The central auditory system and cochlear implantation: Using olfactory testing to evaluate a potential central component in cochlear implant performance

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HYPOTHESIS

We hypothesize that patients with olfactory dysfunction are more likely to have worse hearing outcomes after cochlear implantation (CI).

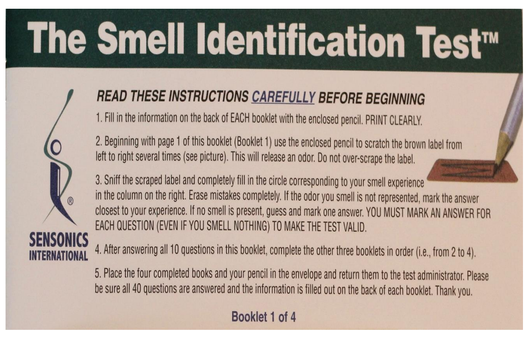
BACKGROUND

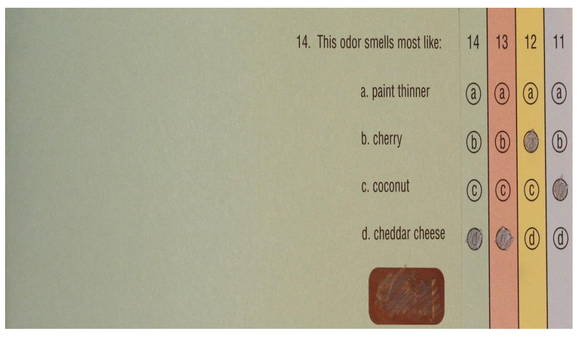
Cochlear implantation is a highly successful intervention that, despite remarkable improvements in hardware and software, continues to show a high degree of variability in outcomes. Performance in adult patients can potentially be affected by the integrity of spiral ganglion neurons or by the performance of the central auditory system. Prolonged deafness and dementia are conditions that affect the central auditory system and can negatively impact cochlear implant outcomes. Central auditory test batteries can evaluate the central component of hearing in patients that have significant residual hearing, but cannot be effectively used in most cochlear implant patients. A wide variety of recent studies have shown that decline in olfaction predates and often predicts a variety of central nervous system degenerative disorders. We set out to evaluate if olfaction testing could predict hearing results after cochlear implantation.

METHODS

Protocols and data collection were reviewed and approved by the institutional review board. We collected data on 29 (n=29) patients and 34 (n=34) ears. Adult (>18y) patients with a history of progressive hearing loss that met FDA criteria for CI were enrolled. To limit variability in data, patients with greater than 10 years of profound hearing loss and patients with congenital deafness were excluded from analysis. All patients underwent preoperative and postoperative evaluation using the testing recommendations outlined in the Minimum Speech Test Battery for Adult Cochlear Implant Users 2011. The AzBio test at + 10dB SNR was administered preoperatively and at 6 months after implantation. Testing was done in best-aided condition binaurally preoperatively and with a cochlear implant and hearing aid in the non-implanted ear postoperatively.[1]

Olfaction Testing: Olfaction testing was carried out using a commercially available version of the University of Pennsylvania Smell Identification Test (UPSIT) (Sensonics Inc., Haddon Heights, NJ). This suprathreshold test is a self-administered test consisting of 40 items and score out of 40 possible points was recorded.

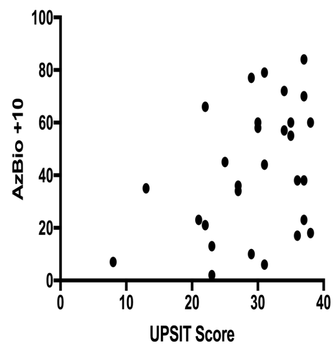




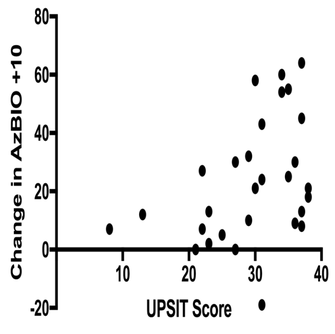
Statistical Methods: Testing variables in the analysis include patient age, UPSIT score, AzBio +10dB score at 6 months post activation, and change in AzBio +10dB score from preoperative to post activation testing times. Pearson correlation coefficients and a two trailed T test

RESULTS

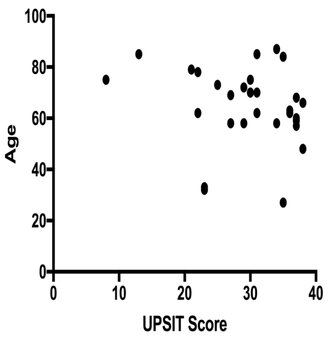
There was a significant correlation between the UPSIT score and the AzBio +10dB post activation (Pearson r=0.38, p=0.04). Lower olfaction scores correlated with poorer hearing outcomes.



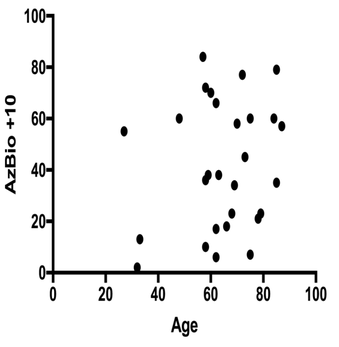
There was a significant correlation between the UPSIT score and the change in AzBio + 10dB score from preoperative to post activation testing times. (Pearson r=0.43, p=0.03). Lower olfaction scores correlated with poorer hearing outcomes.



There was no correlation between the patients' age and their total UPSIT score (Pearson r=-0.19, p=0.3315).



There was no correlation between the patients' age and their AzBio +10dB score at 6 months post implantation (Pearson r=0.18, p=0.3385).



DISCUSSION

Patients with Alzheimer's dementia[2,3] and other neurodegenerative diseases including Parkinson's,[3] Huntington's,[4] Korsakoff,[5] ALS[6] have been shown to perform poorly on smell tests. Poor performance on smell tests has also been shown to be predictive of cognitive decline and development of Alzheimer's dementia.[7,8,9] Hyposmia has also been shown to be predictive of development of dementia in Parkinson's disease.[10] Pathological changes have been shown to occur throughout the length of the olfactory tract in neurodegenerative diseases, from the olfactory epithelium to the primary olfactory cortex and its secondary targets. These changes occur secondary to deposition of pathologic proteins and neurofibrillary tangles.[11]

In the current study a moderate correlation between the UPSIT score and CI outcomes was found. Both the post op AzBio +10dB score and the improvement in AzBio score +10dB from preoperative to post activation testing times correlated to UPSIT scores, with lower olfaction correlating to poorer outcomes. Interestingly there was no correlation of hearing outcomes to age or olfaction to age in this cohort. Based on R^2, approximately 16% of the outcomes effect can be attributed to this correlation. Looking at the overall outcomes it is clear that some of the patients with excellent UPSIT scores had poor performance. Alternate forms of analysis may identity the cause of poor implant patients in this population. Patients with UPSIT scores under 30 tended to have poorer speech outcomes in background noise; this pattern could potentially be used to identify an at-risk cohort for poor cochlear implant performance.

There are multiple confounding factors that need to be considered. This study did not consider peripheral auditory system integrity and overall the sample size is small. Future studies will combine preoperative measures of peripheral auditory system function with olfactory testing to attempt to identify patients at risk for poor performance.

CONCLUSION

Olfactory testing may be useful in preoperative evaluation of CI patients. Identification of patients at risk for central auditory system dysfunction may be possible by evaluation of patients' olfactory function.

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CDH23 Related Hearing Loss: A Genetic Risk Factor for Semicircular Canal Dehiscence?

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Objective

- To investigate the prevalence and relative risk of semicircular canal dehiscence (SCD) in pediatric patients with *CDH23* pathogenic variants (Usher syndrome or non-syndromic deafness) compared to age-matched controls.

Introduction

Semicircular canal dehiscence (SCD) describes thinning or absence of bone over the semicircular canals leading to a third-window effect. The etiology of dehiscence is postulated to stem from congenital (structural) and acquired factors but the exact pathophysiology remains unclear (1-5). *CDH23* is a gene that encodes for cadherin-related 23, a transmembrane protein that is believed to be important in cell-cell and cell-matrix adhesions. *CDH23* is expressed by hair cells in the cochlea, vestibular organs, and in the retina (6). Pathogenic variants in this gene have been linked to syndromic (Usher 1D) and non-syndromic (DFNB12) hearing loss (7-8). While loss of CDH23 in the vestibular hair cells may explain the vestibular dysfunction, the exact mechanism of how *CDH23* contributes to the development of the otic capsule and vestibular organs is not well understood.

Methods and Materials

Study Design: Retrospective cohort study
Setting: Multi-institutional study
Patients: Pediatric patients (ages 0-5 years) with biallelic pathogenic variants in *CDH23* were compared with age matched pediatric controls who underwent computed tomography (CT) temporal bone scan for alternative purposes.
Interventions: Retrospective review of diagnostic high resolution CT temporal bone scans and MRI images for evaluation of SCD.
Main outcome measures: Superior and posterior semicircular canals were evaluated by a neuroradiologist for presence of SCD.

Table 1. : *Demographic information and dehiscent canals in CDH23 variant children*

Case	Age at CT (mo)	Gender	SCD	Phenotype	Variant 1	Variant 2
1	12	M	R/L SSCD	HL	c.3628C>T (p.Gln1210X)	c.6050-9G>A
2	2	F	R/L SSCD	Profound SNHL	c.6968delC (p.Pro2323fs)	c.8781C>A (p.Tyr2927X)
3	67	F	N/A	Usher	c.5712G>A (p.Thr1904Thr)	c.1369C>T (p.Arg457Trp)
4	10	M	R PSCD	Profound SNHL, delayed walking	c.2012delT (p.Phe671fs)	4kb heterozygous deletion including at least one exon in *CDH23* at 10q22.1
5	23	M	R/L PSCD	Profound SNHL	c.5272C>T (p.Gln1758X)	c.9629_9632delTCAA (p.Ile3210fs)
6	23	F	R SSCD	Profound SNHL	c.5272C>T (p.Gln1758X)	c.5712+1G>A
7	20	M	L SSCD	Profound SNHL, delayed walking	c.7483-1G>C	c.7483-1G>C

The c. nomenclature is based on the transcript NM_0022124.5 with the "A" in the "ATG" start codon denoting position "1", and the p. nomenclature is based on the translated peptide sequence. All variants are loss of function and classified as pathogenic based on predicted impact on the protein except for p.Arg457Trp, which is classified as likely pathogenic based on segregation in an affected sibling, in trans with a pathogenic variant, and statistically significant presence in cases over the general population. CT, computed tomography; mo, months; R, Right; L, Left; SSCD, superior semicircular canal dehiscence; PSCD, posterior semicircular canal dehiscence; HL, hearing loss; SNHL, Sensorineural hearing loss; N/A, not applicable.

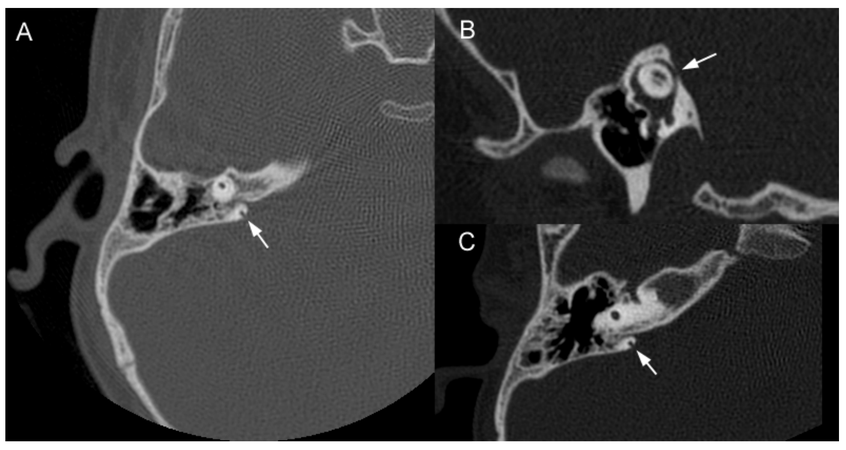

Figure 1. : Superior canal dehiscence in patient six. A. Axial imaging. B. Reformatted images parallel to the canal. C. Reformatted imaged perpendicular to the canal.

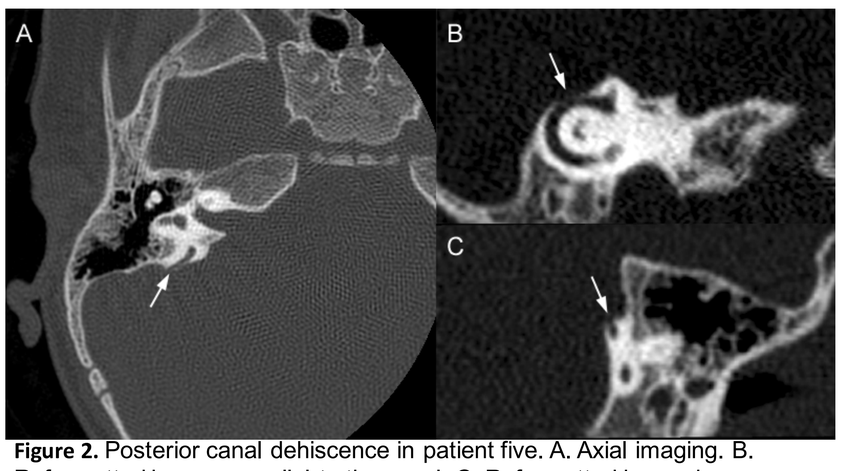

Figure 2. Posterior canal dehiscence in patient five. A. Axial imaging. B. Reformatted images parallel to the canal. C. Reformatted imaged perpendicular to the canal.

Results

- Eighty-six percent of the CDH23 variant group had dehiscence in at least one canal compared to only eight percent in age-matched controls
- Three CDH23 variant children had bilateral dehiscence of the canals.
- No children had dehiscence in both the superior and posterior canals.
- Relative risk of SCD in children with *CDH23* pathogenic variants is 10.3 (p=0.02) compared to the pediatric control population.

Table 2: *Comparison of proportion of patients with posterior semicircular canal dehiscence and superior semicircular canal dehiscence between the CDH23 variant population and the control population.*

	Posterior dehiscence	Superior dehiscence	Any dehiscence
CDH23	29% (2)	57% (4)	86 % (6)
Control	0 % (0)	8% (1)	8% (1)
p value	0.12	0.04	0.002

Discussion

- The rate of dehiscence in the *CDH23* variant children may reflect an impaired or delayed ossification compared to their age-matched controls
- Over 40 different pathologic variants of this gene have been identified but the genotype-phenotype correlation of specific variants are not well understood (6-8).
- *CDH23* is important in cell-cell adhesions and has been found in tip-links of stereocilia in the cochlea and vestibular hair cells, but its specific function in otic capsule development is unknown.(8).
- Our finding of a genetic link between *CDH23* variants and canal dehiscence warrants further research in the potential role of *CDH23* in otic capsule development.
- Distinguishing whether a patient has Usher 1D or non-syndromic DFNB12 phenotype may be difficult in the first years of life. The only patient without SCD in our study was also the only patient with confirmed Usher 1D, but this patient was also the oldest in the *CDH23* variant cohort. It is possible that the abnormalities seen on CT scan may help to differentiate these patient populations.

Conclusions

- Children with *CDH23* pathogenic variants are at significantly increased risk of having SCD and this may be a contributing factor to the vestibular dysfunction in USH1D patient population.

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Investigation of Piezoelectric Sensors for Implantable Otologic Microphones

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Background

- Implantable microphones are essential for development of fully implantable cochlear implants and active middle ear devices
- Currently available implantable microphones have issues with unstable mechanics, high noise and artifact, low sensitivity and low bandwidth
- Here we examine the ability of Piezoelectric sensors to measure umbo motion or intracochlear pressure changes to function as implantable microphones

Methods

- Polyvinlylidene flouride (PVDF) was selected as a piezoelectric material due to its high sensitivity, bandwidth and compliance
- 3 different designs (WORM, DIVING BOARD , DRUM) were tested using either umbo motion (WORM, DIVING BOARD & DRUM) or intracochlear pressure (WORM) as an input
- Magnitude and phase measurements of external auditory canal (EAC) pressure, stapes or umbo velocity, and output from the PVDF sensors were recorded.
- Tones of 10 ms duration between 100 Hz – 10 kHz (63 frequencies) and 80-110 dB SPL were presented to the sealed ear canal with a speaker

Design #1 "Worm"

- **Intracochlear pressure changes** were recorded by inserting a PVDF sensor into the scala vestibuli via a round window approach

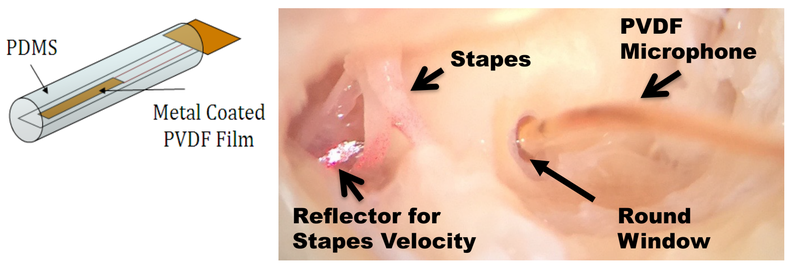

Fig: 1. (Left) Schematic of PVDF sensor embedded in PDMS to provide insulation and simulate a cochlear implant electrode. **(Right)** Image of PVDF sensor inserting into the round window.

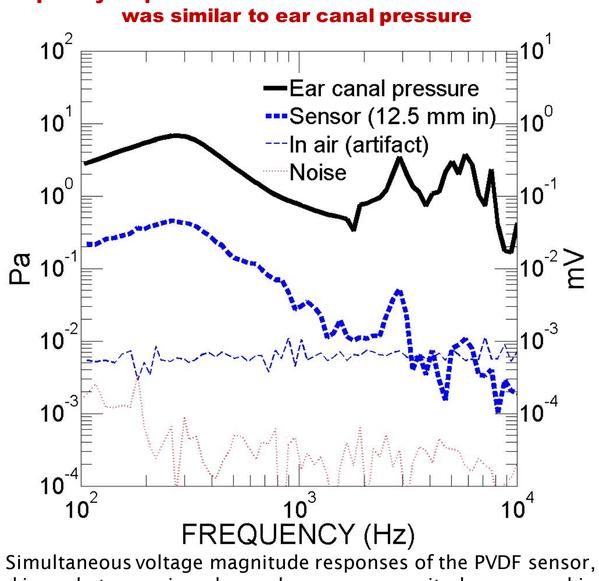

Fig: 2. Simultaneous voltage magnitude responses of the PVDF sensor, fully inserted in scala tympani, and sound pressure magnitude measured in the ear cana

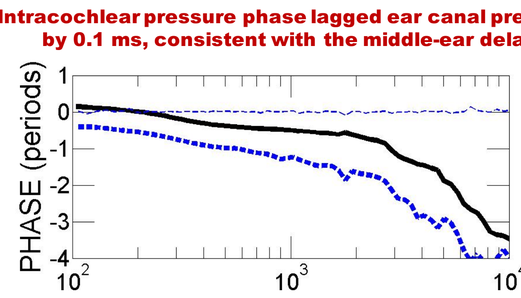

Fig: 3 Phase measurements of ear canal pressure and sensor output. Delay between ear canal pressure and intracochlear sensor output was ~0.1 ms

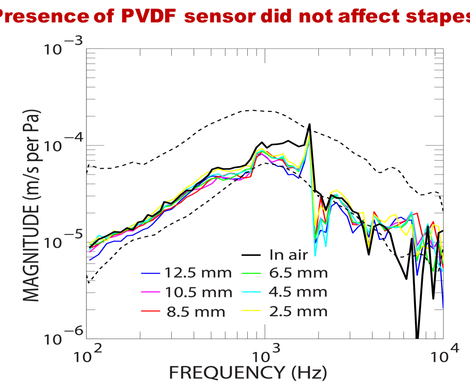

Fig: 4. Ratio of stapes velocity to ear canal pressure at varying sensor insertion depths in the scala tympani. Dashed lines indicate 95% confidence interval of normal human ear stapes velocity.

Design #2 "Diving Board"

- **Umbo motion** was recorded by placing rectangular PVDF sensor under the umbo via an extended facial recess approach

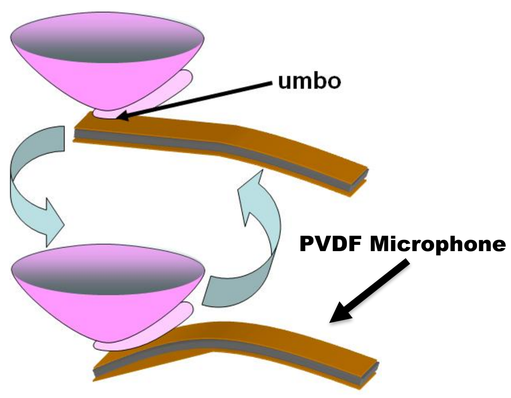

Fig: 5. Schematic of PVDF sensor being deflected by umbo motion

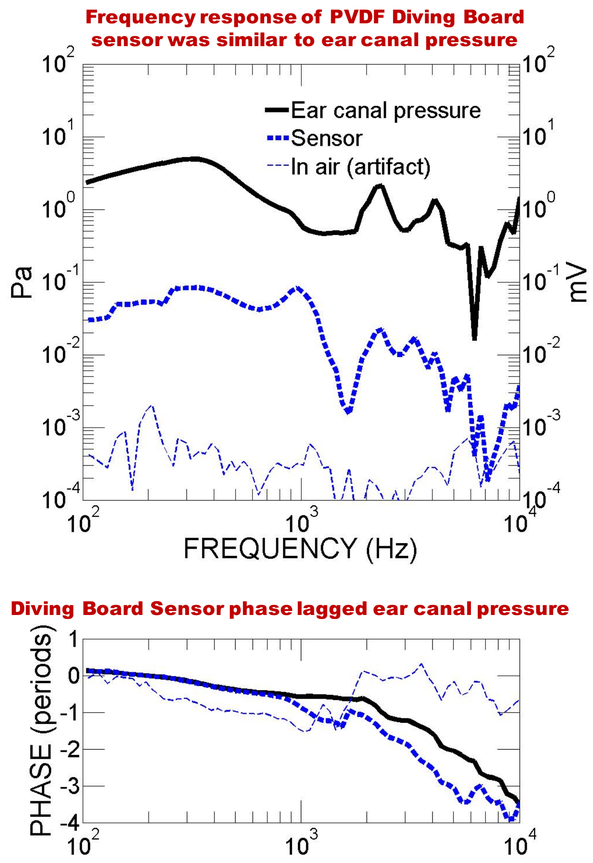

Fig: 6. (Top) Simultaneous voltage magnitude responses of the PVDF sensor contacting umbo, and sound pressure magnitude measured in the ear canal. **(Bottom)** Phase measurements of ear canal pressure and sensor voltage.

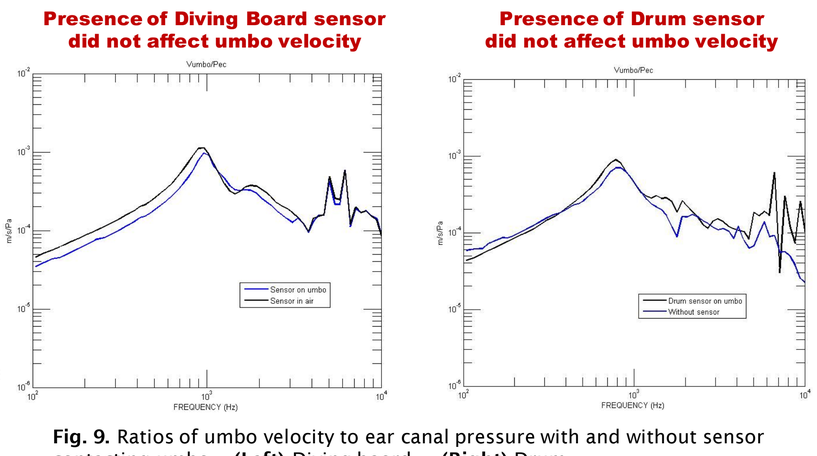

Fig. 9. Ratios of umbo velocity to ear canal pressure with and without sensor contacting umbo. **(Left)** Diving board **(Right)** Drum

Comparison of Designs

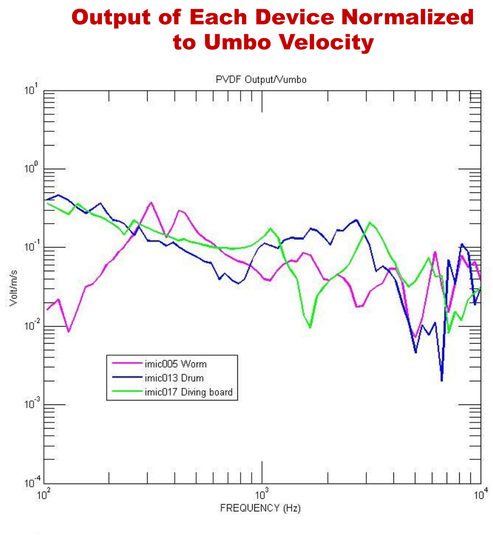

Fig: 10. PVDF output of the Worm, Drum and Diving board designs normalized to umbo velocity. The flatter response curves of the Worm and Drum show frequency responses similar to umbo motion

Design #3 "Drum"

- **Umbo motion** was recorded by placing PVDF "drum" (sensor membrane circumscribed by a rigid cylinder) under the umbo via an extended facial recess approach

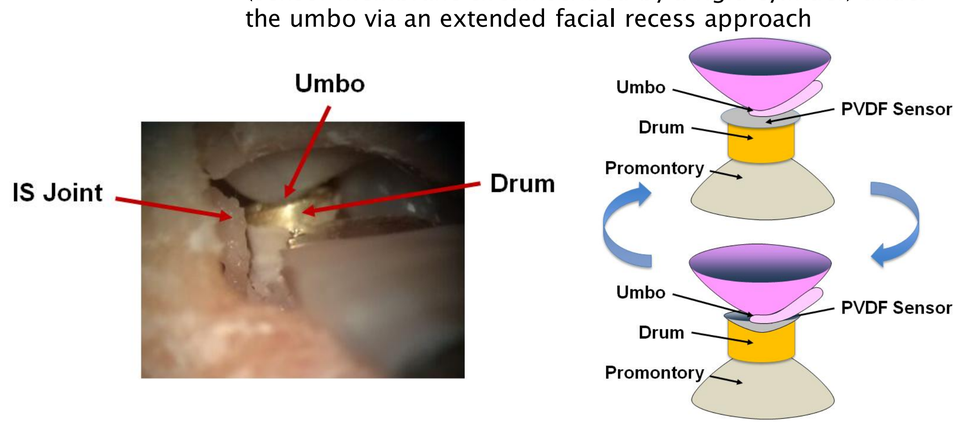

Fig: 7. (Left) Image of PVDF Drum placed on promontory and contacting umbo **(Right)** Schematic of PVDF sensor attached to drum device and being deflected by umbo motion.

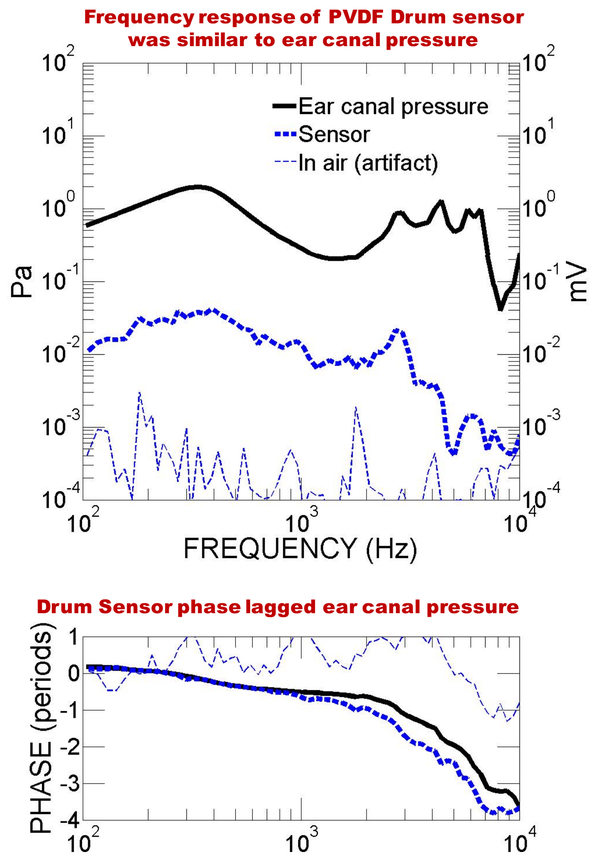

Fig: 8. (Top) Simultaneous voltage magnitude responses of the PVDF sensor contacting umbo, and sound pressure magnitude measured in the ear canal. **(Bottom)** Phase measurements of ear canal pressure and sensor voltage.

Discussion

- Our results indicate that each configuration of the PVDF sensor was able to detect acoustical input into the external auditory canal
- Figs. 2,6,8 show that each PVDF sensor's frequency response were similar to the EAC pressure response or umbo velocity
- Fig. 3 also shows a phase delay of ~ 0.1 ms between ear canal pressure and intracochlear sensor output for the intracochlear worm device, which is similar to previously published reports of the time delay of the middle ear ossicular chain. This indicates the output is from transmission via the ossicular chain and not direct transmission from the speaker due to electrical coupling
- Figs. 6 and 8 also show phase changes consistent with transmission via umbo motion and not direct electrical coupling between speaker and sensor
- Figs. 4 and 9 demonstrate that the presence of sensors in did not affect ossicular motion.
- Fig. 10 shows that measurements of umbo motion with drum and diving board resulted in better sensitivity and bandwidth than the compliant "worm" sensor at the umbo

Conclusion

- This study shows the feasibility of a PVDF piezoelectric sensor prototype to measure both intracochlear changes and umbo motion as an input to a fully implantable microphone
- These devices could be used in the future to function as an internalized microphone and provide input to a speech processor for a fully implantable cochlear implant and active middle ear implants
- Future studies will focus on tuning the material properties and optimizing the designs of the sensors to increase sensitivity and bandwidth while decreasing noise

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