduce both functional and structural measures of inner ear pathology in a rodent model (ABR, OAE, and cochlear histology). This fascinating study proposes a new prophylactic mechanism that not only provides benefits to TBI mitigation, but also may revolutionize our approach to traumatic hearing injury in both the military and possibly even civilian population.

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