10-2014

# Intracranial Pressure Modulates Distortion Product Otoacoustic Emissions: A Proof-of-Principle Study

Eric M. Bershad
*Baylor College of Medicine*

Mian Z. Urfy
*Baylor College of Medicine*

Alina Pechacek
*Smith College*

Mary McGrath
*Smith College*

Eusebia Calvillo
*Baylor College of Medicine*

*See next page for additional authors*

**Neurosurgery Publish Ahead of Print**
**DOI: 10.1227/NEU.0000000000000449**

# Intracranial Pressure Modulates Distortion Product Otoacoustic Emissions: A Proof of Principle Study

Eric M. Bershad, M.D.,[1] Mian Z. Urfy, M.D.,[1] Alina Pechacek, M.S.,[2] Mary McGrath, M.S.,[2] Eusebia Calvillo, R.N.,[1] Nicholas J. Horton, Sc.D.,[3] Susan E. Voss, Ph.D.[2]

[1]Baylor College of Medicine, Department of Neurology, Houston, TX, USA
[2]Smith College, Department of Engineering, Northampton, MA, USA
[3]Amherst College, Department of Mathematics and Statistics, Amherst, MA, USA

**Corresponding author:**
Eric M. Bershad, MD.
Baylor College of Medicine
Department of Neurology
One Baylor Plaza, NB302
Houston, Texas 77030
bershad@bcm.edu
Work – 713-798-8472
Fax – 713-798-3091



**Disclosure**: This work was supported by National Science Foundation CAREER award 0642600, Susan E. Voss, PI. The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

**Acknowledgments**: We thank the subjects who participated in our study, Drs. Rosa Tang and Christian Cajavilca for referring subjects, and Saint Luke's Medical Center for providing space and ancillary support.

**Abstract**

**Background:** There is an important need to develop a non-invasive method for assessing intracranial pressure. We report a novel approach for monitoring intracranial pressure using cochlear derived distortion product otoacoustic emissions, which are affected by intracranial pressure.

**Objective:** We hypothesized that changes of intracranial pressure may be reflected by altered DPOAE responses via an associated change in perilymphatic pressure.

**Methods**: We measured the intracranial pressure and distortion product otoacoustic emissions (magnitude and phase angle) during opening and closing intracranial pressure measurements in 20 patients undergoing lumbar puncture.

**Results:** We collected data in 18 subjects and grouped them based on small (<4 mmHg), medium (5 to 11 mmHg), or large (≥15 mmHg) intracranial pressure changes. A permutation test was applied within each group to determine if distortion product otoacoustic emissions changes differed from zero when intracranial pressure changed. We report significant changes in the distortion product otoacoustic emissions magnitudes and angles, respectively, for the group with the largest intracranial pressure changes and no changes for the group with the smallest changes; the group with medium changes had variable distortion product otoacoustic emissions changes.

**Conclusion:** We report, for the first time, systematic changes in distortion product otoacoustic emissions magnitudes and phase in response to acute intracranial pressure changes. Future studies are warranted to further develop this new approach.

**Running Title**: Distortion Product Otoacoustic Emissions and ICP

**Key Words:** auditory, distortion product otoacoustic emissions, intracranial pressure, non-invasive

## INTRODUCTION

In 1951, Guillaume and Janny reported the first use of a transducer to measure the ventricular fluid pressure in humans, which helped to open a new frontier to understanding brain physiology.[1] It is now well recognized that elevated intracranial pressure (ICP) is an indicator of severely disturbed intracranial physiology, and predicts poor outcome in patients with acute neurological conditions including traumatic brain injury and subarachnoid hemorrhage.[2-6] Standard invasive techniques involve placing a catheter or fiber-optic probe through the skull; while accurate, these techniques have disadvantages including a small risk of catastrophic intracranial hemorrhage, infection, and seizures, which may lead to permanent neurological sequelae or even death. Furthermore, the placement of invasive ICP catheters requires neurosurgical expertise and patient monitoring in a specialized center. Due to these limitations, there is an important need to develop non-invasive approaches to measure ICP.

ICP is determined by the relationship between the cerebrospinal fluid (CSF) production and outflow, downstream resistance in the dural venous sinuses, arterial pulse waves transmitted into the intracranial vault, and craniospinal compliance. The cranial subarachnoid space communicates with the cochlea via the cochlear aqueduct.[7, 8] Therefore, pressure changes in the intracranial compartment are transmitted to the cochlea and can influence auditory function.[9, 10] Increases in ICP likely alter the middle-ear compliance via an increased stiffness of the annular ligament which connects the stapes to the oval window; such increased stiffness attenuates low frequency (<2000 Hz) middle-ear sound transmission from the ear canal to the cochlea.[11-13] Thus, auditory measurements of otoacoustic emissions that depend upon middle-ear function would theoretically be influenced by changes in ICP.

Otoacoustic emissions produced by the cochlea either spontaneously or in response to external stimuli can be recorded with a sensitive microphone in the ear canal.[14] Distortion product otoacoustic emissions (DPOAE) are a subtype of otoacoustic emissions produced by the nonlinear cochlea in response to the presence of two pure tone frequencies ($f_1$ and $f_2$) in the ear canal at a specified ratio ($f_2/f_1$) and sound pressure levels ($L_1$, $L_2$). In humans, the DPOAE generated at the frequency $2f_1 - f_2$ is considered the DPOAE response.

Previous studies in healthy subjects undergoing DPOAE measurements in upright and head down body tilt, as a method to induce changes in ICP, showed significant changes in DPOAE magnitudes and phase angles, but the actual ICP was not measured.[9, 10] Specifically, in the upright position (+90 degrees, presumed lower ICP) compared to the head-down tilt position (-45 degrees to horizontal, presumed higher ICP), the DPOAE magnitudes increased and phase angles decreased with lower ICP for specific frequency ranges.

Based on this previous work, our primary hypothesis is that DPOAE magnitudes will increase and DPOAE phase angles will decrease (500 to 2000 Hz range) when ICP decreases.[10] More specifically, we were interested in determining which DPOAE measures (i.e., magnitude and phase angle) are most sensitive to ICP changes and what degree of ICP change would alter these DPOAE responses.

## METHODS

### Patients

We enrolled 20 subjects in this prospective proof-of-principle cross-sectional study. The subjects were referred from either (1) the clinic of a board certified neuro-ophthalmologist, who sees a high volume of idiopathic intracranial hypertension (IIH) (aka. pseudotumor cerebri) patients in the Houston Metropolitan area or (2) from the Baylor College of Medicine neurology inpatient service at Saint Luke's Medical Center, Houston, Texas.

The inclusion criteria were: (1) age 18-60 years AND (2) clinically indicated lumbar puncture (LP) for diagnostic or therapeutic purposes. An upper limit for age range was chosen, as DPOAE measurements can be affected by inner or middle ear pathology, which increases with age. The exclusion criteria were: (1) known severe hearing loss in both ears, (2) excessive wax in the external ear canal, and (3) focal mass lesion or known obstruction between cranial and lumbar subarachnoid spaces. Excluded were patients with severe hearing loss or ear canal obstruction in both ears, as it is known that DPOAE response would be attenuated in these cases. Also excluded were subjects with focal or obstructive lesions in the brain or craniospinal subarachnoid space for safety purposes related to LP and also to ensure accuracy of the ICP

measurement. In patients without obstruction between the cranial and lumbar subarachnoid space, lumbar CSF pressure assessment is a highly accurate measurement of ICP.[15]

**Setting**

This study was approved by the Baylor College of Medicine Institutional Review Board, and written informed consent was obtained from all subjects. All testing and data collection was performed at Saint Luke's Medical Center, Houston, Texas from July to December 2012.

**Procedure**

Lumbar Puncture

LP was performed at the bedside by an experienced physician directly supervised by the study team. The subject was positioned in the lateral decubitus position, legs extended, and body relaxed. Local anesthesia with 2% lidocaine was given; we did not administer any systemic medications to the subjects. After lumbar needle insertion, we monitored ICP for five minutes to ensure stability before performing DPOAE measurements. The ICP was recorded as the average observed immediately before and after a given DPOAE recording. The stopcock and open tube manometer remained open during the entire DPOAE measurement so that we could observe ICP continuously. After the opening ICP and DPOAE measurements, the CSF was drained as clinically indicated. Next, the closing ICP measurements and DPOAE were repeated. The ICP as measured on the manometer in $cmH_20$ was converted to mmHg by the standard formula, 1 $cmH_20$ = 0.7356 mmHg.

Auditory Testing

First, an otoscopic exam was performed by a study physician to rule out obstructive earwax or gross tympanic membrane abnormalities. Next, the subject was positioned in the left lateral decubitus position (right ear up). Then, tympanometry was performed (Earscan, Micro Audiometrics Corp., ES-T, resolution 6 daPa) to ensure normal middle-ear pressure (range of 0 ± 25 daPa), as abnormal pressure may influence DPOAE measurements. If the pressure was not within this range, the operator instructed the subject to swallow to equalize the pressure, or if not

successful to blow gently through the obstructed nostrils with mouth closed. All patients achieved MEP within the normal range in the right ear pre-CSF drainage in the left lateral decubitus position. Next, an Etymotic ER-10c ear probe was placed in the subject's ear and connected to hardware and software developed by Mimosa Acoustics (HearID v4.5.15.0). To ensure optimal DPOAE response at the lower frequencies, we fixed $f_2/f_1$=1.25 and $L_1$=$L_2$=70 dB SPL; DPOAEs were measured at 13 log–spaced frequencies with $f_2$ approximately 500-4000 Hz. DPOAEs were obtained at the frequency $f_{dp}=2f_1-f_2$ from the discrete Fourier transform of the time-domain average of N responses; here the number of responses N varied with noise level, with a maximum N=200. The artifact rejection algorithm and the noise-floor calculation with HearID were employed as described elsewhere.[10] Each DPOAE measurement took 3 to 5 minutes, depending on the signal to noise ratio for a given measurement. Tympanometry and DPOAE measurements were performed twice in each subject, concurrently with the ICP measurements at opening and closing pressures. All measurements were performed in a standard hospital room with the door closed to the outside hallway and ambient noise minimized as much as possible by instructing the patient and health care personnel not to talk during the procedure. DPOAE data that had magnitudes within 6 dB of the noise floor were considered within the noise for analysis.[10]

**Statistical Analysis**

For analysis, we categorized the participants into three groups (A, B and C) depending on the measured changes in ICP from pre-to-post CSF drainage. The three groups were determined in an ad-hoc manner after all measurements were made, simply based on the measured changes in ICP, as there were no prior studies for which to base this sort of decision upon. The three groups were defined as: Group A with large ICP changes (≥15 mmHg), Group B with medium ICP changes (5 to 11 mmHg), and Group C with small ICP changes (<4 mmHg). A resampling procedure was undertaken to determine if changes in pre-to-post CSF drainage DPOAE magnitudes or phase angles differed from zero. For each group (A, B, and C), a bootstrap method was used to compute a 95% confidence interval for the difference between each DPOAE measurement (magnitude and phase angle separately) made before and after CSF drainage. These confidence intervals were computed using the Matlab function ``bootci'' (Matlab version 7.12.0.635), with 10,000 bootstrap replications ("NBOOT") and all other function inputs at the

default values. The interpretation of these computations is that when the 95% confidence interval contains zero, there is not strong evidence for a statistically significant difference between the pre and post-CSF drainage measurements, but when the confidence interval does not contain zero, then there is likely a difference. We did not have a sample size calculation, given that there was no other data in the literature for which to give estimations of effect size of ICP change on DPOAE measures, as this was the first study on this topic.

## RESULTS

We collected pre- and post-CSF drainage data including ICP and DPOAEs in 90% (n=18) of the participants; in two subjects the data were not obtainable. In subject 7, the data was collected, but the computer malfunctioned and data was lost, and in subject 10, the DPOAE response was below the noise floor, indicating severe hearing loss. Subject characteristics including age, sex, indication for LP, ICPs during opening and closing pressures, tympanometry before opening and after closing pressures, and assigned ICP group are reported in Table 1. We note that the most common indications for LP were IIH (n=10) or headache (n=5).

Figures 1, 2 and 3 illustrate the DPOAE data for each of the three groups.

Figure 1 plots the results from the four subjects in group A with the largest changes in ICP (≥15mmHg). Below about 1000 Hz, for all subjects the DPOAE magnitude increased when the ICP decreased, and above about 1000 Hz the changes in DPOAE magnitude were smaller. Similarly, there were systematic changes in the DPOAE phase angle, with a smaller phase angle when the ICP decreased. The reduction in the phase angle was consistent across all four subjects up to about 2000 Hz, and continued to higher frequencies in at least two of the subjects (5 and 18). At the lowest frequencies, the DPOAE magnitudes were often within 6 dB of the noise floor for the pre-procedure condition when ICP was high (and presumably poor middle-ear transmission). When the ICP decreased after CSF drainage, the DPOAE magnitude increased above the noise floor; in this case we computed the difference between the pre-CSF drainage noise floor and the post-drainage DPOAE magnitude, which is the lower boundary of the actual change in DPOAE magnitude (indicated by solid markers).

Figure 2 plots the results from the ten subjects in group B with the medium changes in ICP (5 to 11 mm Hg). Two of these subjects (2, 11) showed indications of the systematic changes described above for group A, with post-CSF drainage increases in DPOAE magnitudes and post-drainage decreases in DPOAE angles. However, the other 8 subjects did not show systematic DPOAE changes.

Figure 3 plots the results for the subjects in group C in which minimal changes in ICP occurred (< 4 mmHg). In all cases, pre and post-CSF drainage DPOAE magnitudes and angles were similar with no systematic difference in DPOAE pre to post procedure.

Figure 4 summarizes the results from all three groups and shows the bootstrap estimates of the confidence interval for mean difference in DPOAE magnitudes and angles by group. Below 2000 Hz, group A (largest ICP changes) exhibited mean DPOAE changes in both magnitude and angle that were systematically different from zero, as the 95% confidence interval does not generally include zero (with one exception in magnitude at about 1000 Hz). Neither group B nor group C demonstrated a 95% confidence interval that differed from zero, suggesting the means of both of these groups are not significantly different from zero.

## DISCUSSION

The main finding of this study is that DPOAE magnitudes and angles changed systematically when ICP decreased by at least 15 mmHg (Group A). When the ICP changes were smaller, the DPOAEs did not generally show systematic changes (Groups B and C); two subjects within the middle group B did show systematic changes consistent with the subjects in Group A. Collectively, these results demonstrate that it may be possible to detect ICP changes by examining changes in DPOAE magnitudes and angles that result from effect of ICP changes on auditory transmission.

Within group A (ICP changes ≥ 15 mmHg) the DPOAE magnitudes were most sensitive to changes in ICP at the lowest measured frequency (600 Hz) and continued to be sensitive up to about 2000 Hz. The DPOAE phase angle showed the biggest change with ICP at 1400 Hz.

These findings are preliminary and from only four subjects that had relatively larger ICP changes, thus the exact patterns are likely not typical of all subjects.

These findings are consistent to those seen in previous studies of DPOAE testing using head down tilt to increase hydrostatic pressure and presumably ICP.[9, 10] In these studies, healthy volunteers were tilted to angles from upright (90 degrees), supine, and negative 30 and 45 degrees head down tilt with DPOAE testing done at each position. In one study, the DPOAE magnitude changes were highly significant between the upright and negative 45 degree head down tilt position in the low frequency range of 750 to 1500 Hz; the phase angles were not evaluated in this study.[9] In the other study, significant changes in DPOAE magnitude and phase angle shift were seen in the ranges of 500 to 2000 Hz and 500 to 4000 Hz, respectively. The reason for the larger range that was found significant in this later study is likely due to a larger number of measurements, which were repeated multiple times on each subject.[10] We note that the increased ICP due to a hydrostatic pressure increase from head-down tilt could theoretically produce a different effect on DPOAE measures compared to pathological conditions which may have cerebral edema, or other space-occupying lesions (i.e. brain hemorrhages, contusions, or tumors) which may affect structures such as the meninges, brainstem, blood brain barrier, and/or vascular system, which may affect DPOAE responses. Therefore, it would be necessary for further studies to confirm the same results in patients with other etiological factors leading to elevated ICP. The results presented here are consistent with the head-down tilt measurements.

Our study is also consistent with a previous study by Frank et al in 2000,[16] which reported changes in DPOAEs in 12 young adults with different body postures and in 5 patients with simultaneous invasive ICP monitoring for normal pressure hydrocephalus. Specifically, they observed a lower DPOAE magnitude at the lower frequency of 1 kHz with higher ICPs, which is consistent with our findings that DPOAE magnitudes were lower when ICP was higher, especially at lower frequencies.[16] We also note a case report where evoked otoacoustic emissions increased after CSF drainage in a child with acute hydrocephalus from tuberculous meningitis.[17]

Limitations

We acknowledge several limitations to our study. First, our categorization for assigning participants into the three ICP groups was arbitrary, based on post-hoc analysis; however, given that we did not have control over the ICP values in the participants who were undergoing a clinically indicated LP, we were uncertain what ICP ranges we would observe. Also, the aim of this proof of concept study was to determine whether any signal was present linking the ICP changes to DPOAE magnitudes and angles, and thus was not powered to include the entire range of possible ICP changes. It would be important for further studies to be conducted in which higher ICP values are present, since we note that the DPOAE responses were lower in the group A patients with the highest ICP values. While DPOAE responses would likely be within the noise floor for some frequencies in cases of extremely elevated ICP ranges (> 30 mmHg), this information could be useful in detecting a change in ICP from normal to pathologic.

A second limitation is that the absolute DPOAE magnitudes and phase angles are variable across subjects; therefore, a baseline measurement of the DPOAE on the individual patient is required in order to detect changes in ICP. If one wished to have a one-to-one correspondence between DPOAE changes and actual ICP values, it would be necessary to calibrate the DPOAE measurement with an invasive ICP monitor. For example, in hydrocephalus patients, if several DPOAE measurements are made simultaneously with invasive ICP measurements, a calibration may be possible that could be used subsequently once the invasive catheter is removed. Therefore, DPOAE *changes* could be used to estimate changes in ICP for a given patient. Alternatively, changes in DPOAEs that indicate changes in ICP could also be useful without the calibration to detect exact ICP values. Thus, even without calibrating the DPOAE measurement with an ICP monitor, it appears possible to screen patients for elevated ICP based on their baseline normative data. This might be particularly useful for monitoring the patency of shunts associated with hydrocephalus patients.

A third limitation is that DPOAE measurements require a healthy middle and inner ear; therefore, the utility of using this approach in some individuals may be precluded on the basis of inner- or middle-ear pathology. For example, older adults with intracranial hemorrhages or massive ischemic strokes may not be suitable candidates for DPOAE monitoring due to the

expected hearing loss with age; however, in the pediatric population or young adults, who generally have a healthy auditory system, and may have traumatic brain injury (TBI), subarachnoid hemorrhage, obstructive hydrocephalus, or IIH (i.e., pseudotumor cerebri), DPOAE testing may be useful. There is only limited data to determine whether patients with TBI would be suitable candidates for DPOAE testing as an assessment of ICP given that other anatomical lesions that may be associated with TBI such as auditory canal, nerve or brainstem herniation may contribute to changes in DPOAE measures. A study in Sweden, did not find any significant effect on otoacoustic emissions in those with a history of head injuries;[18] however, a rabbit model of closed head injury showed short-term changes in otoacoustic emissions.[19]

The fourth limitation is that DPOAEs may be affected by ambient noise; however, despite the relatively noisy hospital environment, we were able to measure DPOAEs over a wide frequency range in most of our subjects. The issues related to measurements being within the noise floor for some group A subjects resulted from a reduced DPOAE signal and not from an increased noise floor. The DPOAE measurement system does a good job with its artifact rejection algorithm, and ambient noise was not a limiting factor. In the future, the noise floor could be reduced by increasing the number of samples collected; however, this would also add to the measurement time.

A fifth limitation of this study, CSF drainage in patients undergoing clinically indicated LP, limited us to monitoring DPOAE changes in a given patient from a higher opening pressure to lower closing pressure; therefore, we cannot be certain that the opposite direction of ICP change would produce the same results. However, DPOAEs measured from the upright to head down tilt position (lower pressure to higher pressure) provided similar results to those here, suggesting that the direction does not determine the trend in the results[10].

A final limitation for this study involves the ability of the cochlear aqueduct to transmit CSF pressure changes to the cochlea. In the largest temporal-bone study to date that examines the patency of the cochlear aqueduct[8], 93% of ears had either fully patent aqueducts or ducts filled with loose connective tissue; either situation would enable pressure differentials to be transmitted to the cochlea. It is not clear if the 4% of ears with bone in the lumen could transmit pressure

differentials, and it is likely that the 3% lacking the aqueduct altogether would not have any changes in DPOAE as a result of ICP changes. Thus, we expect that about 3-7% of subjects would not show changes in DPOAE as a result of ICP changes. During a baseline measurement, one might confirm that the DPOAE is sensitive to ICP changes by making measurements with a head tilt.

We also offer a few justifications for our study design. We chose a population of relatively stable patients on the regular ward service, rather than the ICU setting, for several reasons. First, we wanted to minimize the number of other variables that may influence the ICP and/or hearing function that are more difficult to control for in the ICU setting, including ventilator effects on ICP, more unstable ICP values due to rapidly changing physiology, and concurrent therapeutic management (i.e. hyperosmolar agents, hyperventilation). Second, the patients undergoing LP, especially those with suspected idiopathic intracranial hypertension, were expected to have an elevated opening pressure; whereas, patients in the intensive care unit setting with invasive ICP monitors usually have only periodic brief elevations of ICP. Also, we acknowledge that the measurement of CSF pressure with rigid tube manometer may alter the lumbar subarachnoid space compliance, but would not expect this to alter the accuracy of the ICP measurement obtained. Finally, our relatively small sample size may have limited the power to detect significant differences in DPOAE measures at specific frequencies, which may exist if a larger sample was studied; however, in this preliminary study, our aim was to determine if any patterns emerged that would indicate the need for further exploration of this novel technique.

Future work should evaluate DPOAEs in other settings such as in neurotrauma and neurological ICUs in patients with TBI, intracranial hemorrhage, and those with acute ICP elevation. It would also be important to establish the expected ranges for DPOAE changes in subjects with elevated ICP to determine if it is possible to approximate a specific ICP from a measured change in DPOAE magnitude and angle. Additional study should be given to further investigate the DPOAE responses at the lower frequency ranges in patients undergoing invasive ICP measurement, since this was where we found the strongest signal of change with regards to the phase angle and magnitudes. It is possible that by focusing on the lower frequencies and monitoring for a longer period of time, that the noise floor would decrease, and allow for more precise characterization of smaller DPOAE magnitudes and phase angles shifts.

If it can be shown that DPOAEs are reliable for differentiating normal from elevated ICP, then DPOAE measures may become a very useful screening test for detecting elevated ICP in some at risk patients including those with TBI, anoxic brain injury, intracerebral hemorrhage, subarachnoid hemorrhage, and ischemic stroke. Other potential uses would be monitoring of pediatric and adult patients with hydrocephalus for detection of shunt malfunction or those with IIH. Since DPOAEs can be measured noninvasively with a soft earplug and portable audiology equipment, many patients in various settings may be amenable for DPOAE testing. There may be settings for which advanced neurocritical care monitoring is not available, such as rural, tropical, or other extreme environments, where ICP screening with non-invasive devices would be indicated. Finally, a major benefit of DPOAE testing is that is does not require any participation by the patient, and can be performed even if the subject is comatose.

## CONCLUSION

We report for the first time that DPOAEs, a noninvasive response from the auditory system, are affected by ICP changes. Specifically, decreases in ICP led to increases in DPOAE magnitudes and decreases in DPOAE phase angles for frequencies up to 2000 Hz. Further work is needed to better understand the relationship between DPOAEs and ICP in a larger prospective study.

## REFERENCES


**1.** Guillaume J, Janny P. [Continuous intracranial manometry; importance of the method and first results]. *Revue neurologique*. Feb 1951;84(2):131-142.

**2.** Bremmer R, de Jong BM, Wagemakers M, Regtien JG, van der Naalt J. The course of intracranial pressure in traumatic brain injury: relation with outcome and CT-characteristics. *Neurocritical care*. Jun 2010;12(3):362-368.

**3.** Badri S, Chen J, Barber J, et al. Mortality and long-term functional outcome associated with intracranial pressure after traumatic brain injury. *Intensive care medicine*. Nov 2012;38(11):1800-1809.

**4.** Treggiari MM, Schutz N, Yanez ND, Romand JA. Role of intracranial pressure values and patterns in predicting outcome in traumatic brain injury: a systematic review. *Neurocritical care*. 2007;6(2):104-112.

**5.** Mack WJ, King RG, Ducruet AF, et al. Intracranial pressure following aneurysmal subarachnoid hemorrhage: monitoring practices and outcome data. *Neurosurgical focus*. Apr 15 2003;14(4):e3.

**6.** Tian Y, Wang Z, Jia Y, et al. Intracranial pressure variability predicts short-term outcome after intracerebral hemorrhage: a retrospective study. *Journal of the neurological sciences*. Jul 15 2013;330(1-2):38-44.

**7.** Bohmer A. Hydrostatic pressure in the inner ear fluid compartments and its effects on inner ear function. *Acta oto-laryngologica. Supplementum*. 1993;507:3-24.

**8.** Gopen Q, Rosowski JJ, Merchant SN. Anatomy of the normal human cochlear aqueduct with functional implications. *Hearing research*. May 1997;107(1-2):9-22.

**9.** Voss SE, Horton NJ, Tabucchi TH, Folowosele FO, Shera CA. Posture-induced changes in distortion-product otoacoustic emissions and the potential for noninvasive monitoring of changes in intracranial pressure. *Neurocritical care*. 2006;4(3):251-257.

**10.** Voss SE, Adegoke MF, Horton NJ, Sheth KN, Rosand J, Shera CA. Posture systematically alters ear-canal reflectance and DPOAE properties. *Hearing research*. May 2010;263(1-2):43-51.

**11.** Buki B, de Kleine E, Wit HP, Avan P. Detection of intracochlear and intracranial pressure changes with otoacoustic emissions: a gerbil model. *Hearing research*. May 2002;167(1-2):180-191.

**12.** Murakami S, Gyo K, Goode RL. Effect of increased inner ear pressure on middle ear mechanics. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery*. May 1998;118(5):703-708.

**13.** Buki B, Avan P, Lemaire JJ, Dordain M, Chazal J, Ribari O. Otoacoustic emissions: a new tool for monitoring intracranial pressure changes through stapes displacements. *Hearing research*. May 1996;94(1-2):125-139.

**14.** Probst R, Lonsbury-Martin BL, Martin GK. A review of otoacoustic emissions. *The Journal of the Acoustical Society of America*. May 1991;89(5):2027-2067.

**15.** Lenfeldt N, Koskinen LO, Bergenheim AT, Malm J, Eklund A. CSF pressure assessed by lumbar puncture agrees with intracranial pressure. *Neurology*. Jan 9 2007;68(2):155-158.

**16.** 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. *Zentralblatt fur Neurochirurgie*. 2000;61(4):177-180.

**17.** Schmutzhard J, Aregger FC, Otieno A, Bunk S, Zorowka P, Schmutzhard E. Release of intracranial pressure leads to improvement of otoacoustic emissions--a case report of a Kenyan child with complicated tuberculous meningitis. *Journal of tropical pediatrics*. Aug 2013;59(4):326-329.

**18.** Engdahl B, Tambs K. Otoacoustic emissions in the general adult population of Nord-Trondelag, Norway: II. Effects of noise, head injuries, and ear infections. *International journal of audiology*. Jan 2002;41(1):78-87.

**19.** Danielidis V, Tsimpiris N, Balatsouras DG, et al. Short-term pathophysiologic changes and histopathologic findings of the auditory pathway after closed head injury, using a rabbit model. *Audiology & neuro-otology*. 2007;12(3):145-154.



**Figure Legend**

**Figure 1 - DPOAE measurements from group A.** DPOAE measurements from group A, where subjects had pre- and post-CSF drainage ICP changes ≥ 15 mmHg. Left: DPOAE magnitudes and angles and corresponding noise floors for pre- (gray) and post-drainage (black) measurements; magnitudes within 6 dB of the noise floor are considered to be within the noise. Right: Differences in DPOAE magnitudes and angles for the post-minus pre-CSF drainage measurement. Solid symbols indicate a difference between the post-CSFdrainage DPOAE magnitude and pre-CSF drainage DPOAE noise floor; these points are lower bounds on the difference that might exist if the DPOAE could have been measured in the pre-CSF drainage condition. Noise floors plotted in gray and black dashed lines correspond to pre and post-CSF drainage measurements.

**Figure 2 - DPOAE measurements from group B**. DPOAE measurements from group B, where subjects had pre- and post-CSF drainage ICP changes in the range of 5 to 11 mmHg. Left: DPOAE magnitudes and angles and corresponding noise floors for pre- (gray) and post-drainage

(black) measurements; magnitudes within 6 dB of the noise floor are considered to be within the noise. Right: Differences in DPOAE magnitudes and angles for the post- minus pre-CSF drainage measurement. Solid symbols indicate a difference between the post-drainage DPOAE magnitude and pre-drainage DPOAE noise floor; these points are lower bounds on the difference that might exist if the DPOAE could have been measured in the pre-CSF drainage condition. Noise floors plotted in gray and black dashed lines correspond to pre and post-CSF drainage measurements.

**Figure 3 - DPOAE measurements from group C**. DPOAE measurements from group C, where subjects had pre and post-CSF drainage ICP changes of less than 4 mmHg. Left: DPOAE magnitudes and angles and corresponding noise floors for pre- (gray) and post-CSF drainage (black) measurements. Right: Differences in DPOAE magnitudes and angles for the post-minus the pre-CSF drainage measurement. Noise floors plotted in gray and black dashed lines correspond to pre and post-CSF drainage measurements.

**Figure 4 - Summary of Results and Resampling Procedure**. Summary of DPOAE changes in magnitude (upper plots) and angle (lower plots) for the three groups. Open points represent calculated DPOAE differences and solid points represent differences from post-CSF drainage DPOAE magnitudes and pre-CSF drainage DPOAE noise floors. Solid lines are the mean differences at each frequency. The gray shaded regions represent a 95% confidence interval for the difference in mean DPOAE, as calculated by a bootstrap procedure. The confidence interval was computed only when three or more data points existed at a given frequency. Confidence intervals were calculated using all available data included the differences determined from the magnitude bounds (solid points). The bounds are lower limits on the actual differences and so any significant differences would potentially only be bigger if the noise floor had not interfered with the measurement. Thus, the magnitude differences for the bounded cases are used in the confidence interval calculation, as this allows use of as much of our data as possible. A bounded measure of phase is not available, as it is impossible to estimate the phase of a signal in the noise. Thus the confidence intervals calculated for the phase cannot include the points.

**Table 1. Subject Characteristics and ICP measurements**

| Subject Number | Age | Sex | Diagnosis | *ICP Opening (mmHg) | ICP Closing (mmHg) | ICP change (mmHg) | ICP Group | MEP before and after LP (daPa) |
|---|---|---|---|---|---|---|---|---|
| 1† | 34 | F | IIH | 28 | 6 | 22 | A | 24/18 |
| 2 | 59 | F | SAH | 15.5 | 6 | 9.5 | B | 6/6 |
| 3 | 41 | F | Meningitis | 14 | 9 | 5 | C | -18/-18 |
| 4 | 25 | M | Diplopia | 11 | 9.5 | 1.5 | C | 0/0 |
| 5 | 52 | F | IIH | 21 | 6 | 15 | A | 12/6 |
| 6 | 25 | F | IIH | 18 | 10 | 8 | B | -6/0 |
| 7 | 46 | F | HA | 24 | 15 | 9 | No DP | 0/0 |
| 8 | 21 | F | Meningitis | 14.5 | 5 | 9.5 | B | -12/-6 |
| 9 | 25 | F | IIH | 20 | 11 | 9 | B | -6/-6 |
| 10 | 37 | M | IIH | 18.5 | 11 | 7.5 | No | n/a |
| 11 | 38 | F | HA | 14 | 9 | 5 | B | 24/18 |
| 12 | 29 | F | HCP | 12 | 9.5 | 2.5 | C | 6/0 |
| 13 | 22 | M | HA | 15.5 | 13 | 2.5 | C | 6/NT |
| 14 | 56 | F | HA | 14 | 11 | 3 | C | 6/6 |
| 15 | 30 | F | HA | 18.5 | 7.5 | 11 | B | -18/NT |
| 16 | 53 | F | IIH | 18.5 | 11 | 7.5 | B | 12/12 |
| 17 | 31 | F | IIH | 18.5 | 12 | 6.5 | B | 6/0 |
| 18 | 20 | F | IIH | 25 | 6 | 19 | A | 12/0 |
| 19 | 58 | F | IIH | 15.5 | 7.5 | 8 | B | 18/72± |
| 20 | 18 | F | IIH | 37.5 | 10.5 | 27 | A | 12/6 |

Abbreviations: DP = distortion product otoacoustic emissions; HA = headache; HCP = hydrocephalus; MEP = Middle ear pressure; NT = not tested; IIH = Idiopathic intracranial hypertension; SAH = Subarachnoid hemorrhage. *ICP values in mmHg rounded to nearest 0.5 mmHg; † Subject 1 the opening pressure was at least 28 mmHg, the actual value was not determined as the manometer extension was unusable for this subject. Define assigned group ICP ranges in caption. ± Subject 19 had middle ear pressure outside of the optimal range during the post-LP measurement.