Distortion Product Otoacoustic Emissions and Intracranial Pressure During CSF Infusion Testing

Michael A. Williams; Jan Malm; Anders Eklund; Nicholas J. Horton; Susan E. Voss

BACKGROUND: A noninvasive method to monitor changes in intracranial pressure (ICP) is required for astronauts on long-duration spaceflight who are at risk of developing the Visual Impairment/Intracranial Pressure syndrome that has some, but not all of the features of idiopathic intracranial hypertension. We assessed the validity of distortion product otoacoustic emissions (DPOAEs) to detect changes in ICP.

METHODS: Subjects were eight patients undergoing medically necessary diagnostic cerebrospinal fluid (CSF) infusion testing for hydrocephalus. DPOAE measurements were obtained with an FDA-approved system at baseline and six controlled ICP levels in ~3 mmHg increments in random order, with a range from 10.8 ± 2.9 mmHg (SD) at baseline to 32.3 ± 4.1 mmHg (SD) at level 6.

RESULTS: For f2 frequencies between 800 and 1700 Hz, when ICP was ≥ 12 mmHg above baseline ICP, DPOAE angles increased significantly and DPOAE magnitudes decreased significantly, but less robustly.

DISCUSSION: Significant changes in DPOAE angle and magnitude are seen when ICP is ≥ 12 mmHg above a subject's supine baseline ICP during CSF infusion testing. These results suggest that the changes in DPOAE angle and magnitude seen with change in ICP are physiologically based, and suggest that it should be possible to detect pathological ICP elevation using DPOAE measurements. To use DPOAE for noninvasive estimation of ICP during spaceflight will require baseline measurements in the head-up, supine, and head-down positions to obtain baseline DPOAE values at different ICP ranges.

KEYWORDS: intracranial pressure, noninvasive measures, otoacoustic emissions, hydrocephalus, idiopathic intracranial hypertension, visual impairment intracranial pressure, spaceflight.

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Noninvasive intracranial pressure (ICP) monitoring has been sought for many decades and, if available, would benefit patient populations, including unconscious patients (e.g., traumatic brain injury or concussion) when evaluated in the field or the emergency department, comatose patients in the ICU when ICP elevation is suspected, and children and adults with disorders of cerebrospinal fluid (CSF) circulation such as hydrocephalus or idiopathic intracranial hypertension (IIH) with or without shunts. In the last decade, NASA has discovered that astronauts on long-duration spaceflight are at risk for developing a syndrome known as visual impairment/intracranial pressure (VIIP) that has many, but not all features of IIH, including papilledema, distension of the retrobulbar optic nerve sheath on MRI, flattening of the optic globe on MRI, and, in the four astronauts who have had lumbar puncture postflight, mildly elevated CSF pressure.[1,10] Nearly 75% of astronauts on spaceflights longer than 6 mo are at risk for this disorder. The risk of visual impairment on very long-duration exploration spaceflight (e.g., to Mars or a near-Earth asteroid) is considered serious enough to be a danger to flight safety.

From the Departments of Neurology and Neurological Surgery, University of Washington School of Medicine, Seattle, WA; the Departments of Clinical Neuroscience and Radiation Sciences, Umeå University, Umeå, Sweden; the Department of Mathematics and Statistics, Amherst College, Amherst, MA; and the Picker Engineering Program, Ford Hall Smith College, Northampton, MA.

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Address correspondence to: Michael A. Williams, M.D., Departments of Neurology and Neurological Surgery, 1959 NE Pacific St., Box 356470, Seattle, WA 98195; maw99@uw.edu.

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The leading hypothesis for the etiology of VIIP is redistribution of CSF, lymphatic fluid, and arterial and venous blood as a result of the microgravity environment, a so-called cephalad fluid shift, that is thought to cause increased ICP. However, invasive ICP measurements have never been performed in humans in space. As a result, NASA and the National Space Biomedical Research Institute (NSBRI) have sought and funded research to evaluate noninvasive methods of measuring ICP that have the potential to assess astronauts during long-duration spaceflight.[6]

The objective of this investigation was to determine the validity of a noninvasive method, distortion product otoacoustic emissions (DPOAEs), to detect changes in the ICP. Briefly, DPOAEs are sounds generated by the cochlea in response to two external tones played simultaneously in the ear canal. DPOAEs can be measured noninvasively within the ear canal.[12] Changes in ICP are associated with changes in DPOAEs, presumably due to changes in the stiffness of the middle-ear system that result from changes in the intracochlear pressure that occur with ICP changes that are conducted from the subarachnoid CSF via the cochlear aqueduct to the cochlea.[4,16,17] In the work presented here, changes in DPOAE measurements with changes in ICP were compared by setting and measuring the ICP using a reference standard in human subjects undergoing diagnostic CSF infusion testing.

METHODS

The protocol was reviewed and approved by the ethical review board at Umeå University and the IRB of Sinai Hospital of Baltimore, which is where the first author was employed at the time the research was conducted. Written informed consent was obtained from all subjects. All testing and data collection were performed within the Department of Neurology at the Umeå University Hospital during the periods of November 18–29, 2013, and March 17–28, 2014.

Subjects

All subjects, mean age 68.5 ± 7.4 yr (range 58–79), were patients with hydrocephalus who were undergoing medically necessary diagnostic CSF infusion testing. Exclusion criteria were: 1) pregnancy, 2) lack of decision-making capacity (Mini-Mental State Exam < 20 points), 3) participation in the study would significantly delay or interfere with the subject's healthcare, 4) prior middle-ear disease or surgery or abnormal inspection of the ear, and 5) excess ear wax that could not be removed safely. DPOAE measurements were made on a total of nine subjects. On some subjects, additional auditory measurements (tympanic membrane displacement) were also made and are not reported here. Of the nine subjects, one did not have DPOAE responses that were above the noise floor. Thus, measurements are reported from eight male subjects.

Equipment

Infusion investigations to diagnose hydrocephalus are a standard of care in Sweden and were performed with the previously described, CE approved CELDA® infusion device (Likvor AB, Umeå, Sweden) that has a peristaltic pump that automatically infuses or withdraws Ringer lactate via one 18-gauge spinal needle while simultaneously measuring CSF pressure via a second 18-gauge spinal needle inserted at the same level.[11] The CSF infusion procedure is fully automated and standardized using a constant-pressure protocol. DPOAEs[2,12] were measured with the FDA-approved HearID system (Mimosa Acoustics, Champaign, IL).

Procedure

The lumbar punctures (LPs) were performed by a staff neurologist at the University of Umeå Hospital. The patient was positioned in a custom-made bed (Modified Futura Plus 8381, Merivaara Corp., Lahti, Finland) with a rectangular opening at the lumbar level to access the patient's back while the head of the bed was elevated so that the subject was sitting for the LP. The spinal needles were first inserted using aseptic technique and local anesthesia, and were then connected to the infusion system. The head of the bed was lowered so that the subject rested supine with the spinal needles in place for the infusion protocol. All ICP measurements were taken with the patient supine. The zero-pressure reference level was the center of the external auditory meatus.

Baseline pressure was recorded for 15 min and two DPOAE measurements were taken (described below). The head of the bed was then elevated to 70° for 20 to 30 min as part of the standard clinical protocol. The patient was then placed supine again and the automated infusion was started. Six assigned ICP levels were planned for each patient in a predetermined random order that was contained in a sealed envelope that was opened at the time of the study. The ICP levels (1–6) ranged from approximately 5 to 22 mmHg above baseline in 3-mmHg increments. Each ICP level was maintained for 7 min after stabilization of the ICP. Difficulty withdrawing CSF with the peristaltic pump was encountered with one subject (subject N) and only for that subject a standard modified protocol of constant flow infusion was used instead. At each ICP level, either 1 or 2 DPOAE measurements were made at each of the 13 frequency combinations. The ICP levels measured by the infusion system at the time of the DPOAE measurement for each subject at each of the levels are reported in **Fig. 1**. Concordance between intracranially assessed ICP and lumbar CSF pressure has been demonstrated.[8]

Prior to the experimental protocol, otoscopy was performed to ensure that the ear canal appeared normal. If present, excess wax was removed. Tympanometry to assess middle-ear function and middle-ear static pressure was performed on all subjects 1 or 2 d before infusion testing; in all cases the tympanometric shape was normal and middle-ear pressure determined via tympanic peak pressure (TPP) was within ±35 daPa of zero.

Because changes in middle-ear static pressure of more than ±50 daPa could affect DPOAE responses[16] during the infusion study, tympanometry (GSI-39 Auto Tymp, Grason-Stadler, Eden Prairie, MN) at 226 Hz was used to monitor TPP. The TPP

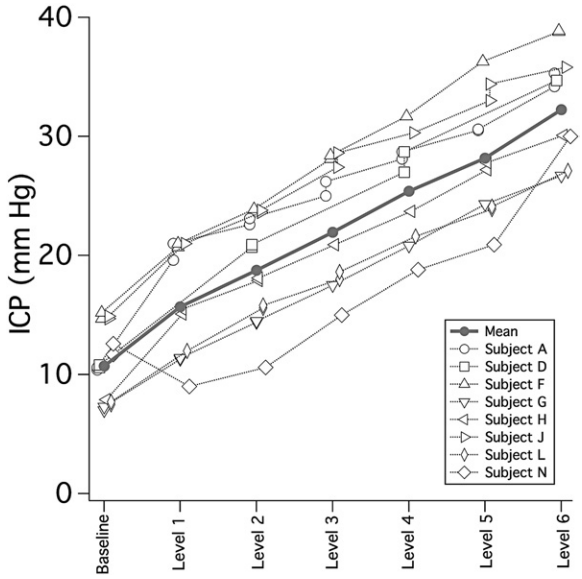

Fig. 1. ICP measured for each experimental condition for each subject. The gray line is the mean ICP. Individual subjects are indicated with unique symbols that are slightly offset to improve visibility. Multiple symbols for a subject at a given level indicate two measurements were made at that level.

was not monitored during the infusion studies on the first four subjects, but was performed on the final four subjects at four times: 1) immediately before the LP; 2) after the baseline ICP recording; 3) immediately before starting the infusion protocol; and 4) upon completion of the infusion protocol. During the infusion protocol, it was not feasible to perform tympanometry due to time constraints. The changes in TPP between the start of the infusion protocol and the completion of the infusion protocol were 5, 50, 10, and 0 daPa for subjects H, J, L, and N, respectively. In the case of subject J, the increase from 10 to 60 daPa during the infusion testing could have altered the middle ear's response enough to affect the DPOAE measurements;[16] the other changes are close enough to zero that their effects on the DPOAEs are assumed to be negligible.

DPOAEs are sounds generated by the cochlea in response to two stimulus tones played simultaneously in the ear canal at the two frequencies, f_1 and f_2. At the frequencies measured here, the largest DPOAE responses in humans are generally found at the distortion product frequency $f_{dp} = 2f_1 - f_2$ and $f_2/f_1 = 1.25$. Here, the level (L) of the two stimulus tones (f_1 and f_2) are set at $L_1 = L_2 = 75$ dB SPL (dB SPL is a measure of sound pressure level in pascals referenced to the standard 20 μPa; 75 dB SPL is a comfortable listening level). Thus, the reported DPOAE is a sinusoid at the frequency f_{dp} that results from the two stimulus tones. As a sinusoid, the DPOAE can be described in terms of its magnitude and angle, where the angle (or phase) represents the time shift in the sinusoid relative to a consistent reference point. Thus, changes in angles of DPOAEs represent time shifts in the sinusoid that can occur with structural changes in the auditory system. Similarly, changes in magnitudes of DPOAEs also represent changes in the auditory system.

DPOAE responses at f_{dp} were measured at 13 log-spaced frequencies with f_2 logarithmically spaced from approximately 500 to 4000 Hz. In cases where the measured DPOAE magnitude was within 6 dB of the noise floor estimated by the HearID system, the data were not considered valid and were eliminated from analysis.[15] Changes in DPOAE magnitudes and angles were calculated and analyzed at 5 consecutive frequencies (f_2 = 844, 984, 1172, 1406, and 1688 Hz) of the 13 measurement frequencies. These five frequencies were selected because they are lower frequencies where larger DPOAE changes are seen with changes in ICP. Changes in DPOAE magnitude and angle were calculated as changes from the baseline measurements. In cases where two baseline measurements were made, the average was used to calculate the change. In cases where all baseline measurements for a particular frequency were within the noise floor, it is not possible to report a change.

Statistical Analysis

We used a random effects model to compare the mean magnitudes and angles for each of seven ICP levels (baseline and six ICP levels).[7] The analysis accounts for repeated measurements on each of the subjects. The null hypothesis for this model is that the population means are the same for each of the seven positions (6 degrees of freedom overall test) after accounting for the subject specific effect (random intercept). The reference group was the baseline, which allowed each of the pairwise comparisons between a given level and baseline to be calculated. These models were fit separately for magnitudes and angles and for each of 5 frequencies (10 models in total). The mean differences are summarized as 95% confidence intervals for the fixed effect predicted difference between each level and baseline. Data at frequencies for which measurements were within 6 dB of the noise floor at baseline were excluded. Analyses were performed using R version 3.2.0.[14]

RESULTS

Although the baseline ICP differed between subjects, the increments between each of the infusion levels were similar (Fig. 1). Due to technical difficulties in the CSF infusion that do not affect the validity of the data, the baseline ICP value for Subject N was slightly higher than the ICP values at levels 1 and 2.

Fig. 2 and **Fig. 3** illustrate 1) the difference between robust and weak DPOAEs, and 2) how the raw DPOAE data is transformed into a format that can be analyzed against ICP. Fig. 2 shows example measurements of DPOAE magnitudes (upper plots) and angles (lower plots) from subject N and subject H at all frequency combinations. Subject N has robust DPOAE magnitudes that are more than 6 dB above the noise floor at all measurement points. In contrast, subject H has poor DPOAE magnitudes, most of which are within 6 dB of the noise floor and are not considered valid, a pattern that can be seen with older subjects with hearing impairment.[3,9]

The data from subject N is replotted in Fig. 3 (left) to demonstrate how the DPOAE magnitudes and angles change as a function of ICP. The absolute DPOAE magnitudes and angles at each of the five frequencies, indicated by vertical lines in the left

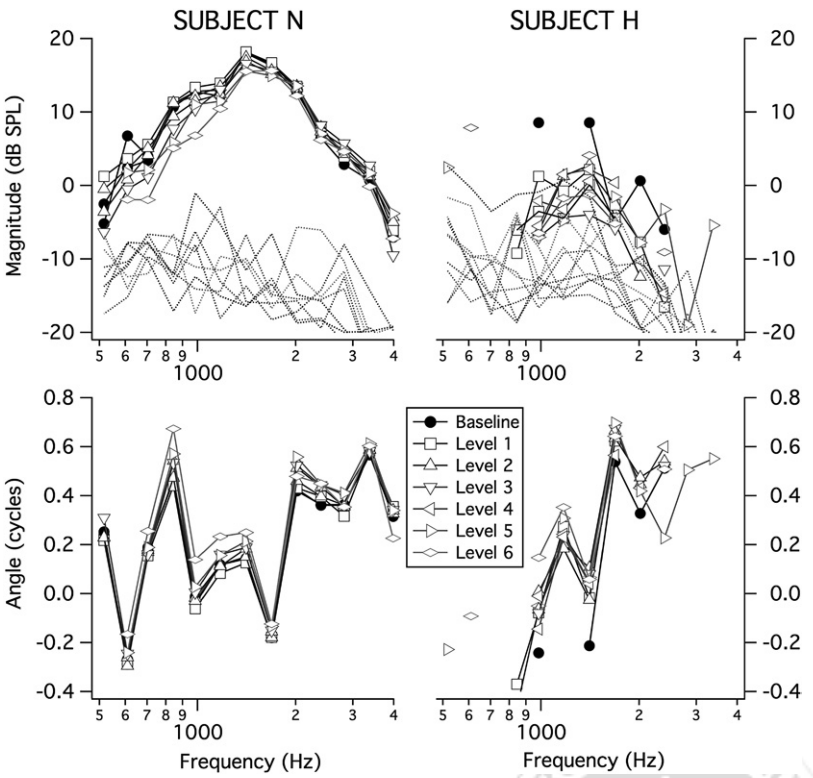

Fig. 2. DPOAE magnitudes (upper) and angles (lower) at all ICP levels for subject N (left) and subject H (right). Noise floors are indicated by the dotted lines. In cases where the DPOAE magnitude was within 6 dB of the noise floor, data are not considered valid and are not included in analyses for the magnitude or the angle.

column, are replotted in the center column to demonstrate their relation to ICP. The changes in DPOAE magnitudes and angles compared to baseline measurements are shown in the right column.

To illustrate the general trend, as well as the variability across subjects, **Fig. 4** shows the relative DPOAE magnitudes and angles at all ICP values for all eight subjects at two frequencies that were chosen because they had the most valid data points above the noise floor. At 1172 Hz, four of the eight subjects (A, J, L, N) had a majority of data above the noise floor, while two subjects (D, F) had valid data for about half of the measurements, and two subjects (G, H) had no valid data. Of the four subjects with the majority of data above the noise floor, the trend is for DPOAE magnitude to decrease with ICP and DPOAE angle to increase with ICP. Subject A does not follow this pattern at all ICP values.

At 1688 Hz, all eight subjects have valid DPOAE data at half or more of the ICP levels. The magnitude shows less change with ICP at 1688 Hz compared to lower frequencies, and no clear pattern exists across the subjects. In contrast, the DPOAE angle tends to increase with ICP for all subjects. The DPOAE angle for Subject G at baseline seems to be an outlier and leads to changes in DPOAE angle for Subject G that might be artificially low because all changes are referenced to baseline.

Fig. 5 shows the changes in DPOAE magnitudes and angles at all five frequencies relative to baseline measurements. The shaded regions indicate the 95% confidence interval of the mean. When the 95% CI region does not include zero, the change is significantly different from zero, whereas when the 95% CI region includes zero, the change is not significantly different from zero.

The DPOAE angles demonstrate significant increases with ICP (Fig. 5, lower plots). At four of the five frequencies (all except 984 Hz), the DPOAE angle increases significantly when ICP is at or above ICP level 3 (22.9 $\pm$ 5.1 mmHg), which is ~12 mmHg above baseline ICP level.

The DPOAE magnitudes at three of the five frequencies (844, 1406, and 1688 Hz) demonstrate significant decreases as ICP increases (Fig. 5, upper plots); however, the reduction in DPOAE magnitudes is significant for only a subset of ICP levels and frequencies, most prominently for 844 Hz at ICP level 3 and higher, and for 1406 and 1688 Hz at some higher ICP levels.

DISCUSSION

To the best of our knowledge, this is the first study to assess DPOAEs in a controlled experiment through a range of ICP that is clinically relevant and covers the same range seen in IIH and hydrocephalus. As ICP increases, systematic and significant changes in the DPOAE measurements are seen. In particular, for frequencies from 800 to 1700 Hz the DPOAE angle shows significant increases when ICP is ~12 mmHg or more above baseline. Changes in DPOAE magnitude are less robust, but also show a systematic and significant change, which is for the DPOAE magnitude to decrease as ICP increases. The relationship of DPOAE angle and magnitude to ICP exists in spite of the fact that the ICP levels were applied in random order, which suggests that the ICP/DPOAE relationship is physiologically based and independent of the direction of ICP change. These results suggest that it should be possible to detect changes in ICP that are above the upper limit of normal by using DPOAE measurements.

Our results are consistent with other reports in the literature. Bershad et al. demonstrated similar trends on subjects undergoing LP for suspected increases in ICP.[2] **Fig. 6** compares the measurements by Bershad et al.[2] to the DPOAE measurements made in this study. The data are plotted individually as a function of change between baseline ICP and measured ICP. In the Bershad et al. work, baseline ICP was the closing CSF pressure of an LP (i.e., after removal of CSF) and the elevated ICP level was the opening LP pressure for each subject, which could not be controlled.[2] In the current study, baseline ICP was the resting ICP before the infusion, and the elevated ICP level was the ICP at each stage of the infusion. Comparison of the two data sets demonstrates consistent trends, with DPOAE angles increasing with higher ICP at all frequencies, and DPOAE magnitudes decreasing with higher ICP, especially at the lowest

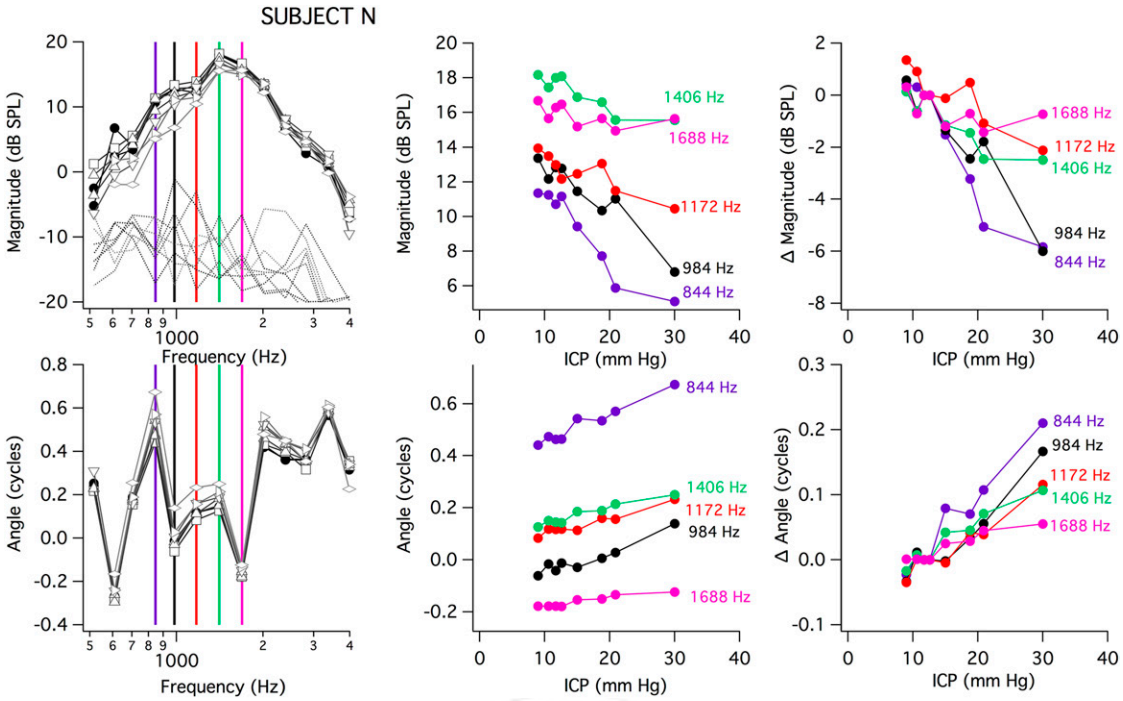

Fig. 3. DPOAE magnitudes (upper) and angles (lower) at all measured ICP values for subject N from Fig. 2 are shown in the left column. Dashed lines (see the online version for color figure: DOI:10.3357/AMHP.4572.2016) indicate the five frequencies for which data are extracted and plotted as a function of ICP in the center and right columns. In the center column, DPOAE magnitudes and angles at five frequencies plotted as a function of ICP. In the right column, change in DPOAE magnitudes and angles at five frequencies from baseline is plotted as a function of ICP.

frequency of 844 Hz. We note that for the five frequencies highlighted in the current work, Bershad et al. found that a significant difference in change in DPOAE magnitudes and angles existed for frequencies up to 2000 Hz when the change in ICP exceeded 15 mmHg^2, which is comparable to the significant DPOAE change at ICP levels 4 and above in the current work. The similarity of these results suggests that DPOAE changes with ICP are reproducible across different disorders and patient populations (predominantly young adults with pseudotumor cerebri and predominantly older adults with iNPH). Both of these disorders are characterized by an enduring change in craniospinal compliance that gives rise to abnormal ICP, and thus

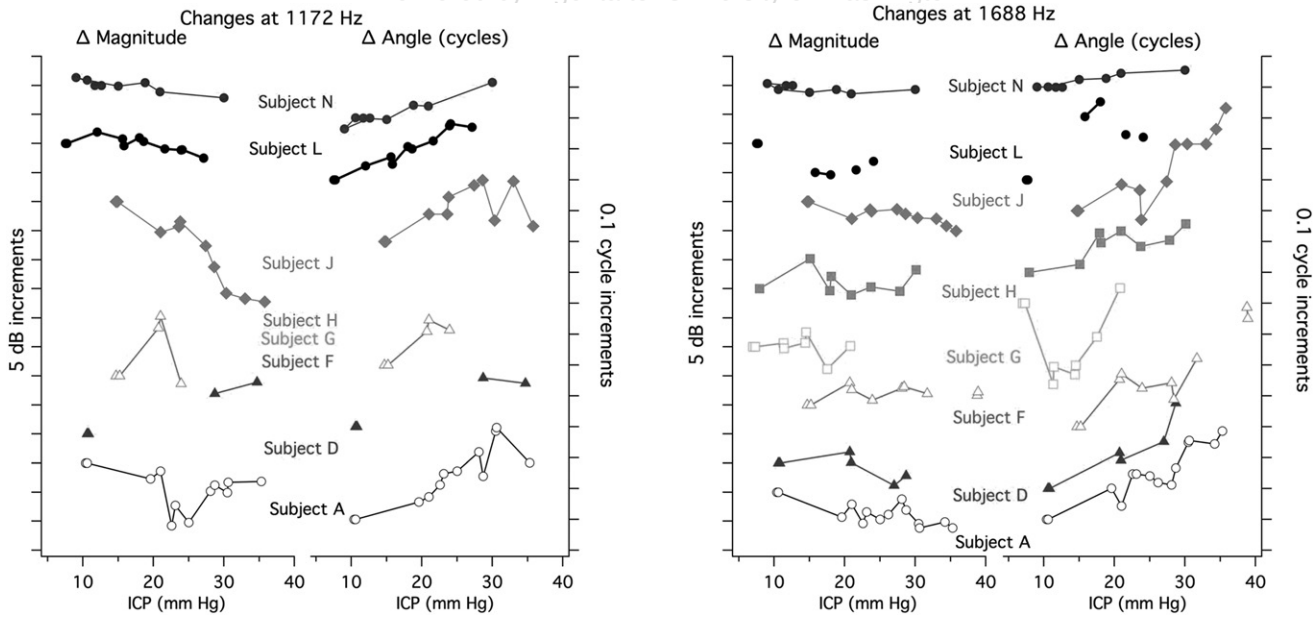

Fig. 4. Relative DPOAE magnitudes and angles at 1172 Hz (left) and 1688 Hz (right) for all 8 subjects (see the online version for color figure: DOI:10.3357/AMHP.4572.2016). Data are missing when the magnitude measurements are within 6 dB of the noise floor. When multiple measurements at a given level (1 through 6) are valid, both measurements are shown. When no valid measurement exists for a level 1 to 6, there are gaps in lines connecting the symbols.

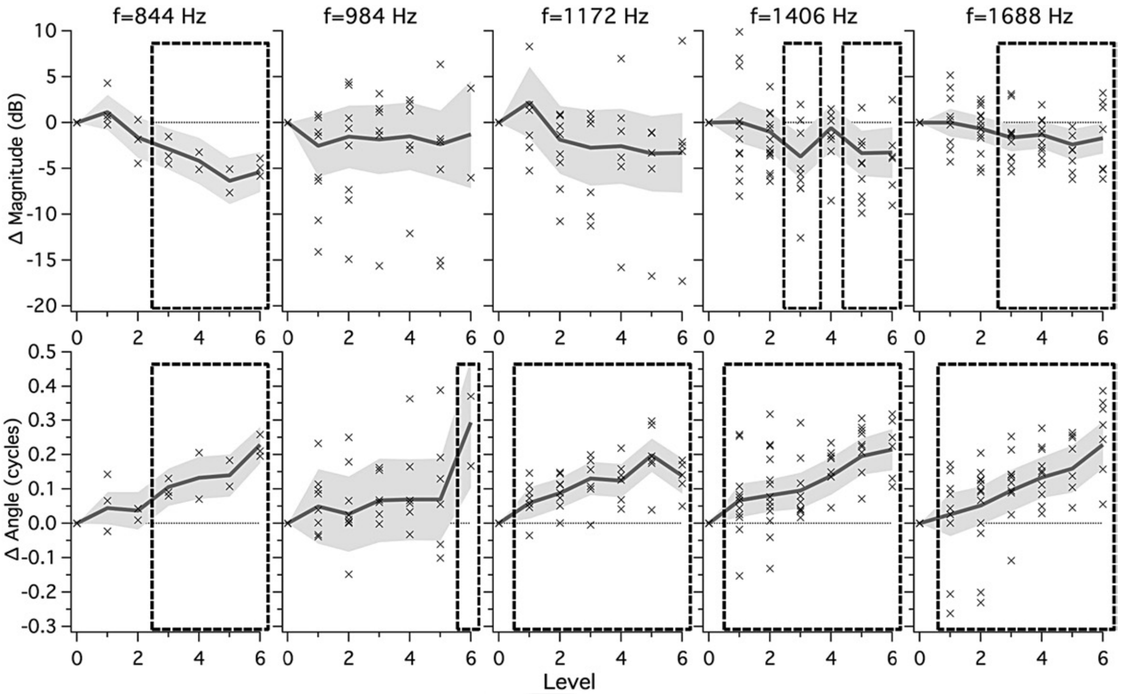

Fig. 5. Summary of changes in DPOAE magnitudes (upper) and angles (lower) from baseline across eight subjects at five frequencies. The data were normalized to the baseline measurement. Individual data are plotted with an x. The mean is plotted in the solid black line and the 95% confidence interval of the mean is shaded. Measurements within the dotted rectangles on each plot are statistically significant.

should be physiologically similar to VIIP, which, based on the documentation of elevated CSF pressure in the few astronauts with VIIP who have had a lumbar puncture after return to Earth,[1] also is likely to have an enduring change in craniospinal compliance.

The results are also consistent with those reported by Voss et al., where DPOAEs were measured at multiple positions on a tilt table to change ICP from upright to head down.[16,17] Physiological conditions in studies that rely on head-up or head-down tilt to change the ICP do not match the physiological conditions in disorders such as IIH or hydrocephalus. ICP change in head-up or head-down tilt is a result of the change in the hydrostatic pressure gradient of both the craniospinal CSF column and the arteriovenous blood columns, and includes a likely increase in cerebral blood volume. In contrast, in the current work the change in ICP was caused by controlled infusion or withdrawal of fluid with the patient supine. Therefore, hydrostatic pressure did not influence the ICP. Contrary to postural changes, cerebral blood volume may be reduced as infused CSF volume increases and ICP increases, which is a normal compensatory mechanism. Our study did not assess change in cerebral blood volume. Thus, the change in ICP and the overall physiology governing intracranial compliance is closer to normal (though not identical) with the CSF infusion method in our study than with the postural-change method.

The goal of this research was to assess the feasibility of using DPOAEs as an indirect and noninvasive measure of ICP for astronauts on long-duration spaceflight. If DPOAEs are to be used for this purpose, we would suggest the following protocol. DPOAE magnitudes and angles and tympanometry should be measured on Earth to establish an individual baseline for each astronaut. Measurements should be made in the upright, supine, and head-down tilt position, with the astronaut on a tilt table.[16,17] From these measurements, the size of change in DPOAE magnitude and angle that would be expected with a change in ICP between 13 and 20 mmHg could be estimated,[13,17] which is approximately equal to the change in ICP at levels 4 and 5 in the current protocol. Ideally, direct ICP measurement via LP should be performed simultaneously via a fluid coupled transducer at the level of the head to establish an individual ICP/DPOAE plot for each astronaut. Measurements of DPOAEs and tympanometry could then be made during spaceflight and compared with those made on Earth. If DPOAE changes during spaceflight are comparable to or greater than the changes measured with head down tilt, then increased ICP could be suspected. It is important to note, however, that DPOAEs have not been described during spaceflight. Repeated DPOAE measurements over time on all astronauts will be necessary to determine whether any change in DPOAEs correlates with VIIP. An additional approach to biological calibration on Earth would be to perform DPOAE before and after lower body negative pressure (LBNP), which is a possible countermeasure for VIIP, as this would avoid potential change to the inner ear due to hydrostatic fluid shifts; however, approximation of the change in ICP is not possible with LBNP unless the procedure is performed with simultaneous direct ICP measurements.

An important limitation of the present study is the small sample number of eight subjects and the even smaller number of four subjects with DPOAEs consistently greater than the noise floor. As a result of the relatively small amount of data, the confidence

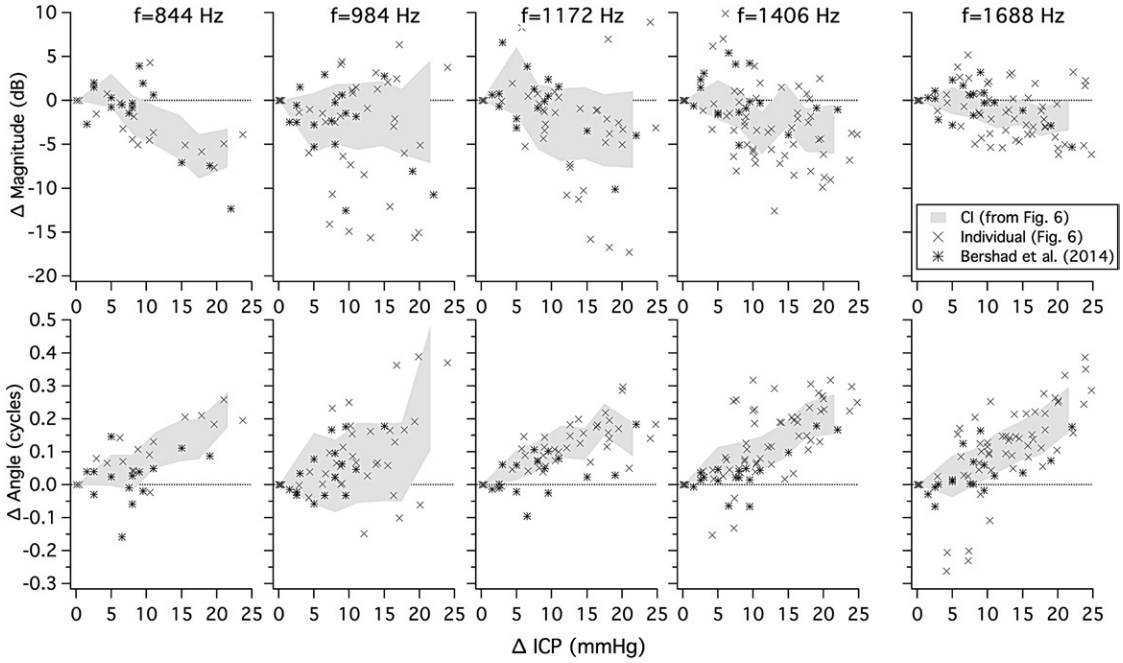

Fig. 6. Changes in DPOAE magnitudes (upper) and angles (lower) from Bershad et al.[2] compared to the measurements made in this study. All data are plotted individually. The data from Bershad et al. (*) are plotted as a function of the change between the closing pressure and the opening pressure during the LP. The data from the current study (x) are plotted as a function of change between the baseline ICP and the elevated ICP at each stage of the infusion.

intervals in Fig. 6 are likely larger than they would be with more data. At the same time, the novel data reported here support the hypothesis that changes in DPOAEs are sensitive to changes in ICP.

Our results only demonstrate a threshold detection of increased ICP (~12 mmHg above baseline) and, although a correlation between ICP DPOAE angle or magnitude appears to exist, further study with more subjects will be required to determine whether such a correlation is present. Based on the data in our study, change in DPOAE angle and magnitude can confirm that ICP is pathologically elevated, but the extent of the elevation cannot be determined.

Although our study assessed DPOAEs through a range of ICP levels as high as 32.3 ± 4.1 mmHg, which is considered to be pathologically elevated, we did not assess spontaneously occurring ICP elevation (e.g., A-waves or B-waves) that is known to occur during sleep in IIH or hydrocephalus. Thus, future studies of DPOAEs for evaluation of elevated ICP should include both the awake and asleep states.

Also, though our study took patients through seven different experimental conditions with ICP in random order, we did not test the reproducibility of DPOAEs. That is, we did not study subjects at another date to determine whether the DPOAE changes are consistent over time. However, it is likely that similar results would be obtained, as a 2010 study that repeated DPOAE measurements on five distinct dates from subjects in both the upright and supine positions on a title table and assessed DPOAE variations across days found that the variation from repeated measures was smaller than the effect introduced by the presumed change in ICP due to tilting.[16]

Bershad et al. provides a detailed description of additional limitations related to using DPOAEs to monitor changes in ICP.[2] Perhaps the most important is the need to obtain a baseline DPOAE measurement on each individual because DPOAEs are highly variable from person to person. In terms of monitoring individual astronauts or patients with disorders such as IIH or hydrocephalus, this limitation can be overcome because baseline measurements are possible.

A challenge with using DPOAEs to assess ICP is that the largest changes in DPOAEs with increasing ICP occur at lower frequencies where the middle-ear stiffness dominates the ear's response; however, the DPOAEs are less robust at these lower frequencies because the data are often not above the noise floor, especially in subjects with hearing impairment. Thus, healthy middle and inner ears are required to measure DPOAEs. Because astronauts are much younger than the subjects in this study, we predict that the changes in DPOAEs would be more robust and prevalent in the astronaut population than in our subjects.

The possibility exists that the cochlear aqueduct, which connects the CSF with the fluid of the inner ear, is not patent in all ears; however, this issue seems to be uncommon. Gopen et al. found that at least 93% of the temporal bones they studied would have been able to transmit pressure differentials to the cochlea,[5] and in previous work, Voss et al. showed systematic changes in DPOAEs in 100% of 19 subjects tilted to induce changes in ICP.[16,17] If necessary, the patency of the cochlear aqueduct in astronauts could be determined on Earth by demonstrating whether DPOAEs change with tilt posture.

In summary, significant changes in DPOAE angle and magnitude are seen when ICP is ≥12 mmHg above a subject's supine baseline ICP during controlled ICP elevation with CSF infusion testing. These results are similar to those seen in studies of

patients having CSF pressure measurement and CSF removal during LP, and in studies of change in ICP with head-up or head-down tilt. These results confirm that changes in DPOAE angle and magnitude with change in ICP are physiologically based, and suggest that it should be possible to detect pathological ICP elevation using DPOAE measurements. More study will be required to demonstrate a correlation between change in ICP and change in DPOAE angle and magnitude. Studies in astronauts during long-duration spaceflight will be required to demonstrate whether changes in DPOAE angle or magnitude correlate with the development of signs and symptoms of VIIP.

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Authors and affiliations: Michael A. Williams, M.D., Departments of Neurology and Neurological Surgery, University of Washington School of Medicine, Seattle, WA; Jan Malm, M.D., Ph.D., Department of Clinical Neuroscience, and Anders Eklund, Ph.D., Department of Radiation Sciences, Umeå University, Umeå, Sweden; Nicholas J. Horton, Sc.D., Department of Mathematics and Statistics, Amherst College, Amherst, MA; and Susan E. Voss, Ph.D., Picker Engineering Program, Ford Hall Smith College, Northampton, MA.

REFERENCES

1. Alexander DJ, Gibson CR, Hamilton DR, Lee SCM, Mader TH, et al. Evidence report: risk of spaceflight-induced intracranial hypertension and vision alterations. 2012. [Accessed April 3, 2016]. Available from http://humanresearchroadmap.nasa.gov/evidence/reports/VIIP.pdf?rnd=0.56451827174263.
2. Bershad EM, Urfy MZ, Pechacek A, McGrath M, Calvillo E, et al. Intracranial pressure modulates distortion product otoacoustic emissions: a proof of principle study. Neurosurgery. 2014; 75(4):445–454; discussion 454–455.
3. Dorn PA, Piskorski P, Keefe DH, Neely ST, Gorga MP. On the existence of an age/threshold/frequency interaction in distortion product otoacoustic emissions. J Acoust Soc Am. 1998; 104(2, Pt. 1):964–971.
4. Frank AM, Alexiou C, Hulin P, Janssen T, Arnold W, Trappe AE. Non-invasive measurement of intracranial pressure changes by otoacoustic emissions (OAEs) – A report of preliminary data. Zentralbl Neurochir. 2000; 61(4):177–180.
5. Gopen Q, Rosowski JJ, Merchant SN. Anatomy of the normal human cochlear aqueduct with functional implications. Hear Res. 1997; 107(1–2):9–22.
6. Human Health Countermeasures. VIIP3: we need a set of validated and minimally obtrusive diagnostic tools to measure and monitor changes in intracranial pressure, ocular structure, and ocular function. 2015. [Accessed September 7, 2015]. Available from http://humanresearchroadmap.nasa.gov/Gaps/gap.aspx?i=537.
7. Laird NM, Ware JH. Random-effects models for longitudinal data. Biometrics. 1982; 38(4):963–974.
8. Lenfeldt N, Koskinen LO, Bergenheim AT, Malm J, Eklund A. CSF pressure assessed by lumbar puncture agrees with intracranial pressure. Neurology. 2007; 68(2):155–158.
9. Lonsbury-Martin BL, Cutler WM, Martin GK. Evidence for the influence of aging on distortion-product otoacoustic emissions in humans. J Acoust Soc Am. 1991; 89(4, Pt.1):1749–1759.
10. Mader TH, Gibson CR, Pass AF, Kramer LA, Lee AG, et al. Optic disc edema, globe flattening, choroidal folds, and hyperopic shifts observed in astronauts after long-duration space flight. Ophthalmology. 2011; 118(10):2058–2069.
11. Malm J, Sandström N, Cesarini KG, Edsbagge M, Kristensen B, et al. Implementation of a new CSF dynamic device: a multicenter feasibility study in 562 patients. Acta Neurol Scand. 2012; 125(3):199–205.
12. Probst R, Lonsbury-Martin BL, Martin GK. A review of otoacoustic emissions. J Acoust Soc Am. 1991; 89(5):2027–2067.
13. Qvarlander S, Sundström N, Malm J, Eklund A. Postural effects on intracranial pressure: modeling and clinical evaluation. J Appl Physiol (1985). 2013; 115(10):1474–1480.
14. R Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing. [Accessed September 7, 2015]. Available from http://www.R-project.org.
15. Roede J, Harris FP, Probst R, Xu L. Repeatability of distortion product otoacoustic emissions in normally hearing humans. Audiology. 1993; 32(5):273–281.
16. Voss SE, Adegoke MF, Sheth KN, Rosand J, Horton NJ. Posture systematically alters ear-canal reflectance and DPOAE properties. Hear Res. 2010; 263(1–2):43–51.
17. Voss SE, Horton NJ, Tabucchi THP, Folowosele F, Shera CA. Posture-induced changes in distortion-product otoacoustic emissions and the potential for noninvasive monitoring of changes in intracranial pressure. Neurocrit Care. 2006; 4(3):251–257.