Hearing Loss After Vestibular Implantation in Sand Rats With Normal Hearing

Aviram Mizrachi, MD; Ohad Hilly, MD; Eyal Raveh, MD; Joseph Attias, PhD; Ben I. Nageris, MD

**IMPORTANCE** Bilateral vestibular failure is a debilitating condition that may lead to oscillopia and adversely affect quality of life. Researchers have suggested that vestibular function might be restored with implantation of an external mechanical stimulation device. However, it is essential that such a device must not interfere with normal hearing.

**OBJECTIVE** To evaluate the effect of vestibular implant insertion on hearing in a sand rat model with normal hearing.

**DESIGN, SETTING, AND SUBJECTS** The study was conducted in a tertiary medical center in accord with the guidelines of the Rabin Medical Center Animal Care and Use Committee. The experiment was performed in 6 adult, 6-month-old, fat sand rats (*Psammomys obesus*), which have a unique aural anatomy that permits access to the inner ear. The study dates were March 2013 to March 2014.

**INTERVENTIONS** The sand rats were anesthetized and electrodes were implanted unilaterally (in 6 sand rats) or bilaterally (in 2 sand rats) in all 3 semicircular canals (lateral, then posterior, and then superior) by fenestration of the respective ampullas. To measure air and bone conduction thresholds, auditory nerve brainstem evoked responses to alternating polarity clicks and 1-kHz tone bursts were tested before surgery, at each operative stage, and after surgery.

**MAIN OUTCOMES AND MEASURES** Air or bone conduction threshold shifts after implantation of a vestibular implant electrode array in each semicircular canal.

**RESULTS** After unilateral implantation of the vestibular implant, sand rats showed a sideways head tilt, whereas after bilateral implantation, sand rats ran around in circles and were unable to stand still or walk on a treadmill. On statistical analysis, statistically significant differences from preoperative values were obtained across all stages of surgery for air conduction thresholds. The largest and statistically significant air conduction shift for 1-kHz stimuli (mean [SD, 13.7 [2.8] dB; *P* < .004) as well as for clicks (12.5 [2.1] dB; *P* < .002) was found for the superior canal electrode insertion. For the posterior canal, the air conduction thresholds to 1-kHz stimuli and to clicks shifted significantly after electrode insertion (mean [SD], 7.5 [2.3] dB; *P* < .01 and 7.5 [0.9] dB; *P* < .001). For the lateral canal, only the threshold to clicks changed significantly (mean [SD], 5.5 [1.7] dB; *P* < .02). Bone conduction thresholds did not change significantly after vestibular electrode insertion.

**CONCLUSIONS AND RELEVANCE** Implantation of a vestibular device is associated with mild to moderate conductive hearing loss in fat sand rats with normal hearing, especially when the device is placed in the posterior and superior semicircular canals. Bilateral implantation is associated with major vestibular pathologic results. Further studies are needed in animals with cochlear or vestibular disorders before it can be definitively concluded that vestibular implantation carries only a minor risk to hearing.

**Author Affiliations:** Department of Otorhinolaryngology–Head and Neck Surgery, Rabin Medical Center, Beilinson Campus, Petach Tikva, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel (Mizrachi, Hilly, Raveh, Nageris); Department of Communication Sciences and Disorders, University of Haifa, Haifa, Israel (Attias).

**Corresponding Author:** Aviram Mizrachi, MD, Department of Otorhinolaryngology–Head and Neck Surgery, Rabin Medical Center, Beilinson Campus, Petach Tikva 49100, Israel (aviramguy@hotmail.com).
he vestibular system is one of the major contributors to spatial orientation, balance control, and image stabilization. Bilateral vestibular failure is a chronic debilitating condition, defined by the US National Center for Health Statistics’ loss of vestibular sensation for longer than 1 year, with failure of the vestibulo-ocular reflex, leading to oscillo-pia and reduced visual acuity.2,3

The reported incidence of bilateral vestibular failure is 0.1% among adults in the United States,4 and it may occur secondary to various disorders, including ototoxicity, infection or trauma to the labyrinth, ischemia, autoimmune disorders, Meniere disease, and others. In approximately 50% of cases, no cause is found. Treatment consists of vestibular exercises and balance training, but there is no clear evidence of its effectiveness.4

Researchers have suggested that it may be possible to modulate vestibular nerve activity by implantation of an external mechanical stimulatory device, analogous to a cochlear implant. This notion is based on experiments in the 19th century by Ewald5 in which vestibular stimulation produced reflexive head movements in birds. Other investigators showed similar responses in multiple species.6-7 For clinical use to restore vestibular function, such a device would have to meet the criteria of biocompatible materials, transcutaneous power transmission technology, and safe electrical stimulation paradigms to elicit action potentials on peripheral nerves.

The first self-contained vestibular prosthesis was developed by Saginaw et al8 in 2000 and tested in a guinea pig model. A single-axis gyroscope was used to sense head rotation, and constant current, charge-balanced, biphasic pulses were delivered to an electrode implanted in one semicircular canal (SCC). This effort was followed by the development of a multichannel vestibular prosthesis by the Johns Hopkins Vestibular NeuroEngineering Laboratory (Baltimore, Maryland), consisting of 3 mutually orthogonal gyroscopes that sense 3-dimensional head rotation velocity and 4 pairs of electrodes, each of which shares a single current source.9 The prosthesis is activated in pulse frequency–modulated fashion.9 A group from the University of Washington (Seattle) designed a multichannel vestibular prosthesis that was sufficiently narrow so as not to compress the membranous canal.10

Given that most patients with bilateral canal paresis have normal or near-normal hearing, it is essential that the vestibular implant must not cause hearing loss. This issue has been addressed in previous experimental and human studies, with inconsistent findings. The objective of the present study was to evaluate the effect of vestibular implant insertion on hearing in a sand rat model with normal hearing.

Methods

The study was approved by the Rabin Medical Center Animal Care and Use Committee. Experiments were conducted on 8 ears in 6 adult, 6-month-old, fat sand rats (Psammomys obesus) weighing 220 to 260 g (mean, 234 g), supplied by Harlan Biotech Israel Ltd. The study dates were March 2013 to March 2014. The fat sand rat has a unique aural anatomy in which the cochlea, vestibule, and SCCs bulge into the bulla cavity and can be easily accessed.

The anatomy of the fat sand rat allows a facile surgical approach for manipulations of the inner ear. This sand rat model was used in our group’s previous inner ear studies. Compared with guinea pigs, which also have a large and accessible otic bulla, the inner ear anatomy and best hearing sensitivity (range, 1-4 kHz) of the fat sand rat more likely resemble those of humans.11

Surgical Procedure

Anesthesia was induced by intramuscular injection of ketamine hydrochloride (0.075 mg/100 g of body weight) and xylazine (0.05 mg/100 g of body weight). Additional doses were given intramuscularly as needed. Before the operative procedure, the external ear canals were inspected to rule out cerumen impaction and to validate the integrity of the tympanic membrane. The sand rat was placed in a prone position on a warm surface to maintain adequate body temperature throughout the procedure.

A horizontal scalp incision was made between the ears using a No. 15 blade scalpel, and a flap was elevated by gently dissecting the subcutaneous tissues. The fascia and muscles over the calvarium were dissected until the otic bulla, a bony structure that contains the middle and inner ear components, was exposed. Next, the bone of the posterior aspect of the otic bulla was drilled and removed until all 3 SCCs were well visualized under an operating microscope. Vestibular implantation was performed first in the lateral SCC and then in the posterior and superior SCCs. This order was maintained across all sand rats.

The SCCs were approached by creating a fenestra in the center of the respective ampullas using a 0.2-mm hand drill to penetrate the thin bony labyrinth. Care was taken not to injure the membranous labyrinth. A 0.15-mm Bear metal electrode (PULSAR/C40+; Medel) was gently inserted until resistance was sensed. A soft surgery technique was used, with no suction after the labyrinth was opened. A thin free fascia graft was used to occlude the gap between the implant and the bony fenestra. This sequence of events was performed for all 3 SCCs in a single surgical procedure.

Hearing Tests

Auditory nerve brainstem evoked responses (ABRs) were elicited and recorded before surgery and at each surgical stage using standard equipment (Navigator Pro Evoked Potential System; Bio-Logic Systems Corporation). Stimuli consisted of alternating polarity clicks presented for 100 milliseconds at a rate of 13.3 per second and alternating polarity tone bursts of 1 kHz generated with the Blackman ramp filter. To measure air conduction thresholds, the stimuli were delivered to the ear through inserted earphones (insert delay, 0.8 milliseconds) and presented to both ears simultaneously through the earphones (580-SINSER; Bio-Logic Systems Corporation) with earplugs. To measure bone conduction thresholds, the same stimuli were delivered to the calvarium via a bone oscillator (B-71, 27154, 300-0; Radioear Corporation) held in place by a tight elastic gauze net. The point of oscillator placement on the...
calvarium was marked to maintain precision on consecutive tests. The ABRs were recorded by 3 electrodes. The active electrode was inserted subcutaneously on the forehead and referred to the pinna of the operated ear, and the ground electrode was placed on the contralateral pinna. The ABR threshold was defined as the lowest stimulus intensity that resulted in a clearly defined wave V response. The recordings at threshold intensity were repeated twice for reproducibility, confirming the presence of an obvious response. During all monaural ABR recordings, the contralateral ear was masked with white noise. Based on previous evidence of interaural attenuation in small rodents, we set the minimum masking levels for air-conducted high-frequency stimulation (clicks and 6 kHz) at 40-dB sound pressure level (SPL) and for 1-kHz tone bursts at 50-dB SPL. For bone conduction measurements, we used the minimum masking level at the bone conduction threshold of the fat sand rat (50-dB SPL), and the masking level was increased as a function of the bone conduction or air conduction threshold of each ear.

In the first 3 operated ears, ABR recordings were repeated immediately after the bulla was opened, and the findings were compared with the preoperative recordings. No changes in ABR thresholds were noted.

The effects of surgical stage (preoperative, opening the bony labyrinth, and vestibular device insertion), mode of stimulation (air or bone conduction), and SCC location (lateral, posterior, and superior) on the threshold shift were statistically analyzed by analysis of variance with repeated measures and post hoc tests. All reported P values are 2 sided. P < .05 was considered statistically significant. All analyses were performed with a statistical software program (SPSS, version 15.0.1; SPSS Inc).

Results

Resistance to Anesthesia and Morbidity and Mortality

Eight ears in 6 sand rats were operated on (24 total SCCs). All surgical procedures were uneventful, and the sand rats recovered as expected. All survived vestibular implantation, with no postoperative complications. In general, the entire vestibular implantation procedure, including the abovementioned tests, took about 90 minutes.

Behavioral Manifestations

Unilateral vestibular implantation (in 6 sand rats) resulted in tilting of the head toward the operated side. Bilateral vestibular implantation (in 2 sand rats) resulted in severe vestibular dysfunction whereby the sand rats ran around in circles and were unable to stand still or walk on a treadmill.

Hearing Thresholds

The Table lists the preoperative air and bone conduction thresholds in the operated ears in response to clicks and 1-kHz tone bursts. These threshold values are typical for normal fat sand rats in our laboratory, as previously reported. The Figure shows threshold shifts for each SCC after insertion of the vestibular electrode relative to preoperative values. Statistically significant changes in air conduction, but not bone conduction, were noted. By SCC location, vestibular implant insertion in the superior canal was associated with the largest air conduction threshold shifts.

Analysis of variance with repeated measures of 6 within-subject air conduction factors (preoperative, opening the bony labyrinth, and vestibular implant insertion by clicks and 1-kHz tone bursts) and 3 between-subject factors (lateral, posterior, and superior canal placement) yielded a statistically significant air conduction threshold shift (F_S = 20.4, P < .001) across the surgical stages and a statistically significant interaction among them (F_{10} = 39.1, P < .006), with statistically significant differences by canal used (F_1 = 7.7, P < .003).
Hearing Loss After Vestibular Implantation in Normal-Hearing Sand Rats

ORIGINAL INVESTIGATION

Research

Discussion

Overall, the present study shows that implantation of a vestibular electrode causes a mild threshold shift in air conduction, primarily when the device is placed in the posterior and superior canals. Bone conduction does not change significantly from the preoperative value regardless of the type of stimuli (clicks and 1-kHz tone bursts) or operative stage.

In all ears operated on in this study, we first implanted the electrode array in the lateral SCC, followed by the posterior and then the superior SCC. This approach mimics the expected course of clinical implantation involving all 3 canals.

Conductive hearing loss was mild, ranging from 0 to 17 dB, with medians of 0 to 10 dB. By contrast, in our group's previous studies\(^1\) of the same animal model, a moderate conductive hearing loss was measured after fenestration of the SCCs. This effect may be attributable to the different loci at which the fenestra was placed in the SCC (the apex in the earlier studies and the ampulla in the present study), which may have variably affected the mechanism of the pressure wave in the inner ear. A possible explanation for this effect may be a third window phenomenon, which occurs when the ampulla is fenestrated and then sealed with fascia around the electrode. Acoustic energy is shunted away through this additional membrane, resulting in less acoustic energy reaching the scala media. This loss of energy through the additional third window, if indeed that is the case, might falsely alter the air conduction threshold curve and cause what some call a pseudoconductive hearing loss, which is actually sensorineural in nature.

One week after the procedure, when the healing process was completed, the hearing loss in a few sand rats remained stable and even larger, probably due to bone growth and fibrosis. Another explanation for hearing loss after vestibular implantation could be endolymphatic hydrops as a result of mechanical pressure applied on the membranous labyrinth by the electrode. However, if that was the case, then all 3 canals should have been affected equally. Further studies are needed to elucidate this issue. Nevertheless, this study clearly shows that vestibular implantation alters only the conductive mechanism of the inner ear without affecting the transduction process of its sensory elements.

In an earlier experimental study, Tran et al\(^16\) investigated the effect of a vestibular implant on hearing in a guinea pig model by inserting an electrode into the lateral SCC via a fenestra created 2 mm from the canal ampulla. They found that electrode implantation at the canal level entailed a risk of hearing loss but that electrical stimulation of the horizontal ampullary nerve did not further alter hearing function. In a study of rhesus monkeys, Dai et al\(^17\) concluded that implantation and activation of vestibular implant electrodes in humans will carry a risk of hearing loss, although unlikely to be severe. By contrast, Rubinstein et al\(^10\) reported good hearing preservation after implantation of a vestibular device in a model of rhesus macaques. However, only 2 SCCs (lateral and posterior) were implanted in 6 of 7 animals.

While all these studies\(^10,16,17\) reported some degree of hearing loss after vestibular implantation, none differentiated between air conduction and bone conduction thresholds. Therefore, we do not know if the hearing loss was conductive, mixed, or cochlear in origin. Furthermore, the level of hearing loss among the studies is unclear. The present study demonstrates that the hearing loss is conductive or pseudoconductive (in the case of a third window phenomenon) and mild. These findings may have important clinical implications for vestibular implantation in humans.

Conclusions

Superior SCC vestibular implant insertion results in mild conductive hearing loss. Implantation on only one side apparently causes minimal if any clinical vestibular disturbances, whereas bilateral implantation is associated with major vestibular pathologic results. However, this study was performed in healthy sand rats with normal hearing, and the findings cannot be extrapolated to animals with a cochlear or vestibular disorder. Therefore, more research is needed to further clarify the mechanism by which this hearing loss occurs before it can be definitively concluded that vestibular implantation carries only a minor risk to hearing.

ARTICLE INFORMATION

Submitted for Publication: January 5, 2015; final revision received May 31, 2015; accepted June 6, 2015.


Author Contributions: Dr Mizrahi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Mizrahi, Raveh, Attias, Nageris. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Mizrahi, Attias, Nageris. Critical revision of the manuscript for important intellectual content: Hilly, Raveh, Attias, Nageris. Statistical analysis: Attias. Administrative, technical, or material support: Mizrahi, Raveh, Attias, Nageris. Study supervision: Attias, Nageris.

Conflict of Interest Disclosures: None reported.

Copyright 2015 American Medical Association. All rights reserved.

jamaotolaryngology.com

JAMA Otolaryngology—Head & Neck Surgery  September 2015  Volume 141, Number 9  843
Previous Presentation: This study was presented at the 29th Politzer Society Meeting; November 14-17, 2013; Antalya, Turkey.

REFERENCES
5. Ewald JR. Physiologische Untersuchungen uber das Endorgan des Nervus Octavus. Wiesbaden, Germany: Bergmann; 1892.